Localized nonlinear modes in microbubbles under the action of ultrasound

Serge Dos Santos, *Senior Member, IEEE*
INSA Centre Val de Loire, COMUE Léonard de Vinci
U930 "Imaging and Brain" Inserm-University Francois-Rabelais
3, rue de la Chocolaterie, CS 23410, F-41034 Blois Cedex, France.
Email: serge.dossantos@insa-cvl.fr

Noé Jiménez
LUNAM Universite, Universite du Maine, CNRS,
LAUM UMR 6613, Av. O. Messiaen,
72085 Le Mans, France.
Email: noe.jimenez@univ-lemans.fr

Víctor Sánchez-Morcillo
Instituto de Investigacion para la Gestion Integrada de Zonas Costeras,
Universitat Politecnica de Valencia, Paranimf 1, 46730 Grao de Gandia, Spain
Email: victorsm@upv.es

***Abstract*—Under specific ultrasound excitation, contrast microbubbles undergo nonlinear oscillations. Considering the size and the complexity of the phenomenon, expensive and complex experiments and/or simulations are required. To overcome this, the use of an analogy has been proposed and validated. A chain of coupled oscillators has been optimized in order to re-scale the bubble ultrasonic oscillation at the macroscopic scale. The parametric oscillation (characteristic of the driving) responsible of the surface mode oscillations exhibit mode mixing behavior including intrinsic localized modes (ILM) that emerge when the frequency of the driving is slightly below the edges of the dispersion curves. This result suggests some optimized ultrasonic excitation in order to exhibit local acoustic response of ultrasound contrast agents (UCA) used for sonoporation. Under parametric excitation, this analogy correctly describes the surface modes of the bubble as a consequence of shape instability.**

I. Introduction

The study of analog models in the field of nonlinear physics is a tool that allows recreating in the laboratory phenomena that are difficult to observe directly [1]–[3]. Concerning microbubbles and Ultrasound Contrast Agent (UCA), some of its dynamic features (vibration modes, subharmonic oscillations, chaos) can be captured by a system of coupled oscillators [4]–[10]. Here, the oscillatory behavior of a microbubble and its vibration modes are investigated through the use of a macroscopic analogy [11]–[13] consisting of a chain of coupled pendula, parametrically excited by a vertical force. Based on a discrete nonlinear model of coupled pendula and its continuous limit describing low frequency excitations, vibration modes are investigated theoretically and experimentally. This approach is used here to set up a formal basis for the acousto-mechanical analogy of a gas microbubble and UCA. Using the analogies evidenced by the symmetry analysis [1], 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 established. 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.



Fig. 1. Macroscopic mechanical analogu of a microbubble (Courtesy of Jennifer Chaline [14])

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 [15]–[18]. 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 [19].

978-1-4673-9897-8/16/$31.00 ©2016 IEEE

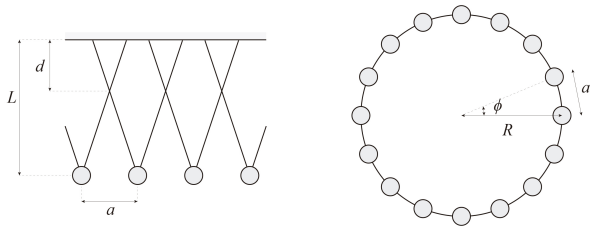


Fig. 2. Scheme of the coupled nonlinear oscillator chain in a ring configuration.

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.

II. Statement of the contribution/Methods

We study the localized modes on the surface of a microbubble. We present an experimental and numerical study of spatiotemporal dynamics in a parametrically driven system presenting a curved geometry. The system is a ring-shaped chain of coupled oscillators subjected to a vertical harmonic acceleration. The theoretical model is the well-known Frenkel-Kontorova lattice [20] (a discrete version of the sine-Gordon equation) with damping and parametric driving.

Thus, we consider a chain of $N = 50$ coupled nonlinear oscillators [21] that are configured in the form of a circular ring, connecting first and last masses. The chain forms a periodic boundary condition lattice as shown in Fig. 2. The coupling of the pendulums is implemented by a nodal junction, which height d governs the coupling factor of the chain. Thus, considering a pendulum lattice formed by equal masses linearly coupled to their nearest neighbors, and neglecting curvature effects, the motion on the n-th pendulum obeys the parametrically-driven damped Frenkel-Kontorova equation:

$$\begin{aligned}\frac{\partial^2\theta_n}{\partial t^2} &= -\gamma\frac{\partial\theta_n}{\partial t} - \left(\omega_0^2 + A\cos\left(2\omega t\right)\right)\sin\theta_n \\ &\quad +\kappa\left(\theta_{n-1} - 2\theta_n + \theta_{n+1}\right), \end{aligned} \tag{1}$$

