Modulational Instability and Localized Modes for Ultrasound Contrast Microbubbles Surface Oscillations

Serge Dos Santos
Centre - Val de Loire Université,
INSERM U930 "Imagerie et Cerveau" - CNRS ERL 3106,
ENI Val de Loire, 3 Rue de la Chocolaterie, BP3410,
41034 Blois cedex, FRANCE

Víctor Sánchez-Morcillo, Noé Jiménez
Departamento de Fisica Aplicada, IGIC,
Universidad Politecnica de Valencia,
c/ Paranimf 1, 46730 Grao de Gandia, SPAIN

Jennifer Chaline, Ayache Bouakaz
INSERM U930 "Imagerie et Cerveau" - CNRS ERL 3106,
Université Francois Rabelais, Bâtiment B1A, 1er Etage,
CHRU Bretonneau 2 boulevard Tonnellé, 37044 Tours Cedex, FRANCE

***Abstract*— Microbubble surface modes appear when contrast agents are insonified with specific ultrasound pulses. In this case, the radius becomes a space-dependent function which can be expanded on the basis of spherical harmonics describing the spatial vibrational modes of the bubble. The radial symmetry-breaking, which appears through a Modulational Instability (MI), is typical of many extended nonlinear systems subjected to an external driving. Here we present a mechanical analogue of bubble pulsations, consisting in a macroscopic ring of coupled oscillators driven by parametric forcing. Depending on the amplitude and the frequency of the driving, the mechanical ring presents a parametric instability leading to surface modes and localized modes oscillating at subharmonics of the parametric excitation. Bubbles are used as contrast agent in medical ultrasound imaging and to carry some drug to special locations. The perspective of this analysis is to define practical optimized ultrasound pulses exciting the bubble and leading to drug delivery applications.**

I. Introduction

Targeted drug delivery is one of the most important, but not yet attained, goals of modern pharmacology and therapy. In recent years, new promising possibilities for targeted drug delivery have been discovered that can be realized by using microbubble ultrasound contrast agents (UCA). These agents can carry drugs and selectively adhere to specific sites in the human body. This capability provides great possibilities for localized drug delivery in combination with a phenomenon know as sonoporation. Sonoporation is a process in which ultrasonically activated contrast agent microbubbles, pulsating nearby biological barriers (cell membrane or endothelial layer), increase their permeability and thereby enhance the penetration and the extravasation of external substances [1]–[3]. In this way drugs can be delivered inside individual cells without serious consequences for the cell viability. At present, however, there is no consensus on the underlying mechanisms of sonoporation and the problem of acoustic microstreaming [4]:

One of the mechanisms which may enhance the above described processes is the excitation of particular surface modes of UCA, as the result of insonification with specific ultrasound pulses [5]. The basic, radially symmetric mode may become unstable via a Modulational Instability (MI) [6]. Such instability brings a system from a spatially uniform state to a spatial dependent state (a higher order vibration mode) in nonlinear systems subjected to an external driving.

The objective of this work is to study microbubble surface modes which appear when UCA are driven by ultrasound and exhibit shape-unstable behavior caracterized by parametric instability. Using the analogies evidenced by the symmetry analysis, the study is performed with a mechanical macroscopic ring of coupled oscillators, which is easier to measure and characterize. The vertical oscillation of the ring is equivalent to the external pressure field incident on the bubble. Thus a correspondence between both systems can be stablished. Our interest in this study would be to determine the external acoustical pressure on a bubble to a given excitation frequency for a specific surface mode. As the parametric driving increases, in both systems the radially symmetric wall oscillation ($R(t) = R_0 + r(t)$) is no more present and an unstable behavior coming from breathing mode appears and some spherical modes grow, resulting in symmetry breaking: $R(t) \rightsquigarrow R(t, \theta, \phi)$. Surface modes can be analytically described as a linear composition of spherical harmonics ([7] and [8]). Our aim is also to link the appearance of one or several spherical harmonics with the existence of a modulational instability in the system.

