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Simulation Study of the Variations in Driving Pressure and Frequency on Microbubbles Contras Agents Behavior.

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Abstract

The difference between the density of the gas core of microbubbles and the surrounding media causes the behavior of microbubbles contrast agents in an ultrasound field to be nonlinear and intricate. In addition, many factors affect the radial oscillations of these microbubbles. Some of these factors are related with the bubble structure and its shell material such as the initial radius of the bubble, shell thickness, viscosity of the shell material and its elasticity. Other factors are related with the incident acoustic wave such as the driving frequency and driving pressure amplitude. In this simulation study the effects of pressure and frequency as influential factors on the stability of the microbubble were studied in wide range (frequencies are extend from $f < f_r$ to $f \approx 3 f_r$, pressure extends from 0.05 to 1.5 MPa.), and analyzed using the bifurcation theory to visualize and characterize the effect of these factors on the microbubbles behavior. The study expounded theoretically that the generation the higher order of subharmonic oscillations is possible to result at high driving frequencies with low and appropriate driving pressures.

Keywords: Ultrasound contrast agents, Microbubbles, Bifurcation, Nonlinear behavior, Driving pressure and frequency.

1. Introduction

The contrast agents of ultrasound imaging composed of microbubbles smaller than 7 µm in diameter, encapsulated by a stabilizing thin shell of different composition, and filled with air or a gas of lower solubility than air such as a perfluorocarbon [1]. The oscillation of the microbubble under ultrasound beam is governed by many parameters such as the initial bubble radius, the rheological properties of its shell material, and the local acoustic power [2]. Due to the low density of the gas core, these microbubbles are highly compressible when they are driven by an ultrasound field. Based on that, at low acoustic power, the microbubbles destruction by the ultrasound beam is minimized and microbubbles oscillate synchronously with the incident ultrasound and emit non-linear echoes. With increasing acoustic power of the incident ultrasound beam, signals returning from microbubbles are increased by several orders of magnitude due to interactions between the incident beam and the microbubbles, which include fundamental scattering, harmonic resonance and microbubble destruction. In other words, the bubbles respond in linear or non-linear mode, the radius of the bubble change linearly in relation with the amplitude of the applied ultrasound wave at low acoustic pressure which result in linear pulsation of bubble, but at high acoustic pressures the bubbles pulsation become nonlinear in principle, expansion of bubbles is unlimited unlike the compressibility of the bubble [3]. So, it can be considered that the gas bubble driven in motion by acoustic field is a perfect example to describe a system with highly nonlinear behavior which may be considered as a degree of chaos [6]. This phenomenon of nonlinearity happens when applying a high frequency, high amplitude of acoustic field on the bubbles within the liquid. This complex and nonlinear behavior gave the microbubbles a great importance as contrast agent of ultrasound imaging [3]. Understanding the behavior of the microbubbles under ultrasound field gives a good tool for predicting its dynamic behavior, which help in designing a new and good contrast agent. To reach this goal we need to expand our perceptions on behavior of an individual bubble under a wide range of possible acoustic field conditions such as driving frequency and pressure. These perceptions help in selecting a regime to avert messy motion, because when a system slips into chaos become tricky to prognosticate and result in the control loss of its dynamic behavior [5].

2. Theoretical Model

The common bubbles concentrations in clinical use of the contrast agents are in order of 10^{-5} to 10^{-6}, At these low concentrations, the bubbles oscillations do not interact. The bubbles oscillate, absorb and scatter sound independently of one another. Accordingly, the total radiation power is the sum of the radiations that comes from each individual bubble [3]. There are several models that describe the dynamic behavior of the microbubbles. The model which was derived by Lord Rayleigh in 1917 is the oldest and has become the basis for all other models. All these models are second order nonlinear ODE and they describe the dynamic behavior of an individual bubble. Church's model is the common model which describes the radial oscillations of encapsulated bubble have a shell thickness much smaller than the bubble radius [6]. Hoff's model is a simplification of Church's model, is developed for visco-elastic thin shelled bubbles. This model describes the radial oscillations R of the bubble as a function of time and is given by equation 1:

$$R\ddot{R}+\frac{3}{2}\dot{R}^2=\frac{P_0\left(\left[\frac{R_0}{R}\right]^{3\gamma}-1\right)-P_{i(t)}}{\rho_l}-\frac{4\mu_l\dot{R}}{\rho_l R}-\frac{1}{\rho_l}\left[12\frac{d_{se}}{R_e}\left(G_s\left(1-e^{-\frac{R-R_0}{x_0 R_0}}\right)\frac{R-R_0}{R_0}+\mu_s\frac{\dot{R}}{R_0}\,e^{-\frac{R-R_0}{x_1 R_0}}\right)\right]+\frac{R}{\rho_l c}\dot{P}_{G(t)} \quad (1)$$

Where R_0 is the initial radius, R is the time dependent radius, $\dot{R}$ and $\ddot{R}$ are the velocity and acceleration of the bubble's wall, P_0 is the equilibrium pressure inside the bubble, ρ_l is the density of the liquid, γ is the polytropic exponent, μ_l is the viscosity of the surrounding liquid, G_s is the shear modulus, μ_s is the shell viscosity, d_{se} is the shell thickness, c is the speed of sound in the liquid, $\dot{P}_{G(t)}$ is the gradient of the gas pressure inside the bubble, x_0 and x_1 are two constants respectively ⅛, ¼ [7], and $P_{i(t)}$ is the driving acoustic pressure which is given by equation 2:

$$P_{i(t)}=A\sin 2\Pi ft \quad (2)$$

Where A is the amplitude of the driving frequency.

One of the important parameters in applications of microbubbles oscillations is the backscattered pressure. Medical imaging applications of contrast enhanced ultrasound are the best examples of using the backscattered pressure from the tissue and ultrasound contrast agents. The signal that is received is filtered before establishing the image taken.

Hilgenfeldt et. al calculated the backscattered pressure by using a 4th order Runge-Kutta for solving equation (1) using equation (2) as driving pressure [8], they find the general formula of the backscattered pressure $P_{s(t)}$ for far-field ($D \gg wave\ length$) from an oscillating body (bubble) of given volume as in equation (3):

$$P_{s(t)}=\frac{\rho_l R}{D}(2\dot{R}^2+R\ddot{R}) \quad (3)$$

Where D is the distance from the center of the bubble to the reviser (in BubbleSim D is one meter). In this paper the effects of the driving pressure and frequency are studied for a single bubble with wide range of parameters domain. By collecting the data and analyzing the results more comprehensive knowledge and better understanding would be gained about the complex dynamics and nonlinear phenomena of microbubbles.

3. Complex dynamics of the bubble's model and stability range

The oscillation of gas bubbles is known to be highly nonlinear and complex for moderate driving pressure amplitudes [4]. "Moderate amplitude means amplitude value that extends from 100 kPa to 750 kPa, amplitudes that used frequently with diagnostic ultrasound imaging". Because of the lack of knowledge of the rheological parameters of the bubble's shell and the complexity of the system resulting from the interaction of several control parameters (initial radius, frequency, pressure , viscosity and elasticity of the shell and surrounding field) it is difficult to expect and designa the parameters that provide an insight into the bubble dynamics [9]. The bifurcation diagram (the mathematical meaning of the Bifurcation is the study of changes in the topological structure of multiple control parameters of dynamic fields of a system) enables us to visualize the bubble behavior in a wide range and provides a qualitative and valuable information about where and when a nonlinear response is likely to occur, and it gives an impression of the strength of this response.

