

Numerical study on a polymer-shelled microbubble submerged in soft tissue

F Ghalichi¹, S Behnia^{2,4}, F Mottaghi¹ and M Yahyavi^{3,4} 

¹Department of Biomedical Engineering Division of Biomechanics, Sahand University of Technology, Sahand New Town, Tabriz, Iran

²Department of Physics, Urmia University of Technology, Urmia, Iran

³Department of Physics, Bilkent University 06800, Ankara, Turkey

E-mail: s.behnia@sci.uut.ac.ir and yahyavi.mohamad@gmail.com

Received 21 April 2020, revised 20 June 2020

Accepted for publication 29 June 2020

Published 7 July 2020



Abstract

Ultrasound contrast agents have been recently utilized in therapeutical implementations for targeted delivery of pharmaceutical substances. Radial pulsations of the encapsulated microbubbles under the action of an ultrasound field are complex and high nonlinear, particularly for drug and gene delivery applications with high acoustic pressure amplitudes. The dynamics of a polymer-shelled agent are studied through applying the method of chaos physics whereas the effects of the outer medium compressibility and the shell were considered. The stability of the ultrasound contrast agent is examined by plotting the bifurcation diagrams, Lyapunov exponent, and time series over a wide range of variations of influential parameters. The findings of the study indicate that by tuning the shear modulus of surrounding medium and shell viscosity, the radial oscillations of microbubble cluster undergoes a chaotic unstable region as the amplitude and frequency of ultrasonic pulse are increased mainly due to the period doubling phenomenon. Furthermore, influences of various parameters which present a comprehensive view of the radial oscillations of the microbubble are quantitatively discussed with clear descriptions of the stable and unstable regions of the microbubble oscillations for typical therapeutic ultrasound pulses.

Keywords: bubble dynamics, chaos theory, nonlinear dynamics

(Some figures may appear in colour only in the online journal)

1. Introduction

Ultrasound contrast agents (UCAs) are coated microbubbles by a stabilizing layer such as albumin, polymer or lipids which are usually formed with a high-molecular-weight gas [1–3]. These agents are originally designed for diagnostic ultrasound imaging (for liver imaging, cardiac and other organs) since they are highly detectable with ultrasound imaging due to their great scattering properties, hence this acoustic trait caused to the progression of more sensitive imaging methods [4, 5]. Recently, in addition to diagnostic implementations, their employment in the biomedical field is translating to therapeutic applications [6] such as drug and gene delivery [7, 8], sonothrombolysis [9], opening of the blood-brain barrier and drug delivery to the CNS [10–12].

Indeed, they are employed as transporters of pharmaceutical agents to carry them into the site of interest to deliver their cargo just where it is needed by applying a focused ultrasound field [8, 13–15]. This novel method has emerged immense clinical potentials such as minimizing drug-related toxicity to the healthy cells and tissues, drug dosage modifications, promoting transmembrane and extravascular drug transport, preventing drug-drug interactions, decreasing costs for the patient, additionally, transference and release can be visualized with real-time ultrasound and as a whole result treatment efficacy will be enhanced [16–18].

UCAs undergo complex dynamic behaviors while they are exposed to an ultrasound field [19]. Depending on the applied acoustic amplitudes, the microbubble structure and the properties of the host media, they will respond linear or nonlinear pulsations [20–22]. Several investigations also demonstrated that a microbubble and microbubble cluster

⁴ Authors to whom any correspondence should be addressed.

behavior in ultrasonic fields [23–25]. Fundamental perception of UCAs dynamics and precisely predicting their behavior will promote their diagnostic and therapeutic capabilities; indeed a quantitative understanding of UCAs dynamics is a necessary step to attain a better hardware design and successful clinical applications. Many sophisticated theoretical treatments for describing the coated microbubble response in an ultrasound field have been performed whereas most of the presented models are on the foundation of the Rayleigh-Plesset (RP) equation form. De Jong and co-workers [26, 27] introduced the first theoretical model that considers the encapsulation as a viscoelastic solid shell, as well as a damping coefficient term, is added to the RP equation. Church [28] presented a more accurate model by considering the shell thickness to describe the effects of the shell on UCA behavior. Morgan (see also Zheng) [29, 30] and Allen [31] offered their models for thin and thick encapsulated microbubbles, respectively. Another rigorous model which treats the outer medium as a slightly compressible viscoelastic liquid is due to Khismatullin and Nadim [32]. Chatterjee and Sarkar [33] attempted to take account of the interfacial tension at the microbubble interface with infinite small shell thickness. Sarkar [34] improved this model to contain the surface elasticity by using a viscoelastic model. Stride and Saffari [35] demonstrated the presence of blood cells and the adhesion of them to the shell have a negligible effect. Tamadapu and coworkers [36, 37] investigated an air-filled thick polymer encapsulated nonspherical microbubble suspended in bulk volume of water. Marmottant [38] exhibited a simple model for the dynamics of phospholipid-shelled microbubbles while taking account of a buckling surface radius, shell compressibility, and a break-up shell tension. Doinikov and Dayton [39] refined the church model and also considered the translational motion of the UCA. Shengping Qin and Katherine W. Ferrara [40] have presented a model to explain the radial oscillations of UCAs by considering the effects of liquid compressibility, the surrounding tissue, and the shell. Although the aforementioned discussion expressed that considerable efforts have been performed, nonlinear dynamics of encapsulated microbubble by considering variations in different effective parameters is not fully realized by any means [41, 42] and require supplemental developments. The nonlinear nature of the equation needs specialized tools for analyzing because linear and analytical solutions are inadequate. Lauterborn and his colleagues [43–45] have made great contributions by introducing the method of chaos physics to a model of a driven spherical gas bubble in water to determine its dynamic properties, especially its resonance behavior and bifurcation structure. Also, based on the previous works, the chaotic behavior of free bubbles observed both theoretically and experimentally [46–50], but this is not investigated for the case of UCAs, and it will be helpful to survey from this point of view because the method of chaos physics provides extensive knowledge about rich nonlinear dynamical systems. Moreover, neglecting liquid compressibility is not suitable for high-pressure amplitudes where the wall velocity of the agent is equal to the speed of sound in liquid [31], so the effects of

liquid compressibility on the microbubble dynamics should be considered [40, 41].

In this paper, the effects of substantial parameters that influence the UCA dynamics are studied in a large domain applying method of chaos physics [43–45] and considering the compressibility of the outer medium and the shell. It will represent comprehensive information about extremely nonlinear pulsations of UCAs, particularly for drug and gene delivery applications.