where θ_n is the angle of the n-th pendulum with the normal, γ is the damping coefficient, $\omega_0 = \sqrt{g/L}$ is the natural frequency of the uncoupled pendulum, g is the acceleration due to Earth's gravity, L is the pendulum length, κ is the coupling constant related on the height d of the junction, and A and ω are the amplitude and the frequency of the parametric excitation. After linearization, the dispersion relation of the parametrically-excited pendulum chain can be expressed as

$$\left(\frac{\omega_n}{\omega_0}\right)^2 = \frac{1}{1-\eta}\left(1 - \eta\cos^2\left(\frac{\pi}{2}\frac{m}{N}\right)\right), \tag{2}$$

where $\eta = d/L \in [0, 1]$ measures the strength of the coupling and m is the mode index number and N the number of pendulums. This surface mode can be analytically described as a linear composition of spherical harmonics [22] and [23]. Thus, dispersion relation is bounded by the lower cutoff frequency $\omega_l = \sqrt{g/L}$ and upper cutoff frequency $\omega_u = \sqrt{g/(L-d)}$ which corresponds to the natural frequency of pendulum oscillating either from the rigid support or from the knot. In order to obtain a solution of the coupled pendulum motion equation, finite differences are applied to partial differential operators of Eq. 1.

In addition, experiments were improved considering previous work. A new chain was built by using a set of $N = 50$ pendulums of $L = 103$ mm length, and a mass of 5 g disposed around a ring of $R = 330$ mm radius. The distance between pendulums was $a = 50$ mm and the junction, according to Fig. 2, was done by a knot at $d = 30$ mm. Thus, the natural frequency of pendulum oscillating from the rigid support was $f_l = 3.1$ Hz (lower cutoff mode), and the natural frequency of pendulum oscillating from the knot was $f_u = 3.69$ Hz (upper cutoff mode). Assuming classical values for bubble's physical parameters, one have the approximate condition $f_0[MHz]R_0[\mu m] \simeq 1$.. For the new chain, similar property can be written $f_0[Hz]R_0[m] \simeq 1$ and explain the typical sizes chosen for this macroscopic experiment (Table I) with the $N = 50$ coupled pendulum array [11].

The parametric excitation was exerted by a vertical displacement by means of a 18" audio sub-woofer driven by a harmonic low frequency signal. The low frequency signal was generated by a arbitrary function generator, amplified by a 50 Watts audio amplifier and then connected to the 8 ohms input of the loudspeaker. The sub-woofer was facing up on a rigid table and the pendulum ring lies directly on the diaphragm cone of the loudspeaker. The oscillation patterns of the ring were recorded by means of video camera placed on the top of the system using images of 720/480 pixels at 240 frames per second. The position of the pendula was tracked and the time dependent displacement was estimated. The initial excitation of the chain was exerted manually by moving one of the pendulum, that implies a high bandwidth excitation as initial condition of the chain.

III. Results

A. Mode mixing

The ring of pendula show a variety of oscillation patterns in both, simulation and experiments. Surface modes with

TABLE I
Table of analogies between parameters of microbubble and those of the pendula ring [11].

Parameter	Microbubble	Pendula ring
R_0 [m]	$\simeq 10^{-6}$	$\simeq 0.3$
f_e [Hz]	$\simeq 10^6$	$\simeq 3$
$f_e \cdot R_0$	1	1
ω_n^2	$(n-1)(n+1)(n+2)\frac{\sigma}{\rho R_0^3}$	$\frac{g}{L} + n^2\frac{c}{R_0^2}$
f_p	$\frac{(2n+1)}{2}\omega_e^2\left(\frac{R_\varepsilon}{R_0}\right)$	$4\omega_e^2\left(\frac{A}{L}\right)$

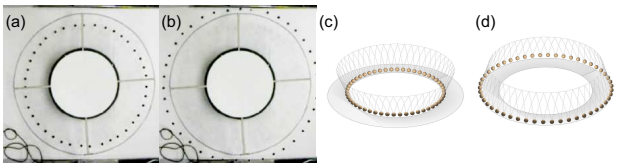


Fig. 3. (a-b) Experimental and (c-d) numerical observation of the radial mode in the ring of coupled pendula for $f = 2f_0$