II. Similarity Analysis

Starting from the continuous Marmottant's model [9], for the vibration of the bubble radius $R(t)$, and a discrete nonlinear model for the discretized radius with periodic boundary conditions and nonlinear coupling between surface modes, MI in bubbles is investigated numerically. After a first step of

Symmetry Analysis [10] applied to the nonlinear equations associated to the physical systems, invariant properties allow an identification of dimensionless similarity variables that link both continuous and discrete models. Thanks to this similarity analysis, the bubble can be studied with a macroscopic mechanical 1D ring chain. A theoretical model for the ring chain is proposed. Our experimental setup consist in a ring with diameter $D = 73$ cm, formed by $N = 48$ nonlinearly coupled pendula with mass $m = 6$ g and length l_0 between 3.2 cm and 15 cm, with periodic conditions. The second step consists in studying numerically the MI criterion versus the amplitude of external field applied to the bubble. The analysis and the experiments reveals the existence of Intrinsic Localized Modes (ILMs), similar to those found in other more generic systems of nonlinearly vibratory lattices. The observation of ILM in 1D chain of coupled oscillators [11], [12], presenting many similarities with the discrete bubble model, showed to play a role in creating spatio-temporal localized excitations leading to the breaking of the bubble. In our periodic pendulum lattice apparatus describing the macroscopic equivalence of the bubble, the system parametrically driven at 5.4 Hz presents subharmonic behavior and localized modes oscillating at 2.7 Hz. Versus the amplitude and the frequency of the driving, the mechanical ring presents parametric instability surface modes and localized modes oscillating at subharmonics of the parametric excitation (see multimedia files and http://ultrasons-inserm.med.univ-tours.fr/aTelecharger/sDos/SergeMovies/).

III. Real and analog bubble modeling

There are several approaches for the modeling of nonlinear bubble dynamics, all of them taking a starting point the Rayleigh-Plesset equation. It was been recently proposed a generalized description using a Hamiltonian formalism [13], where the expansion of the radius in a series of spherical harmonics is given by

$$R(t) \rightsquigarrow R(t,\theta,\phi) = R(t) + \epsilon \sum_{l=0}^{\infty} \sum_{m=-l}^{l} a_l(t) Y_l^{(m)}(\theta,\phi). \quad (1)$$

The monopole pulsation ($l = 0$) is characterized by the resonance frequency

$$\omega_0^2 = \frac{3}{\rho_l R_0^2} K_V = \frac{3}{\rho_l R_0^2} \left(\kappa P_{atm} + \frac{2(3\kappa - 1)\sigma}{R_0} \right), \quad (2)$$

the dipole mode ($l = 1$) corresponds to translational motions (displacement of the bubble center of mass), and shape oscillations ($l > 2$) are characterized by a frequency

$$\omega_l^2 = (l-1)(l+1)(l+2)\frac{\sigma}{\rho R_0^3}. \quad (3)$$

Marmottant's model for ultrasound contrast agents [9], which describes coated bubbles, stand on the Rayleigh-Plesset equation with some boundary conditions, given by the dependence of the surface tension on the coordinate on the bubble surface, $\sigma(R)$. Three particular cases are considered, describing buckled bubbles, elastics bubbles and ruptured bubbles. The last

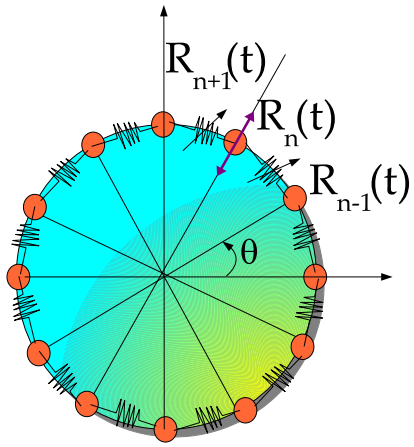


Fig. 1. Simplified model of the bubble with discrete radius $R(t,\theta,\phi) \rightsquigarrow R(t,\theta) \rightsquigarrow R_n(t)$. Each particle produce a radial evolution $R_n(t)$ depending on the substrat potential and a linear/nonlinear coupling depending on the first neighbors $f(R_{n-1}(t), R_n(t), R_{n+1}(t))$

one can be seen as free bubbles, i.e. bubbles without shell. The boundary condition on the Rayleigh Plesset equation is

$$P_g(t) - P_l(t) = \frac{2\sigma(R)}{R} + 4\mu\frac{\dot{R}}{R} + 4\kappa_s\frac{\dot{R}}{R^2}, \quad (4)$$

where $P_g(t)$ the pressure of the gas in the bubble, $P_l(t)$ the pressure of the liquid surrounding, $\sigma(R)$ the surface tension, μ the viscosity and κ_s the surface dilatational viscosity. By taking it into Rayleigh-Plesset equation a space dependent surface tension, one obtains the Marmottant's model:

$$\rho_l \left(R\ddot{R} + \tfrac{3}{2}\dot{R}^2 \right) - \left(P_0 + \tfrac{2\sigma(R_0)}{R_0} \right) \left(\tfrac{R}{R_0} \right)^{-3\kappa} \left(1 - \tfrac{3\kappa}{c}\dot{R} \right) + P_0 + 2\tfrac{\sigma(R)}{R} + \tfrac{4\mu\dot{R}}{R} + \tfrac{4\kappa_s\dot{R}}{R^2} = -P_{ac}(t) \quad (5)$$

where $\rho_l, \sigma, \kappa, c, \mu, \kappa_s$ are bubble's parameters. With an external driving defined by $P = P_0 + P_{ac}(t)$, the linearization consist in assuming $R(t) = R_0 + \epsilon r(t)$, and $\sigma(R) = \sigma(R_0) + 2\epsilon\kappa\left(\frac{R}{R_0} - 1\right)$, with ϵ a small quantity, and retaining terms in the leading order of ϵ. In this case, it can be shown that the radius behaves as a linear driven-damped oscillator, as

$$\ddot{r}(t) + 2\gamma\dot{r}(t) + \omega_0^2 r(t) = -\frac{P_{ac}(t)}{\rho_l R_0^2}, \quad (6)$$

where ω_0 is given by Eq. (2)

Assuming classical values for bubble's physical parameters, one have the approximate condition

$$f_0[MHz]R_0[\mu m] \simeq 3. \quad (7)$$

The similarity property can be written $f_0[Hz]R_0[m] \simeq 3$ and explain the typical sizes chosen for the macroscopic experiment with coupled pendulum. Using the Prosperetti's model for the expansion in spherical harmonics $Y_l^{(m)}(\theta,\phi)$, the linearized bubble oscillation is then described by

$$\ddot{a}_l(t) + 2\gamma\dot{a}_l(t) + \omega_l^2 a_l(t) = 0, \quad (8)$$

where ω_l is given by Eq.(3). If the spherical (radial) mode is unstable, *i.e.* $R(t) \rightsquigarrow R(t,\theta)$, a modulational instability

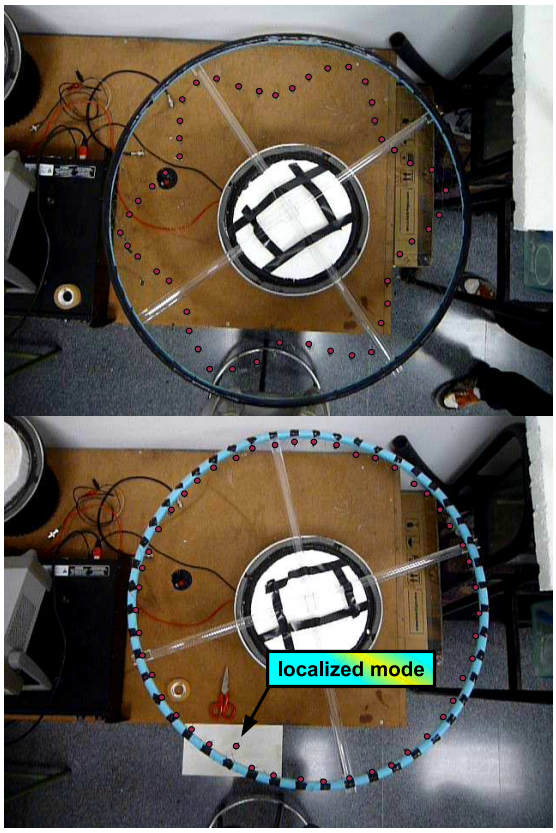


Fig. 2. Macroscopic pendulum chain with the following parameters $N = 48$, $R_0 = 36.5$cm, $m = 6$g and $l_0 = 15$cm(top), $l_0 = 3$cm(bottom). When the parametric excitation is driven at frequency $f_e = 2.57$ Hz, the spherical mode $Y_{l=8}^{(m)}$ appears. When the parametric excitation is driven at $f_e = 4.5$ Hz, the localized mode appears and oscillation of the single particule is around $f_{osc} = \frac{f_e}{2}$. Multimedia files can be found at http://ultrasons-inserm.med.univ-tours.fr/aTelecharger/sDos/SergeMovies/

appears. As known from literature, this instability is also related with the excitation of localized modes, which have been observed both in the ring of oscillators and in the real bubbles driven by an ultrasound field.