2. Mathematical model: dynamics of a coated spherical microbubble

The theoretical description of radial motion for a spherical encapsulated microbubble submerged in blood or tissue has been derived by Qin and Ferrara [40] which is utilized for numerical simulation. This justified equation also explains the effects of variations of the shell and the surrounding tissue on the UCA behavior and is given by:

$$\begin{aligned} & \left[\rho_L \left(1 - \frac{\dot{R}_2}{c} \right) + \rho_S \left(1 + \frac{\dot{R}_2}{c} \right) \left(\frac{R_2}{R_1} - 1 \right) \right] R_2 \ddot{R}_2 \\ & + \left\{ \frac{3}{2} \rho_L \left(1 - \frac{1}{3} \frac{\dot{R}_2}{c} \right) \right. \\ & + \left. \rho_S \left(1 + \frac{\dot{R}_2}{c} \right) \left[-\frac{3}{2} + 2 \left(\frac{R_2}{R_1} \right) - \frac{1}{2} \left(\frac{R_2}{R_1} \right)^4 \right] \right\} \dot{R}_2^2 \\ & = \left(1 + \frac{\dot{R}_2}{c} \right) \left\{ p_g(t) - \frac{2\sigma_1}{R_1} \right. \\ & - \frac{2\sigma_2}{R_2} - \frac{4}{3} G_S \left[1 - \left(\frac{R_{20}}{R_2} \right)^3 \right] \frac{R_S}{R_2^3 - R_S} \\ & - 4\mu_S \frac{R_S}{R_2^3 - R_S} \frac{\dot{R}_2}{R_2} - \frac{4}{3} G_L \left[1 - \left(\frac{R_{20}}{R_2} \right)^3 \right] \\ & \left. - 4\mu_L \frac{\dot{R}_2}{R_2} - p_0 - p_i(t) \right\} - 3\gamma \frac{\dot{R}_2}{c} \left(\frac{R_2}{R_{10}} \right)^3 \frac{p_g(t)}{\left(\frac{R_1}{R_{10}} \right)^3 - \frac{b}{V_m}}. \quad (1) \end{aligned}$$

where $p_i(t) = P_a \sin(2\pi ft)$ is the ultrasound pressure at infinity. Also, the pressure-volume relation, p_g , is defined as follows

$$p_g(t) = \left(p_0 + \frac{2\sigma_1}{R_{10}} + \frac{2\sigma_2}{R_{20}} \right) \left[\frac{1}{\left(\frac{R_1}{R_{10}} \right)^3 - \frac{b}{V_m}} \right]^\gamma \quad (2)$$

The equation (1) is applied to describe nonlinear oscillations of a polymer-shelled agent versus variations of several important parameters. This model was developed to describe the dynamics of UCAs *in vivo* while taking account of the effects of the surrounding tissue, the shell tissue, and liquid compressibility. In the literature, the correction term for compressibility has different forms for different considerations. In this work, we choose the form $(R/c)(dp_g(t)/dt)$ as in [51]. Since the time derivative of the driving pressure

Table 1. Physical constants parameters for polymer-shelled agent [22, 35].

Symbol	Parameter	Value	Unit
ρ_S	Shell density	1150	$\frac{kg}{m^3}$
ρ_L	Liquid density	1060	$\frac{kg}{m^3}$
μ_L	Liquid viscosity	0.015	Pa s
σ_1	Surface tension at inner radius	0.04	$N m^{-1}$
σ_2	Surface tension at outer radius	0.056	$N m^{-1}$
R_{10}	Equilibrium inner radius of agent	2.3750	μm [40]
R_{20}	Equilibrium outer radius of agent	2.5	μm [40]
p_0	Hydrostatic pressure	1.01	$\times 10^5$ Pa
c	Sound speed in liquid	1540	$\frac{m}{s}$
b	Van der Waals constant	0.1727	$\frac{J}{mol}$
V_m	Universal molar volume	22.4	$\frac{mol}{mol}$
γ	Polytropic gas exponent	1.4	

Table 2. Physical varied parameters for polymer-shelled agent [22, 35].

Parameter	Range of value	Unit
Driving pressure	$0 < P_a < 2$	MPa
Driving frequency	$0.5 < f < 5$	MHz
Shear modulus of surrounding medium	$0 < G_L < 1.5$	MPa
Shell viscosity	$0 < \mu_s < 5$	Pa s
Shear modulus of shell	$0 < G_S < 200$	MPa
Shell thickness	$0 < R_S < 0.15$	μm

$(dp_g(t)/dt)$ is small and not dominant for violent oscillation. The assumption used in this paper is that the shell thickness is finite and the shell material behaves as a Voigt viscoelastic solid. The Qin-Ferrara is similar to the Church model [28], but, the Church shell elastic term is valid only for small deformation since in the Qin-Ferrara's model, the shell elastic term is stated to be valid for finite deformation of the shell.

2.1. Variables and its domain

The evolution of microbubble dynamics corresponds to the different parameter, which should be explained separately. As the inner and outer radius of the agent is described with R_1 and R_2 , then \dot{R}_1 and \dot{R}_2 are the inner and outer wall velocity of the agent, respectively. \ddot{R}_2 is the outer wall acceleration of the agent. Naturally, R_{10} and R_{20} used as initial outer and inner radius of bubbles. Also, $R_S = R_{20}^3 - R_{10}^3$ and ρ_L is the density of the liquid and ρ_S is the Shell density. c is the speed of sound in the liquid. σ_1 is the inner surface tension, σ_2 is the outer surface tension, p_g is the gas pressure within the agent. G_S is the shear modulus, G_L is the shear modulus of the surrounding medium which represent the stiffness of the surrounding tissue. μ_L is the viscosity of the liquid, μ_s is shell viscosity. Finally, f is the ultrasound center frequency, b is the van der Waals constant, V_m is the universal molar volume, p_0 is the hydrostatic pressure. The introduced constants and varied parameter values for polymer-shelled agent are summarized in tables 1 and 2 [22, 35]. Actually, in this paper, all

physical parameters were kept constant at values given in table 1. This model assumes a single microbubble dispersed within an infinite medium, with no boundary conditions, no bubble-bubble interactions, no flow. Furthermore, bubble-bubble interactions, primary and secondary Bjerknes forces, clustering, coalescence, and generally ultrasound-propelled motions are ignored. Most importantly, bubble destruction, gas diffusion in every acoustic cycle, polymer shedding, and other shell-modifying phenomena are not taken into account here.

3. Results

For a better visualization of the evolution of the effect of acoustic pressure alterations on microbubble dynamics, radial motion of a UCA is investigated versus a prominent domain of acoustic pressure from 10 kPa to 2 MPa. Figures 1(a)–(f) show the bifurcation diagrams and Lyapunov exponent (λ) [48, 52, 53] of the normalized microbubble radius against acoustic pressure as the control parameter for several values of applied frequency of the ultrasound field which they are 0.6, 1, 1.5, 1.8, 2.2 and 2.8 MHz, respectively. In each one stable and chaotic pulsations can be observed, regarding the sign of the corresponding Lyapunov exponent. The existence of the negative or positive Lyapunov exponent indicates the non-chaotic or chaotic behavior. It is perceived that by raising pressure the microbubble stability is reduced and chaotic oscillations will be evident which this trend can be confirmed by other works [38, 53, 54]. Regarding figures 1(a)–(f), the microbubble experiences distinctive behaviors in different frequency while the control parameter (acoustic pressure) is increasing. As it is followed in figures 1(a)–(f), by increasing the center frequency the microbubble stability is enlarged in superior driving pressures which is in a good agreement with the work of [55]. This is obvious in figure 1(f), where the accessibility to the stable range concerning variations of pressure has the maximum extent.