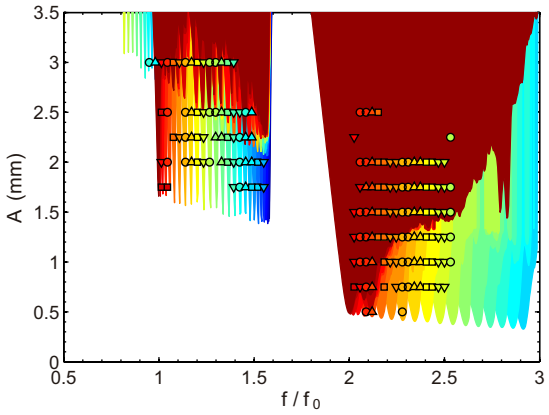


Fig. 4. Oscillation modes as a function of parametric frequency and the excitation amplitude for (markers) experiments and (surfaces) simulations. Each color represent one different spatial mode.

mode mixing for parametric excitation frequencies within the pass-band of the dispersion relation, the intrinsic localized modes for frequencies just below the low cut-off frequency. First, as it was recently published [13], the ring of coupled pendula under parametric forcing develop surface modes that for small excitation amplitudes follow the dispersion relation given by Eq.2, in analogy with the surface modes developed by microbubles [24], [25]. At frequencies around $2f_0$, the radial mode is observed as shown in Fig. 3, in analogy with the well-known radial mode of microbubbles under the action of ultrasound [26]. Figure 4 shows the experimental and numerical modes as a function of parametric frequency and the excitation amplitude. It is interesting to show that for high amplitudes mode mixing appear. The oscillation pattern for a fixed excitation frequency is not a chromatic spatial harmonic. Instead, shape instability leads to a more complicated pattern that, first, its main resonant frequency is shifted down from the dispersion relation (a typical signature of softening nonlinearity) and, second, the pattern is composed by a spectra of spatial modes. If extended to the behavior of UCAs under complex ultrasonic excitations, it gives the potential of studying optimized ultrasonic radiations of UCA for specific medical applications.

B. Intrinsic Localized Modes

Of special interest are the dynamical features for excitation frequencies just below $2f_0$. In this regime, localized modes can be easily observed in experiments and numerical results. Figure 5 shows an example of a localized surface mode, an intrinsic localized mode (ILM), that emerge when the frequency of the parametric driving is slightly below the edges of the dispersion relation. These ILMs are similar to those found in other more generic systems of nonlinearly vibratory lattices. The observation of ILM in 1D chain of coupled oscillators [27], [28], 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. The position of the ring has been captured in two different times (Fig.5(a,b)), where Fig.5(c) shows the superposition of such frames. It can be observed haw the energy became spatially trapped in the ring in this non-propagating soliton, while the oscillators in the opposite side of the chain are almost at rest. This behavior is highly needed for sonoporation applications where a local drug delivery process is fundamental for targeted therapy. The dynamics of the ILM present a rich amplitude-dependent dynamical features: the ILM time period exhibits a regular cycle of period three. As expected, at higher driving amplitudes the ILM also display regular cycles of every other length and chaotic behavior. This leads to the localized modes to disaggregate, strongly perturbing the rest of the surface of the bubble.

IV. Discussion and Conclusion

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. A simple dynamical model of a single microbubbles under the action of ultrasound is presented. The analogue model is based of a ring of coupled nonlinear oscillators which describes pragmatically the main behavior at another mechanical scale. On the basis of the proposed analogy, the oscillation patterns and localized modes observed experimentally in acoustically driven bubbles are interpreted, discussed and commented within the context of sonoporation applications. First, the results of modal behavior are in agreement with simulations and are similar to those obtained from gas microbubbles. Second, we demonstrate experimentally and numerically the existence of intrinsic localized modes (ILM). The analogy between the macroscopic behavior of the pendula ring and the microscopic behavior of a microbubble presented here is valid in the low frequency regime, where the chain of oscillators can be considered as a quasi-continuum. Is in this regime where ILMs emerge, so one can thus expect to observe these oscillatory behaviors in real microbubbles. 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 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.