4. Methods

The bifurcation diagrams are used to study the dynamics of the system by normalizing the bubble radius versus different values of driving acoustic pressure, driving frequency as control parameters using rheological parameters values of Sonazaid as contrast agent { G_s =50 Mpa, μ_s =0.99 Pa.s, d_{se} =4 nm} [10,11], with a 3 µm initial radius bubble, and a resonant frequency of 1.847 MHz. The procedure had been done using the output data of "BubbleSim" which is the numerical software package in Matlab, written by Lars Hoff to solve his model and simulates the response of a bubble exposed to an ultrasound pulse. These data included the response of the bubble's radius due to the acoustic pressure, the power spectra of the backscattered signal, and many information of the bubble behavior. The bubble had been excited by acoustic frequency signal which is consisted of 150 cycles. After the system has been reached its stable vibration, the values of the radial oscillations ((R(t))) for the last 50 periods have been calculated at the end of each driving period , and normalizing (normalized radius $=\frac{R}{R_0}$) , this resulted in 50 values (the range consists of 50 period) These values has been plotted versus a parameter of the system, which was called a "control parameter.". The control parameter is then changed by a small amount and the same procedure is repeated. In the linear region, all values calculated at the end of each driving period in this specific range are sketched on each other (which represents a period single oscillation) and one point is seen on the bifurcation diagram in this region. While two points are seen on the bifurcation diagram when the bubble exhibits period doubled oscillations, i.e. repeats only after two oscillations of the driving sound field. By changing the control parameter progressively, the period oscillations increase and more than two point appear in the diagram until the system response becomes chaotic [12]. It should be noted that simulation results with $\frac{R}{R_0} > 2$ were not considered as they lose their practical importance due to the possible microbubble destruction [13]. The bifurcation diagram appears a slight but important modification to analyze the dynamics of the nonlinear phenomena and the condition for each control parameter. According to this procedure, the stability of bubble response are studied versus driving pressure amplitude and driving frequency as control parameters as follow:

First **-** The effect of the driving acoustic pressure amplitude: The normalized of the bubble radius which is dependent on time with its typical initial radius (3 µm) was sketched with the applied pressure values of acoustic field as the control parameter domain in the range between 0.05MPa to 1.5 MPa. This procedure enable us to visualize and characterize the effect of changing in the driving acoustic pressure on the bubble behavior in wide rang of acoustic pressure.

Second **-** The effect of the driving frequency: Repeats the same procedure, but in this time with fixed amplitude of acoustic pressure and range of driving frequencies which are extending from $f < f_r$ to $f \approx 3\, f_r$ where f_r is the resonance frequency of the bubble. This procedure enable us to visualize and characterize the effect of changing the driving frequency on the bubble behavior in wide rang of frequencies.

5. Results and Discussion

5.1. Effect of pressure variations

The bifurcation diagrams figures 1A to 1D illustrates the variations of the normalized bubble radius versus pressure, with driving frequencies of 1.25, 1.85 (resonance frequency), 3.75, and 5 MHz respectively. These figures represent the stable and chaotic oscillations of the microbubble in wide range of driving pressure. In figure 1A the frequency is 1.25 MHz, which is less than the resonance frequency, the oscillation of the microbubble significantly and linearly increases when the pressure exceeds 25 kPa and the curve touches the threshold limit of disruption at 325 kPa. In figure 1B the frequency is 1.85 MHz (resonance frequency) at this frequency the microbubble oscillation increases linearly with the increase of acoustic pressure until reachs 350 kPa, then, through a saddle node bifurcation the microbubble exhibit period doubling (in this region the bubble repeats the same oscillatory response once in every two driving periods. So that, the bubble radiates subharmonic frequency with order 1/2 of the incident frequency). The chaotic oscillations begin at 425 kPa and the bifurcation diagram touches the threshold limit of disruption with this chaotic oscillations at 540 kPa. In figure 1C the frequency is 3.75 MHz which is near the double of the resonance frequency of the bubble, at this frequency the oscillation increases linearly up to 260 kPa , then through a saddle node bifurcation the microbubble exhibit period doubling and continue up to 810kPa above which it the microbubble exhibit a period with quadruple oscillations (in this region the bubble repeats the same oscillatory response once every four driving periods. So that, the bubble radiates subharmonic frequency with order 1/4 of the incident frequency). The curve touches the threshold limit of disruption with this chaotic oscillations at 975 kPa. In figure 1D the frequency is 5 MHz. The bubble exhibits linear oscillation with slightly increases in its amplitude up to 900 kPa, above this driving pressure the oscillation shows suddenly large nonlinear behavior, then shifted to tri-oscillations period (in this region the bubble repeats the same oscillatory response once every three driving periods). So that, the bubble radiates subharmonic frequency with order 1/3 of the incident frequency),then the bifurcation diagram touches the threshold limit of disruption at 1.48 MPa.