According to figure 1(d), the radial motion of the microbubble in frequency 1.8 MHz manifests stable behavior of period one till 352 kPa which is followed by a period doubling up to 615 kPa, after that the system demonstrates a period four for a small interval and it is pursued by the first chaotic window in 680 kPa ($\lambda > 0$). Then the microbubble exhibits its periodic behavior again before the next jump to chaos in 867 kPa. These intermittent transitions between chaotic oscillations and stable behavior persist until 1.3 MPa, afterward, the system turns into severely chaotic oscillations which continues to the termination of pressure interval, i.e., 2 MPa. This behavior is also observed experimentally in [56]. The microbubble experience more stability in a broad domain of driving pressure and chaotic pulsations and the expansion ratio of the UCA is reduced while the applied frequency is higher (see figure 1(f)).

Also for studying the effect of frequency alterations on microbubble dynamics, the dynamical behavior of UCA is inspected by considering the ultrasound frequency as the control parameter which varies from 600 kHz to 5 MHz, the

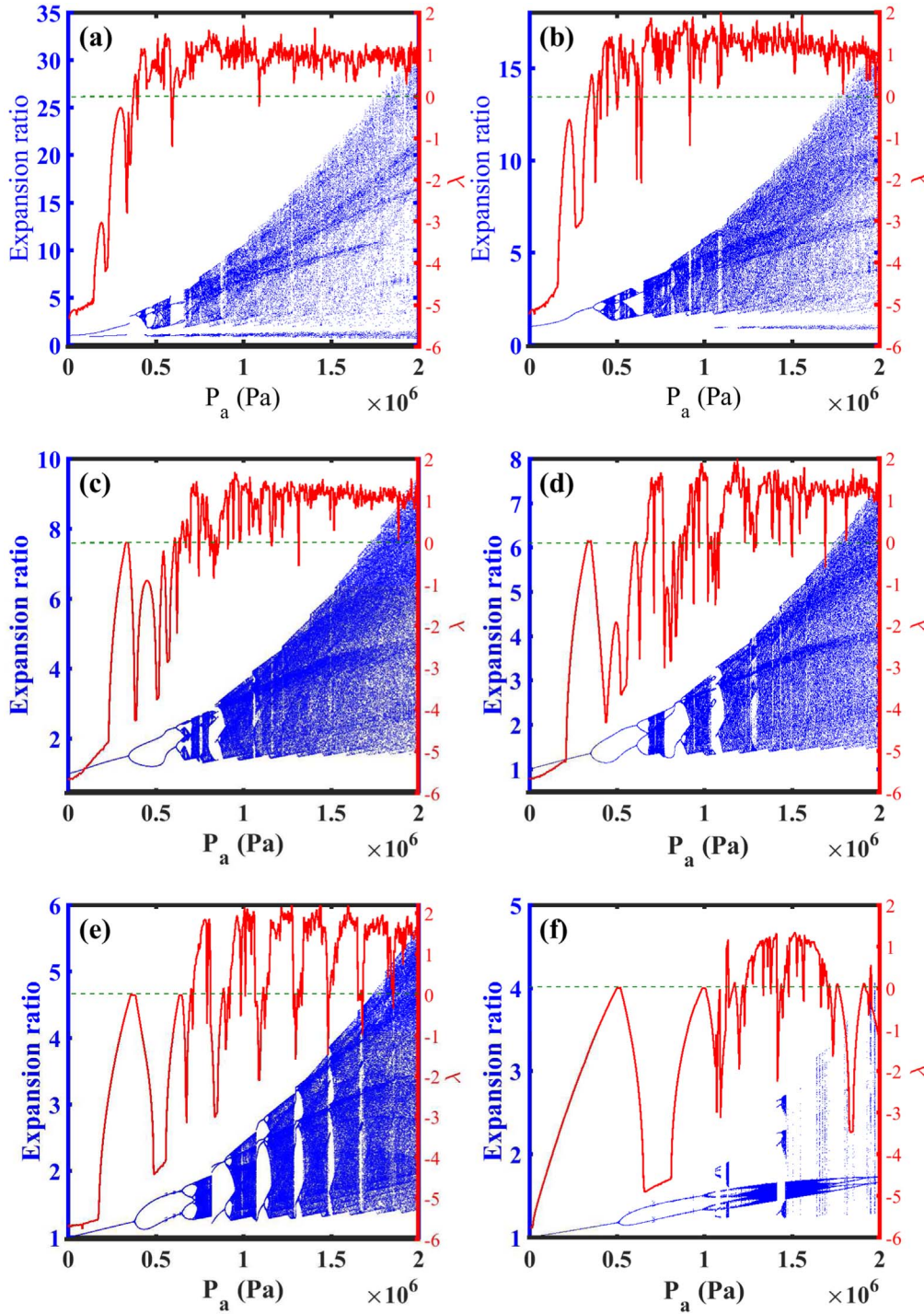


Figure 1. Bifurcation diagrams (Expansion ratio-blue dot points) and Lyapunov exponent (λ -red solid line) of normalized microbubble radius versus driving pressure within blood ($G_L = 0$ MPa) with $\mu_s = 0.45$ Pa s, and $G_S = 11.7$ MPa while the frequency is (a) 0.6 MHz, (b) 1 MHz, (c) 1.5 MHz, (d) 1.8 MHz, (e) 2.2 MHz and (f) 2.8 MHz. All other physical parameters were kept constant at values given in table 1.

corresponding bifurcation diagrams and Lyapunov exponent of the normalized microbubble radius is shown in figure 2(a)–(f) for the applied pressure values of 0.3, 0.5, 0.9, 1.2, 1.7, 2.2 MPa, respectively.

The stable behavior of microbubble is presented for the low amplitude of pressure ($\lambda < 0$), i.e., 0.3 MPa (figure 2(a)). The chaotic behavior ($\lambda > 0$) of UCA appears by increasing the values of applied pressure (figure 2(b)), and the

microbubble shows more chaotic oscillations as the pressure is intensifying (figures 2(b)–(f)) which this phenomenon is seen in [21, 57]. It is seen in all figures 2(a)–(f) that, the magnitude of pulsations reduces significantly and the chaotic region becomes smaller when the control parameter (frequency) is increasing, and the UCA shows the stable behavior of period one which reveals the stabilizing property of superior frequencies which is confirmed in [31]. It is seen in