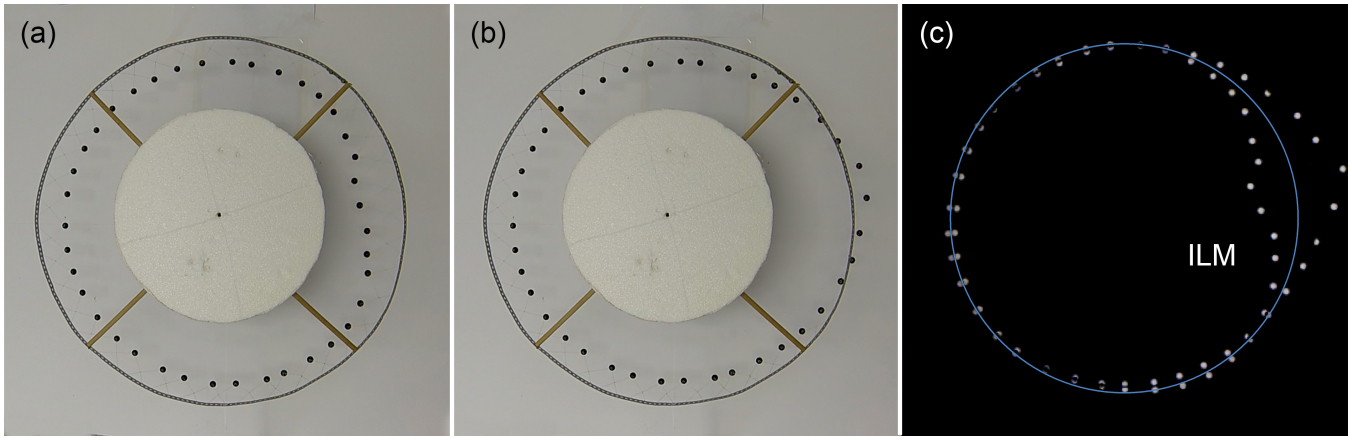


Fig. 5. Localized surface mode for $f = 0.98(2f_0)$ at different times (a,b), (c) shows the superposition of both frames. Energy is spatially localized inducing various possibilities for sonoporation applications.

REFERENCES

[1] S. Dos Santos, V. Sánchez-Morcillo, N. Jiménez, J. Chaline, and A. Bouakaz, "Modulational instability and localized modes for ultrasound contrast microbubbles surface oscillations," in *International Ultrasonics Symposium (IUS), 2011 IEEE International*. IEEE, 2011, pp. 648–651.

[2] V. Sánchez-Morcillo, N. Jiménez, J. Chaline, A. Bouakaz, and S. Dos Santos, "Spatio-temporal dynamics in a ring of coupled pendula: analogy with bubbles," in *Localized Excitations in Nonlinear Complex Systems*. Springer, 2014, pp. 251–262.

[3] R. H. Goodman, A. Rahman, M. J. Bellanich, and C. N. Morrison, "A mechanical analog of the two-bounce resonance of solitary waves: Modeling and experiment," *Chaos*, vol. 25, no. 4, 2015.

[4] T. Gross, D. Hennig, and L. Schimansky-Geier, "Modulational instability and resonant wave modes act on the metastability of oscillator chains," *Physical Review E*, vol. 90, no. 3, p. 032919, 2014.

[5] C. Desjouy, P. Labelle, B. Gilles, J.-C. Bera, and C. Inserra, "Acoustic bubble behavior in a standing wave field," *The Journal of the Acoustical Society of America*, vol. 133, no. 5, pp. 3277–3277, 2013. [Online]. Available: http://scitation.aip.org/content/asa/journal/jasa/133/5/10.1121/1.4805338

[6] S. Zhang, Z. Cui, T. Xu, P. Liu, D. Li, S. Shang, R. Xu, Y. Zong, G. Niu, S. Wang, X. He, and M. Wan, "Inverse effects of flowing phase-shift nanodroplets and lipid-shelled microbubbles on subsequent cavitation during focused ultrasound exposures," *Ultrasonics Sonochemistry*, vol. 34, pp. 400 – 409, 2017.

[7] Y. Gu, C. Chen, J. Tu, X. Guo, H. Wu, and D. Zhang, "Harmonic responses and cavitation activity of encapsulated microbubbles coupled with magnetic nanoparticles," *Ultrasonics Sonochemistry*, vol. 29, pp. 309 – 316, 2016. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S1350417715300493

[8] C. Chen, Y. Gu, J. Tu, X. Guo, and D. Zhang, "Microbubble oscillating in a microvessel filled with viscous fluid: A finite element modeling study," *Ultrasonics*, vol. 66, pp. 54 – 64, 2016.

[9] Y. B. Gaididei, J. F. R. Archilla, V. J. Sánchez-Morcillo, and C. Gorria, "Energy localization and shape transformations in semiflexible polymer rings," *Phys. Rev. E*, vol. 93, p. 062227, 2016.

[10] N. V. Alexeeva, I. V. Barashenkov, and G. P. Tsironis, "Impurity-induced stabilization of solitons in arrays of parametrically driven nonlinear oscillators," *Phys. Rev. Lett.*, vol. 84, pp. 3053–3056, 2000.

[11] J. Chaline, A. Bouakaz, J.-M. Escoffre, V. Sánchez-Morcilló, N. Jiménez, and S. Dos Santos, "Lattice of nonlinear coupled oscillators: An acousto-mechanical analogy of gas microbubble," in *2014 IEEE International Ultrasonics Symposium*. IEEE, 2014, pp. 2277–2279.