A basic hypothesis is the discretization of the spatial coordinates describing the motion of the bubble surface. Also we reduce the dimension of the problem, the relevant dynamics being that which occurs on a plane (e.g. defined by the equator of a bubble). This agrees with the approach developed by Maksimov *et al* [13] for describing nonlinear spatial modes in bubbles. We assume that

$$R(t,\theta,\phi) \rightsquigarrow R(t,\theta) \rightsquigarrow R_n(t) \tag{9}$$

where $R_n(t)$ is the position of one mass in the oscillator chain (proportional to the angle with respect to vertical). It describes the spatio-temporal dependence of the mechanical bubble radius at angle $\theta = n\theta_0$, $\theta_0 = 2\pi/N$ being the sampling step of the θ-discretization ($n = 0, ..., N-1$). The following model is then derived

$$\begin{aligned} &\ddot{R_n}(t) + \gamma\dot{R_n}(t) + R_n(t)\left[\omega_0^2 + \eta\cos(2\omega_{ext}t)\right] \\ &= f_c\left(R_{n-1}(t), R_n(t), R_{n+1}(t)\right) \end{aligned} \tag{10}$$

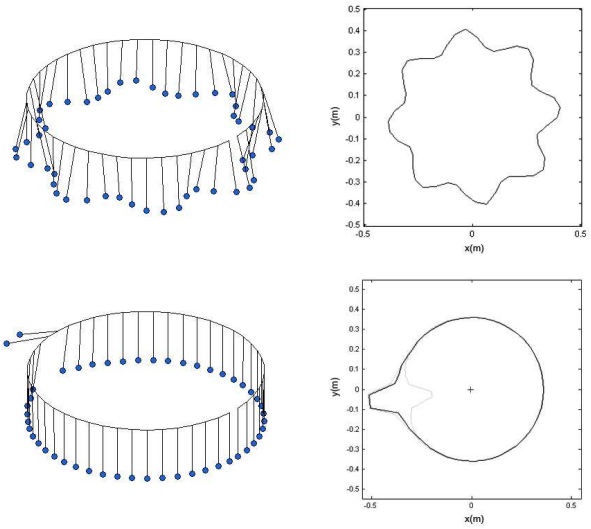


Fig. 3. Spherical mode $Y_{l=8}^{(m)}$ observed when $f_0 = \frac{f_{ext}}{2.25}$. Modulational instability is observed in the time and frequency domain (top right curve). Localized mode observed at $f_0 = \frac{f_{ext}}{1.92}$ showing a trapping like behavior of energy. Modulation instability is observed in the time and frequency domain (top right curve)

where η is proportional to the driving amplitude, ω_0 is the natural frequency and $f_c\left(R_{n-1}(t), R_n(t), R_{n+1}(t)\right)$ is proportional to the nonlinear coupling between nearest neighbor masses with the periodic condition $R_N(t) = R_0(t)$. The potential force $f_s(R_n(t), t) = -R_n(t)\left[\omega_0^2 + \eta\cos(2\omega_{ext}t)\right]$ (analogue to a substrate potential) describes the time-dependant parametric force corresponding to the external pressure $P_{ac}(t)$ applied to the bubble. This term is produce by the time-dependant gravity force in the macroscopic spherical pendulum chain. The parameter ω_0 represents the linear spherical mode of the system (lowest frequency in the dispersion curve), η the amplitude of the parametric excitation which is identified to the amplitude of $P_{ac}(t)$, and ω_{ext} is the angular frequency of the parametric excitation.

This model has been simulated numerically, and a experimental setup has been designed to confirm the predictions. As shown in the Fig.IV, the $N = 8$ mode (top) and a localized mode (bottom) are observed numerically.

IV. Conclusion and Perspectives

We propose to analyze UCA spherical modes in complete analogy with the properties of parametric instability of a linear chain of coupled pendula, with nonlinear coupling and periodic properties. The possibility to evaluated the optimized ultrasonic excitations of UCA for sonoporation applications is underlined through the study, in complete analogy, of optimized mechanical excitations of macroscopic mechanical experiments in the laboratory. The perspective is to complete the Symmetry Analysis [10], [14]–[16] method where all variables are studied thanks to a transformation by using the group G a one parameter a

$$G : \bar{S} = C^S(a)S + K^S(a), \tag{11}$$

where S denotes physical variables used in both nonlinear models of the bubble and the mechanical chain. The perspective of this analysis is to define practical optimized ultrasound pulses exciting the bubble and leading to drug delivery applications. It is also planned to establish conditions under which the surface modes developing in the bubble shell near a boundary (blood vessel wall) become unstable, causing the disruption of the shell and the escape of the internal gas, for sonoporation applications.

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