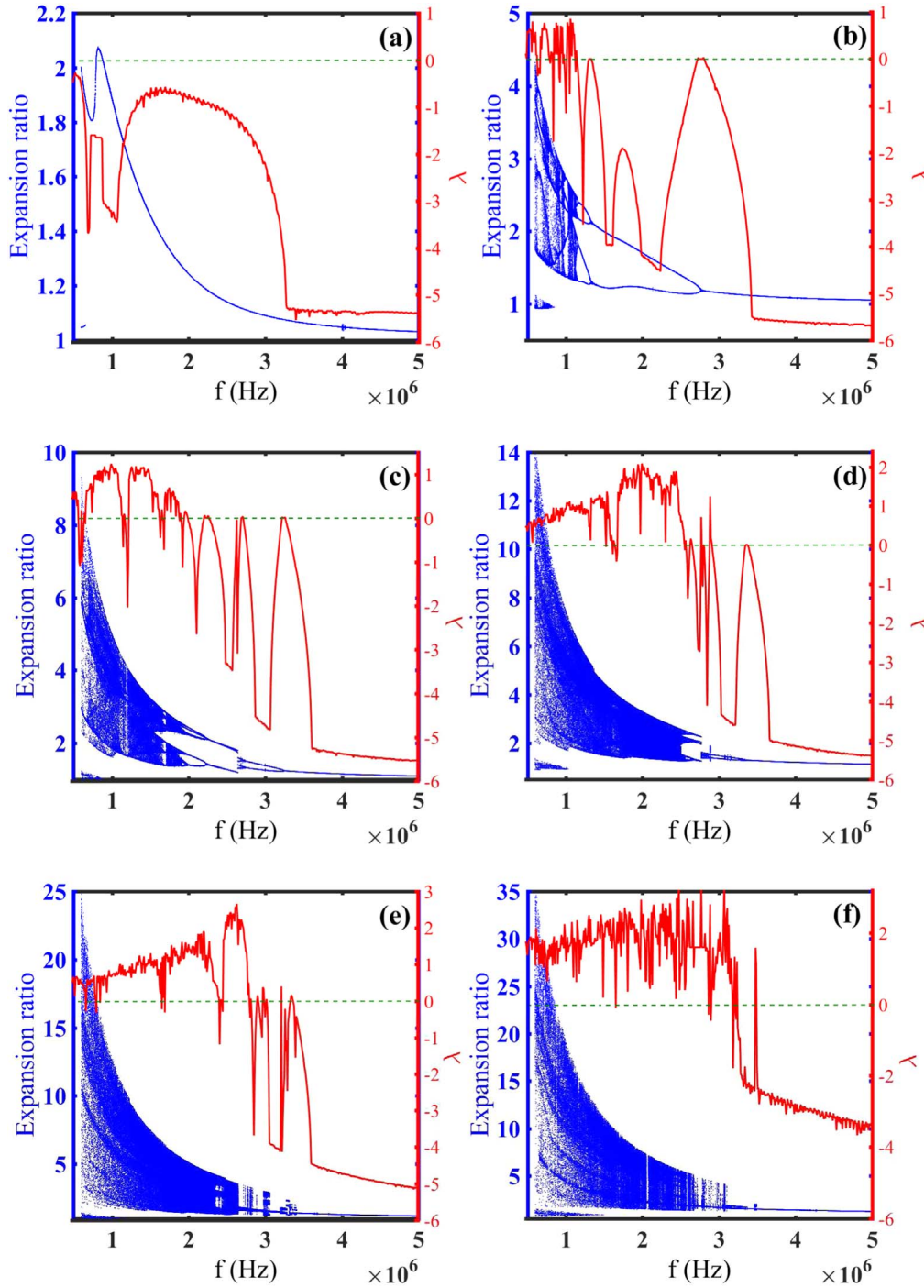


Figure 2. Bifurcation diagrams (Expansion ratio-blue dot points) and Lyapunov exponent (λ -red solid line) of normalized microbubble radius versus driving frequency while $G_L = 0$ MPa, $\mu_s = 0.45$ Pa s, and $G_S = 11.7$ MPa while the acoustic pressure is (a) 0.3 MPa, (b) 0.5 MPa, (c) 0.9 MPa, (d) 1.2 kPa, (e) 1.7 MPa and (f) 2.2 MPa.

all of them (figures 2(a)–(f)) that UCA goes to stable manner at high values of frequency and microbubbles exposed to superior pressures become stable at superior frequencies.

The mechanical characteristics of the medium that surrounds the UCA are varied with kind of tissue and its composition. Therefore, the effects of shear modulus of tissue on microbubble behavior are studied by considering shear modulus variations from 0 to 1.5 MPa. Bifurcation diagram and Lyapunov exponent of normalized microbubble radius

are demonstrated by taking the shear modulus of the surrounding medium as the control parameter (figure 3) whereas the acoustic pressure amplitude is 1.5 MPa and the ultrasound frequency is 1.5 MHz. Moreover, bifurcation diagrams and Lyapunov exponent of normalized microbubble radius versus acoustic pressure (figures 4(a)–(b)) and applied frequency (figures 5(a)–(b)) are plotted within the soft tissue and proportionately stiff tissue with $G_L = 0.5$ and 1 MPa, respectively.

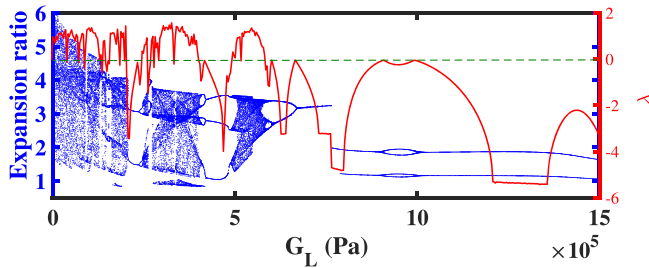


Figure 3. Bifurcation diagrams (Expansion ratio-blue dot points) and Lyapunov exponent (λ -red solid line) of normalized microbubble radius versus shear modulus of surrounding medium with $\mu_s = 0.45$ Pa s, and $G_s = 11.7$ MPa when the driving frequency and pressure are, respectively, 1.5 MHz and 1.5 MPa. Here we have different regions: blood $G_L = 0$ MPa, soft tissue $G_L \leq 0.5$ MPa, and stiff tissue $G_L \geq 1.5$ MPa.

It is observed that the microbubble behavior is chaotic for low values of shear modulus (figure 3) and as the shear modulus of the outer medium is increasing the expansion ratio of the microbubble and chaotic pulsations are reducing. The microbubble finally goes to the stability by increasing the magnitude of shear modulus of the surrounding medium up to 765 kPa which can be confirmed in [40].

In the same conditions, the microbubble behavior is probed versus acoustic pressure for two different values of the shear modulus of the surrounding medium, i.e., 0.5 and 1 MPa (see figures 4(a)–(b)). Comparing these figures in figure 1(c) reveals that the oscillations abate by increasing the magnitude of the shear modulus of the medium; indeed the system has more stability when the external medium is more rigid. The microbubble demonstrates various dynamical behaviors in 3 values of G_L . When the microbubble is surrounded by blood with $G_L = 0$ (see figure 1(c)), it undergoes more chaotic oscillations in lower pressure amplitudes, e.g., the first chaotic window is indicated in 677 kPa, this incident takes place in 1.27 MPa beside soft tissue (Figure 4(a)) and the system is completely stable for the case of comparatively hard tissue with $G_L = 1$ MPa (figure 4(b)).