[12] V. J. Sánchez-Morcillo, N. Jiménez, N. González, S. Dos Santos, A. Bouakaz, and J. Chaline, "Modeling acoustically driven microbubbles by macroscopic discrete-mechanical analogues," *Modelling in Science Education and Learning*, vol. 6, pp. 75–87, 2013.

[13] J. Chaline, N. Jimnez, A. Mehrem, A. Bouakaz, S. D. Santos, and V. J. Snchez-Morcillo, "Macroscopic acousto-mechanical analogy of a microbubble," *The Journal of the Acoustical Society of America*, vol. 138, no. 6, pp. 3600–3606, 2015. [Online]. Available: http://scitation.aip.org/content/asa/journal/jasa/138/6/10.1121/1.4936949

[14] J. Chaline, "Macroscopic and acousto-mechanic analogy of gas microbubble:," PhD Thesis, Université François-Rabelais de Tours, 2015. [Online]. Available: https://tel.archives-ouvertes.fr/tel-01256967

[15] C.-T. Hsiao, X. Lu, and G. Chahine, "Three-dimensional modeling of the dynamics of therapeutic ultrasound contrast agents," *Ultrasound in Medicine & Biology*, vol. 36, no. 12, pp. 2065 – 2079, 2010.

[16] S.-H. Hung, C.-K. Yeh, T.-H. Tsai, T. Chen, and R.-C. Chen, "A simple method for quantifying ultrasound-triggered microbubble destruction," *Ultrasound in Medicine & Biology*, vol. 37, no. 6, pp. 949 – 957, 2011.

[17] F. Yan, X. Li, Q. Jin, C. Jiang, Z. Zhang, T. Ling, B. Qiu, and H. Zheng, "Therapeutic ultrasonic microbubbles carrying paclitaxel and lyp-1 peptide: Preparation, characterization and application to ultrasound-assisted chemotherapy in breast cancer cells," *Ultrasound in Medicine & Biology*, vol. 37, no. 5, pp. 768 – 779, 2011.

[18] N. McDannold, N. Vykhodtseva, and K. Hynynen, "Blood-brain barrier disruption induced by focused ultrasound and circulating preformed microbubbles appears to be characterized by the mechanical index," *Ultrasound in Medicine & Biology*, vol. 34, no. 5, pp. 834 – 840, 2008.

[19] A. A. Doinikov and A. Bouakaz, "Acoustic microstreaming around a gas bubble," *J Acoust Soc Am*, vol. 127, no. 2, p. 703, 2010.

[20] O. M. Braun and Y. S. Kivshar, *The Frenkel-Kontorova model: concepts, methods, and applications*, Springer-Verlag, Ed. Springer, 2004.

[21] B. Denardo, B. Galvin, A. Greenfield, A. Larraza, S. Putterman, and W. Wright, "Observations of localized structures in nonlinear lattices: Domain walls and kinks," *Physical review letters*, vol. 68, no. 11, p. 1730, 1992.

[22] U. H. Augsdörfer, A. K. Evans, and D. P. Oxley, "Thermal noise and the stability of single sonoluminescing bubbles," *Physical Review*, vol. 61, pp. 5278–5286, May 2000.

[23] R. Nabergoj and A. Francescutto, "On thresholds for surface waves on resonant bubbles," *Journal de Physique*, vol. 40, pp. 306–309, 1979.

[24] X. Guo, Q. Li, Z. Zhang, D. Zhang, and J. Tu, "Investigation on the inertial cavitation threshold and shell properties of commercialized ultrasound contrast agent microbubbles," *The Journal of the Acoustical Society of America*, vol. 134, no. 2, pp. 1622–1631, 2013.

[25] X. Xi, F. Cegla, R. Mettin, F. Holsteyns, and A. Lippert, "Study of non-spherical bubble oscillations near a surface in a weak acoustic standing wave field," *The Journal of the Acoustical Society of America*, vol. 135, no. 4, pp. 1731–1741, 2014.

[26] T. Leighton, *The acoustic bubble*. London: Academic Press, 2012.

[27] E. Kenig, B. A. Malomed, M. C. Cross, and R. Lifshitz, "Intrinsic localized modes in parametrically driven arrays of nonlinear resonators," *Phys. Rev. E*, vol. 80, p. 046202, Oct 2009.

[28] A. J. Sievers and S. Takeno, "Intrinsic localized modes in anharmonic crystals," *Phys. Rev. Lett.*, vol. 61, pp. 970–973, Aug 1988.