The effects of frequency variations on microbubble behavior for the values of $G_L = 0.5, 1$ MPa are plotted when the acoustic pressure is 1.7 MPa (figures 5(a)–(b)). Comparing these results with figure 2(e) which shows the effect of frequency variations in $G_L = 0$ manifests this fact that by increasing the magnitude of shear modulus of the surrounding medium, the chaotic oscillations decrease significantly and as it is seen in (figure 5(b)) the chaotic behavior disappears for $G_L = 1$ MPa. It is also evident that the expansion ratio of the microbubble is smaller for higher magnitudes of G_L , in fact, the nonlinearity intensifies for smaller values of G_L .

During our investigation, to explore the effect of shell viscosity alterations on microbubble dynamics, bifurcation diagrams and Lyapunov exponent of normalized microbubble radius are plotted versus shell viscosity as the control parameter. Its value varies in the range 0.01 to 5 Pa s for 3 values of G_L (0, 0.5, 1 MPa) in frequency = 1 MHz and acoustic pressure = 1.5 MPa.

Results represent that the expansion ratio of the microbubble is much higher for low values of shell viscosity in $G_L = 0$ (figure 6(a)) and also it is evident that by increasing the value of shell viscosity the nonlinearity and the maximum microbubble expansion decrease which is seen in [28, 32, 58]. Figure 6(b) demonstrates the normalized oscillations of the microbubble versus time in frequency = 1 MHz and acoustic pressure = 1.5 MPa when the microbubble is surrounded by blood with $G_L = 0$. This figure represents the chaotic oscillations of the microbubble for a definite value of the shell viscosity, i.e., 0.45 Pa s and as it is seen the maximum expansion ratio in this value is the same as figure 6(a).

The microbubble exhibits fully chaotic behavior for small values of shell viscosity which is pursued by period doubling and the system reaches to period one stability in 0.66 Pa.s for $G_L = 0.5$ MPa. The UCA dynamics is completely stable in $G_L = 1$ MPa when the UCA is surrounded by relatively stiff tissue (results was not shown here).

Next, by employing the values of 1.5 MHz and 1 MPa for driving frequency and pressure, respectively, but this time considering the shear modulus of the shell as the control parameter while varying between 0 to 200 MPa, the bifurcation diagrams are presented for 3 values of G_L (0, 0.5, 1 MPa).

By figures 7(a)–(c), the microbubble response is entirely disparate in $G_L = 0$ (figure 7(a)) with regards to $G_L = 0.5$ MPa (Figure 7(b)) and $G_L = 1$ MPa (figure 7(c)). Its dynamics is stable for the values of $G_L = 0.5$ and 1 MPa (figures 7(b)–(c)) while it exhibits chaotic oscillations and high expansion ratio in $G_L = 0$ and the chaotic region becomes narrower in $G_s = 171$ MPa (figure 7(a)).

One of the most important parameters that influence the microbubble behavior is the shell thickness of the microbubble which is utilized as the control parameter and varying in the range of 0 to 150 nm [28, 31, 32] with the values of frequency and pressure of 1 MHz and 1.5 MPa, respectively. The bifurcation diagrams are sketched for three values of G_L (0, 0.5, 1 MPa).

Figure 8(a) exposes that the UCA endures chaotic pulsations in a small magnitude of the shell thickness and increasing the shell thickness decreases the expansion ratio of the microbubble diameter and the system becomes stable when the shell thickness of the agent is 124 nm. These results confirm the previous works in a very wide range of shell thickness variations [28, 31, 32]. Figure 8(b) presents the corresponding time series of the normalized oscillations of the microbubble in frequency = 1 MHz and acoustic pressure = 1.5 MPa while the shell thickness of the agent is 50 nm and the microbubble is surrounded by blood with $G_L = 0$. It is evident that the amplitude of pulsations is the same value as figure 8(a).

For 0.5 MPa of G_L the microbubble dynamics is chaotic for a small interval of shell thickness up to 18 nm and goes to the stable manner which lasts as a predominant situation to the end of the interval. For 1 MPa of G_L the microbubble remains stable in the whole range of shell thickness and any chaotic behaviors is not viewed (results was not shown here).

The stable domains of the polymer-shelled agent are summarized in table 3 for some consequential parameters.

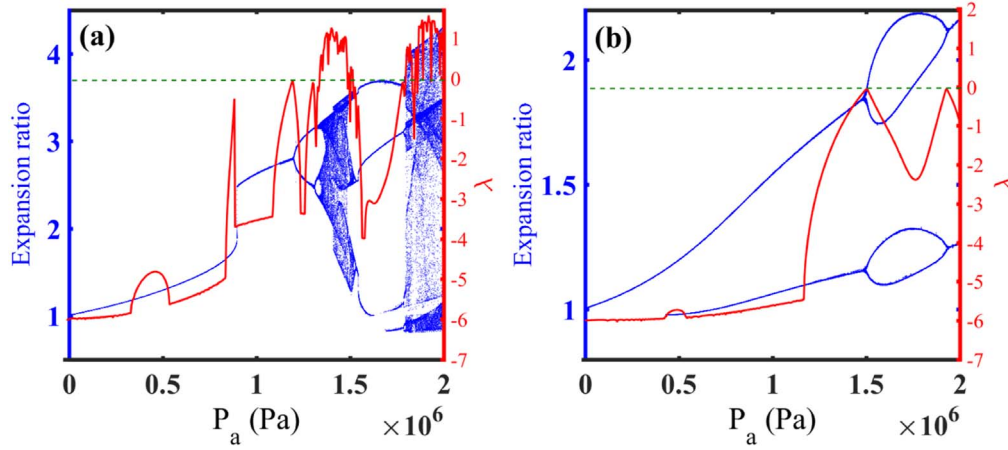


Figure 4. Bifurcation diagrams (Expansion ratio-blue dot points) and Lyapunov exponent (λ -red solid line) of normalized microbubble radius versus driving pressure while $\mu_s = 0.45$ Pa s, and $G_s = 11.7$ MPa when the applied frequency is 1.5 MHz for the surrounding medium with G_L (a) 0.5 MPa, (b) 1 MPa.

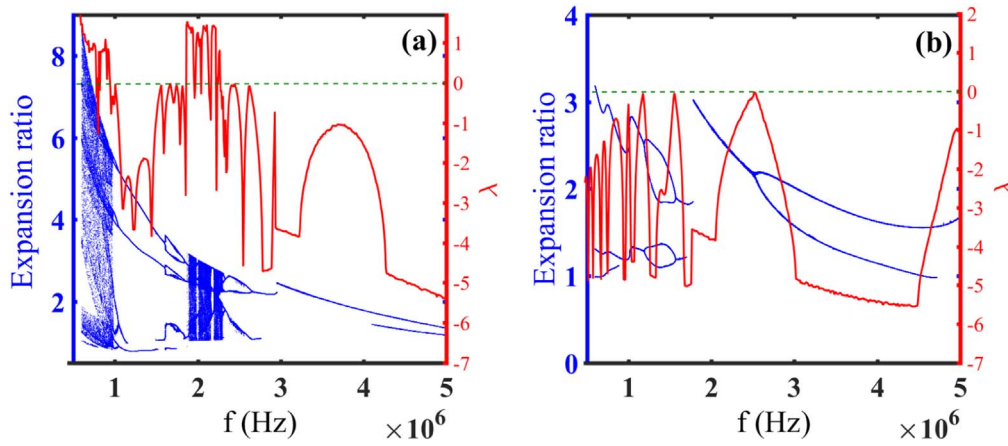


Figure 5. Bifurcation diagrams (Expansion ratio-blue dot points) and Lyapunov exponent (λ -red solid line) of normalized microbubble radius versus driving frequency while $\mu_s = 0.45$ Pa s, and $G_s = 11.7$ MPa when the acoustic pressure is 1.7 MPa for the surrounding medium with G_L (a) 0.5 MPa, (b) 1 MPa.

These results reveal that the stiffness, of the surrounding medium influences the UCA behavior impressively and also demonstrates the chaotic oscillations of UCA under the action of an ultrasound field which can be used to distinguish stable and unstable regions of microbubble pulsations and the expansion ratio of the UCA.

4. Conclusions

This article explained the dynamics driven a polymer-shelled gas microbubble submerged in soft tissue by using the techniques of chaos physics and the ranges in which microbubble has stable behavior has been shown and also been tabulated to show stability limits of the microbubble, which is extremely important in applications. Actually, in order to understand the behavior of an UCA in sonified by high intensity ultrasound in therapeutic medicine *in vivo*, it is necessary to model the UCA as a shelled gas bubble surrounded by soft tissue. In this paper, we used this model because Qin-Ferrara [40] have presented this model to explain the radial oscillations of

UCAs *in vivo* while by considering the effects of the surrounding tissue, liquid compressibility, and the shell. Results of the radial motion of a polymer-shelled agent display that Qin-Ferrara model which reported in this paper is capable of capturing the essential features of the drug and gene delivery applications. The comprehension of UCA behavior is indispensable to improve its diagnostic and therapeutic implementations in which the nonlinearities cannot be prevented. Nonlinear oscillations of encapsulated microbubble immersed in blood or tissue are scrutinized. The complex dynamics of the microbubble is examined in high acoustic pressure amplitudes with the great magnitude of pulsations which is prevalently utilized in drug and gene delivery applications. The effects of several significant parameters on the behavior of the agent are shown for a wide range of variations which has not been inspected previously. These results provide an exact and comprehensive insight into the system dynamics versus a spacious domain of control parameters i.e. pressure and frequency thresholds for stability in blood are summarized in table 3. By focusing on the mechanisms governing the transition from the chaotic oscillations to the stable region,

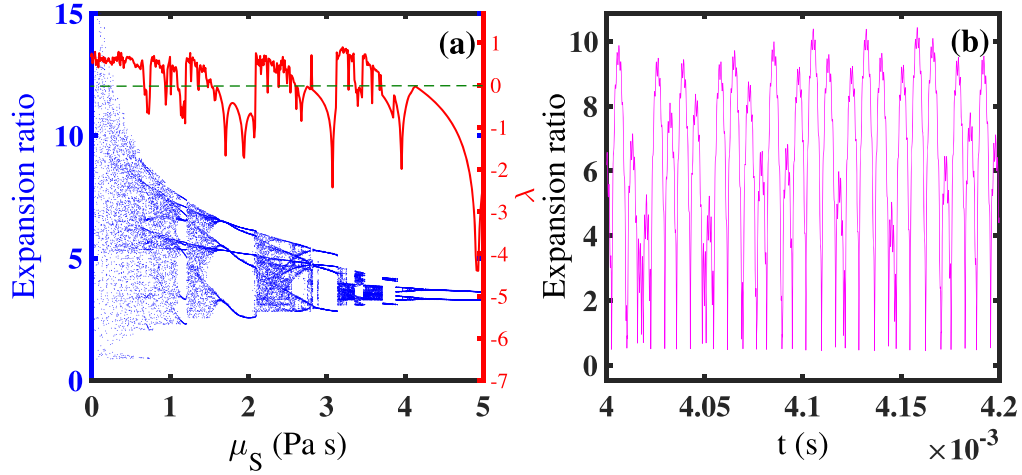


Figure 6. (a) Bifurcation diagrams (Expansion ratio-blue dot points) and Lyapunov exponent (λ -red solid line) of normalized microbubble radius versus shell viscosity when the driving frequency and pressure are, respectively, 1 MHz and 1.5 MPa for $G_L = 0$, and $G_S = 11.7$ MPa, (b) The corresponding time series of normalized oscillations with the shell viscosity $\mu_s = 0.45$ Pa s.

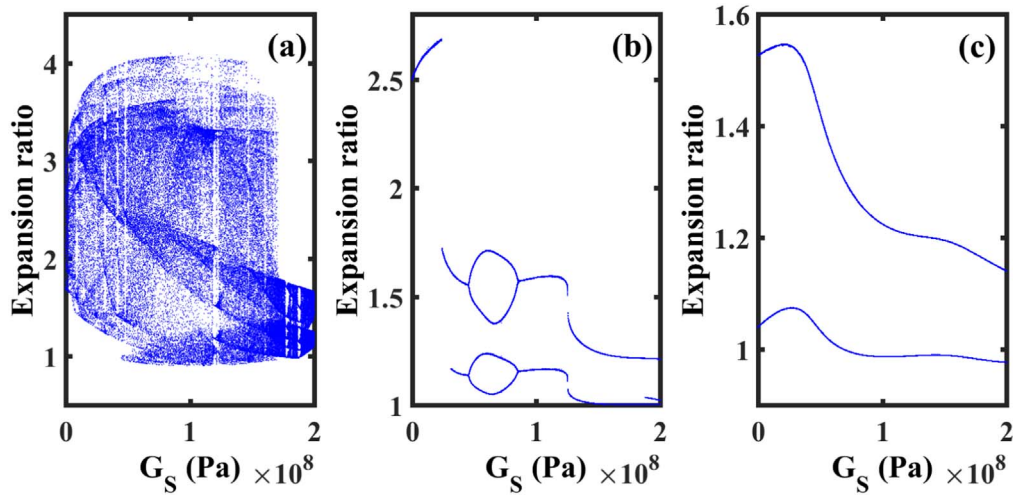


Figure 7. Bifurcation diagrams of normalized microbubble radius versus shear modulus of shell when the driving frequency and pressure are, respectively, 1.5 MHz and 1 MPa for $\mu_s = 0.45$ Pa s, $G_S = 11.7$ MPa, and G_L is (a) 0 MPa, (b) 0.5 MPa, (c) 1 MPa.

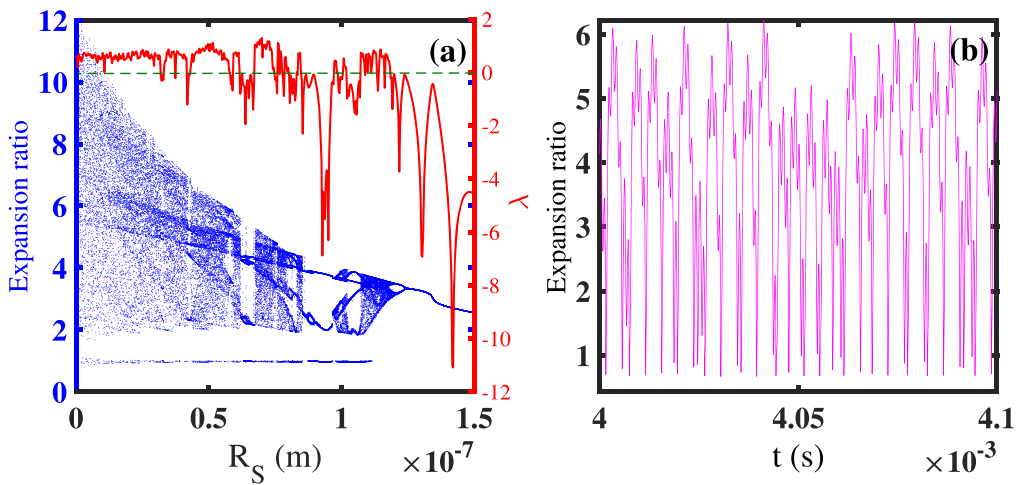


Figure 8. (a) Bifurcation diagrams (Expansion ratio-blue dot points) and Lyapunov exponent (λ -red solid line) of normalized microbubble radius versus shell thickness when the driving frequency and pressure are, respectively, 1 MHz and 1.5 MPa for $\mu_s = 0.45$ Pa s, $G_S = 11.7$ MPa, and $G_L = 0$, (b) The corresponding time series of normalized oscillations with the shell thickness. $R_S = 50$ nm.

Table 3. Stable regions of polymer-shelled agent versus variations of various parameters in $G_L = 0$ (blood), 0.5 (soft tissue) and 1.5 (stiff tissue) MPa.

Parameter	$G_L = 0$	$G_L = 0.5$	$G_L = 1.5$	Unit
Pressure	<0.65	<1.3	entirely stable	MPa
Frequency	>2.65	>2.45	entirely stable	MHz
Shell viscosity	>2.82	>0.53	entirely stable	Pa s
Shell thickness	>124	>18	entirely stable	nm
Shear modulus of shell	>171	entirely stable	entirely stable	MPa

this study opens a new horizon in studying the chaotic behavior of nonlinear dynamics of a shelled gas bubble submerged in soft tissue or blood.

ORCID iDs

M Yahyavi  <https://orcid.org/0000-0003-0062-203X>

References

- [1] Decuzzi P, Godin B, Tanaka T, Lee S-Y, Chiappini C, Liu X and Ferrari M 2010 Size and shape effects in the biodistribution of intravascularly injected particles *J of Controlled Release* **141** 320–7
- [2] Sirsi S R and Borden M A 2009 Microbubble compositions, properties and biomedical applications *Bubble Sci. Eng. Technol.* **1** 3–17
- [3] Borrelli M J, O'Brien W D Jr, Bernock L J, Williams H R, Hamilton E, Wu J, Oelze M L and Culp W C 2012 Production of uniformly sized serum albumin and dextrose microbubbles *Ultrason. Sonochem.* **19** 198–208
- [4] Mitterberger M, Pelzer A, Colleselli D, Bartsch G, Strasser H, Pallwein L, Aigner F, Gradl J and Frauscher F 2007 Contrast-enhanced ultrasound for diagnosis of prostate cancer and kidney lesions *Eur. J. Radiol.* **64** 231–8
- [5] Klivanov A L 2006 Microbubble contrast agents: targeted ultrasound imaging and ultrasound assisted drug-delivery applications *Invest. Radiol.* **41** 354–62
- [6] Shohet R V and Grayburn P A 2006 Potential bioeffects of ultrasonic destruction of microbubble contrast agents *J of the American College of Cardiology* **47** 1469–70
- [7] Hynynen K 2008 Ultrasound for drug and gene delivery to the brain *Adv. Drug Delivery Rev.* **60** 1209–17
- [8] Sirsi S R, Hernandez S L, Zielinski L, Blomback H, Koubaa A, Synder M, Homma S, Kandel J J, Yamashiro D J and Borden M A 2011 Polyplex-microbubble hybrids for ultrasound-guided plasmid DNA delivery to solid tumors *J. Controlled Release* **157** 224–34
- [9] Porter T R and Xie F 2001 Ultrasound, microbubbles, and thrombolysis *Prog. Cardiovasc. Dis.* **44** 101–10
- [10] Hynynen K, McDannold N, Vykhodtseva N, Jolesz F and Noninvasive 2001 MR imaging-guided focal opening of the blood–brain barrier in rabbits *Radiology* **220** 640–6
- [11] Yang F Y, Fu W M, Yang R S, Liou H C, Kang K H and Lin W L 2007 Quantitative evaluation of focused ultrasound with a contrast agent on blood-brain barrier disruption *Ultrasound Med. Biol.* **33** 1421–7
- [12] McDannold N J, Vykhodtseva N I and Hynynen K 2006 Microbubble contrast agent with focused ultrasound to create brain lesions at low power levels: MR imaging and histologic study in rabbits *Radiology* **241** 95–106
- [13] Lentacker I, De Smedt S C and Sanders N N 2009 Drug loaded microbubble design for ultrasound triggered delivery *Soft Matter* **5** 2161–70
- [14] Bull J L 2007 The application of microbubbles for targeted drug delivery *Expert. Opin. Drug Deliv.* **4** 475–93
- [15] Sheffield P, Trehan A, Boyd B and Wong O L 2008 Microbubbles as ultrasound contrast agents and in targeted drug delivery *Crit. Rev. Biomed. Eng.* **36** 225–55
- [16] Böhmer M R, Chlon C H T, Raju B I, Chin C T, Shevchenko T and Klivanov A L 2010 Focused ultrasound and microbubbles for enhanced extravasation *J. Controlled Release* **148** 18–24
- [17] Unger E C, Porter T, Culp W, Labell R, Matsunaga T and Zutshi R 2004 Therapeutic applications of lipid-coated microbubbles *Adv. Drug Deliv. Rev.* **56** 1291–314
- [18] Ferrara K, Pollard R and Borden M 2007 Ultrasound microbubble contrast agents: fundamentals and application to gene and drug delivery *Annu. Rev. Biomed. Eng.* **9** 415–47
- [19] Wu J, Pepe J and Dewitt W 2003 Nonlinear behaviors of contrast agents relevant to diagnostic and therapeutic applications *Ultrasound Med. Biol.* **29** 555–62
- [20] Chomas J E, Dayton P, May D and Ferrara K 2001 Threshold of fragmentation for ultrasonic contrast agents *J. Biomed. Opt.* **6** 141–50
- [21] Morgan K E, Allen J S, Dayton P A, Chomas J E, Klivanov A L and Ferrara K W 2000 Experimental and theoretical evaluation of microbubble behavior: effect of transmitted phase and bubble size *IEEE Transact. Ultrasonics Ferroelect. Freq. Control.* **47** 1494–509
- [22] Hoff L, Sontum P C and Hovem J M 2000 Oscillations of polymeric microbubbles: effect of the encapsulating shell *J. Acoust. Soc. Am.* **107** 2272–80
- [23] Lauterborn W and Koch A 1987 Holographic observation of period-doubled and chaotic bubble oscillations in acoustic cavitation *Phys Rev A* **35** 1974–6
- [24] Dzaharudin F, Suslov S A, Manasseh R and Ooi A 2013 Effects of coupling, bubble size, and spatial arrangement on chaotic dynamics of microbubble cluster in ultrasonic fields *J Acoust Soc Am.* **134** 3425–34
- [25] Chong K J Y, Quek C Y, Dzaharudin F, Ooi A and Manasseh R 2010 The effects of coupling and bubble size on the dynamical-systems behaviour of a small cluster of microbubbles *J Sound Vib* **329** 687–99
- [26] De Jong N 1993 Acoustic properties of ultrasound contrast agents *Ph.D. Thesis* <http://hdl.handle.net/1765/39138> Erasmus University, Rotterdam, The Netherlands
- [27] De Jong N and Hoff L 1993 Ultrasound scattering of Alunex microspheres *Ultrasonics* **31** 175–81
- [28] Church C C 1995 The effects of an elastic solid surface layer on the radial pulsations of gas bubbles *J. Acoust. Soc. Am.* **97** 1510–21
- [29] Morgan K E 2001 Experimental and theoretical evaluation of ultrasonic contrast agent behavior *Ph.D. Thesis* University of Virginia, Ann Arbor, USA

- [30] Zheng H, Dayton P A, Caskey C, Zhao S, Qin S and Ferrara K W 2007 Ultrasound driven microbubble oscillation and translation within small phantom vessels *Ultrasound Med. Biol.* **33** 1978–87
- [31] Allen J S, May D J and Ferrara K W 2002 Dynamics of therapeutic ultrasound contrast agents *Ultrasound Med. Biol.* **28** 805–16
- [32] Khismatullin D B and Nadim A 2002 Radial oscillations of encapsulated microbubbles in viscoelastic liquids *Phys. Fluids* **14** 3534–57
- [33] Chatterjee D and Sarkar K 2003 A Newtonian rheological model for the interface of microbubble contrast agents *Ultrasound Med. Biol.* **29** 1749–57
- [34] Sarkar K, Shi W T, Chatterjee D and Forsberg F 2005 Characterization of ultrasound contrast microbubbles using *in vitro* experiments and viscous and viscoelastic interface models for encapsulation *J. Acoust. Soc. Am.* **118** 539–50
- [35] Stride E and Saffari N 2004 Theoretical and experimental investigation of the behavior of ultrasound contrast agent particles in whole blood *Ultrasound Med. Biol.* **30** 1495–509
- [36] Tamadapu G, Grishenkov D and Eriksson A 2016 Modeling and parametric investigation of thick encapsulated microbubble's nonspherical oscillations *J. Acoust. Soc. Am.* **140** 3884
- [37] Tamadapu G, Nordmark A and Eriksson A 2015 Resonances of a submerged fluid-filled spherically isotropic microsphere with partial-slip interface condition *J. Appl. Phys.* **118** 044903
- [38] Marmottant P, van der Meer S, Emmer M, Versluis M, de Jong N, Hilgenfeldt S and Lohse D 2005 A model for large amplitude oscillations of coated bubbles accounting for buckling and rupture *J. Acoust. Soc. Am.* **118** 3499–505
- [39] Doinikov A and Dayton P A 2006 Spatio-temporal dynamics of an encapsulated gas bubble in an ultrasound field *J. Acoust. Soc. Am.* **120** 661–9
- [40] Qin S and Ferrara K W 2010 A model for the dynamics of ultrasound contrast agents *in vivo* *J. Acoust. Soc. Am.* **128** 1511–21
- [41] Frinking P, Segers T, Luan Y and Tranquart F 2020 Three Decades of Ultrasound Contrast Agents: A Review of the Past, Present and Future Improvements *Ultrasound in Medicine & Biology* **46** 892–908
- [42] Helfield B 2019 A review of phospholipid encapsulated ultrasound contrast agent microbubble physics *Ultrasound Med. Biol.* **45** 282–300
- [43] Lauterborn W and Parlitz U 1988 Methods of chaos physics and their application to acoustics *J. Acoust. Soc. Am.* **84** 1975–93
- [44] Parlitz U, Englisch V, Scheffczyk C and Lauterborn W 1990 Bifurcation structure of bubble oscillators *J. Acoust. Soc. Am.* **88** 1061–77
- [45] Parlitz U, Scheffczyk C, Akhatov I and Lauterborn W 1995 Structure formation in cavitation bubble fields *Chaos, Solitons Fractals* **5** 1881–91
- [46] Lauterborn W and Suchal E 1984 Bifurcation superstructure in a model of acoustic turbulence *Phys. Rev. Lett.* **53** 2304–7
- [47] Behnia S, Zahir H, Yahyavi M, Barzegar A and Mobadersani F 2013 Observations on the dynamics of bubble cluster in an ultrasonic field *Nonlinear Dyn.* **72** 561–74
- [48] Behnia S, Yahyavi M and Mobadersani F 2014 Intelligent controlling microbubble radial oscillations by using Slave-Master Feedback control *Appl. Math. Comput.* **245** 404–15
- [49] Behnia S, Mobadersani F, Yahyavi M and Rezavand A 2013 Chaotic behavior of gas bubble in non-Newtonian fluid: a numerical study *Nonlinear Dyn.* **74** 559–70
- [50] Behnia S, Mobadersani F, Yahyavi M, Rezavand A, Hoesinpour N and Ezzat A 2015 Effect of magnetic field on the radial pulsations of a gas bubble in a non-Newtonian fluid *Chaos, Solitons Fractals* **78** 194–204
- [51] Brenner M P, Hilgenfeldt S and Lohse D 2002 Single-bubble sonoluminescence *Rev. Mod. Phys.* **74** 425–84
- [52] Wolf A, Swift J B, Swinney H L and Vastano A 1985 Determining the Lyapunov exponents from a time series *Physica D* **16** 285–317
- [53] Sarkara K, Shi W T and Chatterjee D 2005 Flemming Forsberg, Characterization of ultrasound contrast microbubbles using *in vitro* experiments and viscous and viscoelastic interface models for encapsulation *J. Acoust. Soc. Am.* **118** 539–50
- [54] Sboros V 2008 Response of contrast agents to ultrasound *Adv. Drug Delivery Rev.* **60** 1117–36
- [55] King D A and Orien W D Jr. 2011 Comparison between maximum radial expansion of ultrasound contrast agents and experimental postexcitation signal results *J. Acoust. Soc. Am.* **129** 114–21
- [56] Zheng H, Dayton P A, Casky C, Zhao S, Qin S and Ferrara K W 2007 Ultrasound-driven microbubble oscillation and translation within small phantom vessels *Ultrasound Med. Biol.* **33** 1978–87
- [57] Kooiman K, Vos H J, Versluis M and de Jong N 2014 Acoustic behavior of microbubbles and implications for drug delivery *Adv. Drug Delivery Rev.* **72** 28–48
- [58] Doinikov A A, Haac J F and Dayton P A 2009 Modeling of nonlinear viscous stress in encapsulating shells of lipid-coated contrast agent microbubbles *Ultrasonics* **269**–75