5.2. Effect of frequency variations

The bifurcation diagrams figure 2A to 2D illustrates the variations of the normalized bubble radius versus wide range of driving frequency extends from 0.8 MHz to 5 MHz. While the applied acoustic pressure amplitude are 0.1 , 0.3 , 0.5 , and 0.7 MPa respectively. Figure 2A shows that applying small driving pressure and frequency the bubble oscillates with rough chaotic oscillations. Increasing the driving frequency causes reduction of the amplitude of the bubble oscillations then the behavior rapidly shifts to almost stable oscillations after 1.2 MHz. In figures 2B to 2D the chaotic behavior emerges in bubble response as the pressures increases. These figures show the chaotic oscillation begins also at low frequencies, but it extends over a wide range of frequencies. As the frequency increases, a kind of behavior appears, which is the transition from chaotic oscillations to stable to chaotic oscillations again this happens via period doubling, as the pressure amplitude increased the regions of stable behavior between two chaotic transitions became narrower. It is worth noting, that at high frequencies the transition from chaos to stable behavior is happening via inverse period doubling followed by a saddle node bifurcation. According to these observations, arguably the microbubbles driven with higher acoustic pressures become oscillated roughly stable at higher frequencies.

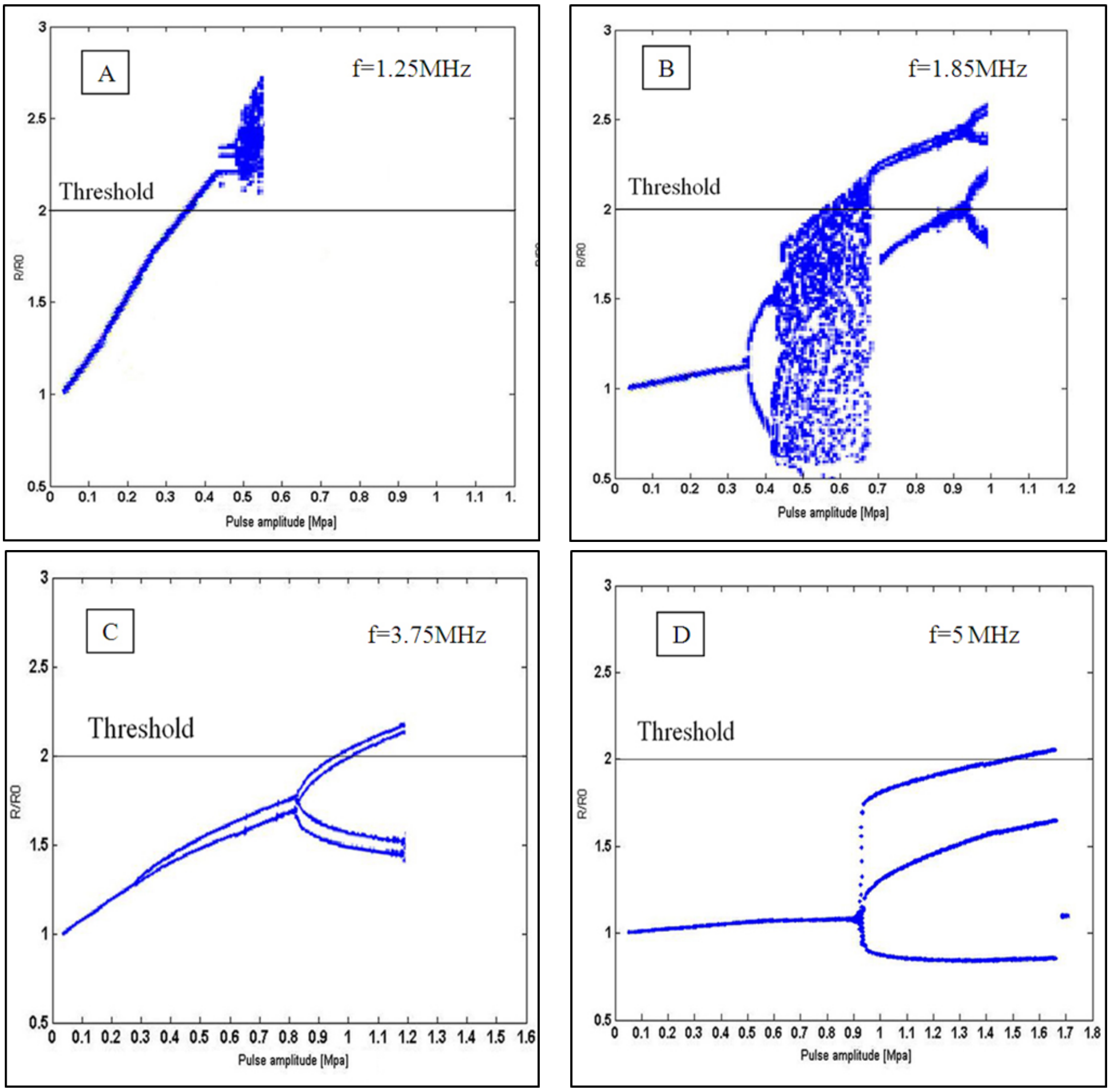
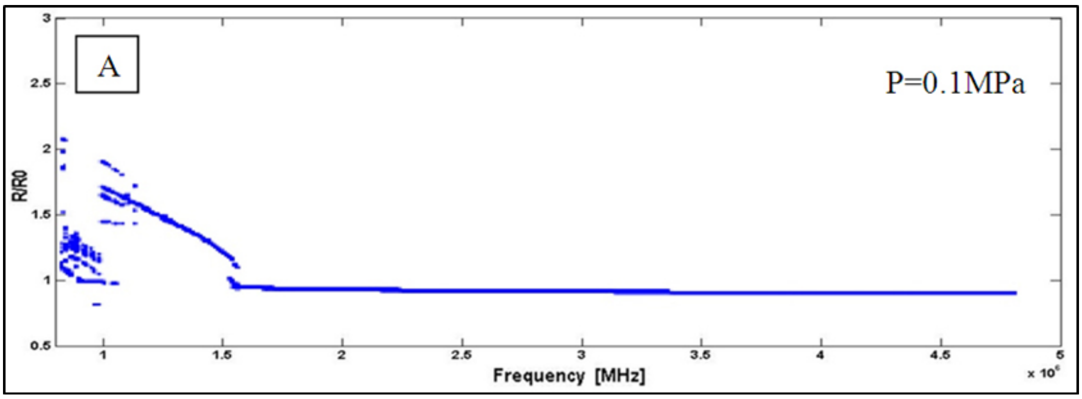


Figure 1:. Bifurcation diagrams of normalized bubble radius which have resonant frequency 1.847 MHz, versus incident acoustic pressure of the frequency (A) 1.25 MHz, (B) 1.85 MHz, (C)3.75 MHz, and (D) 5MHz



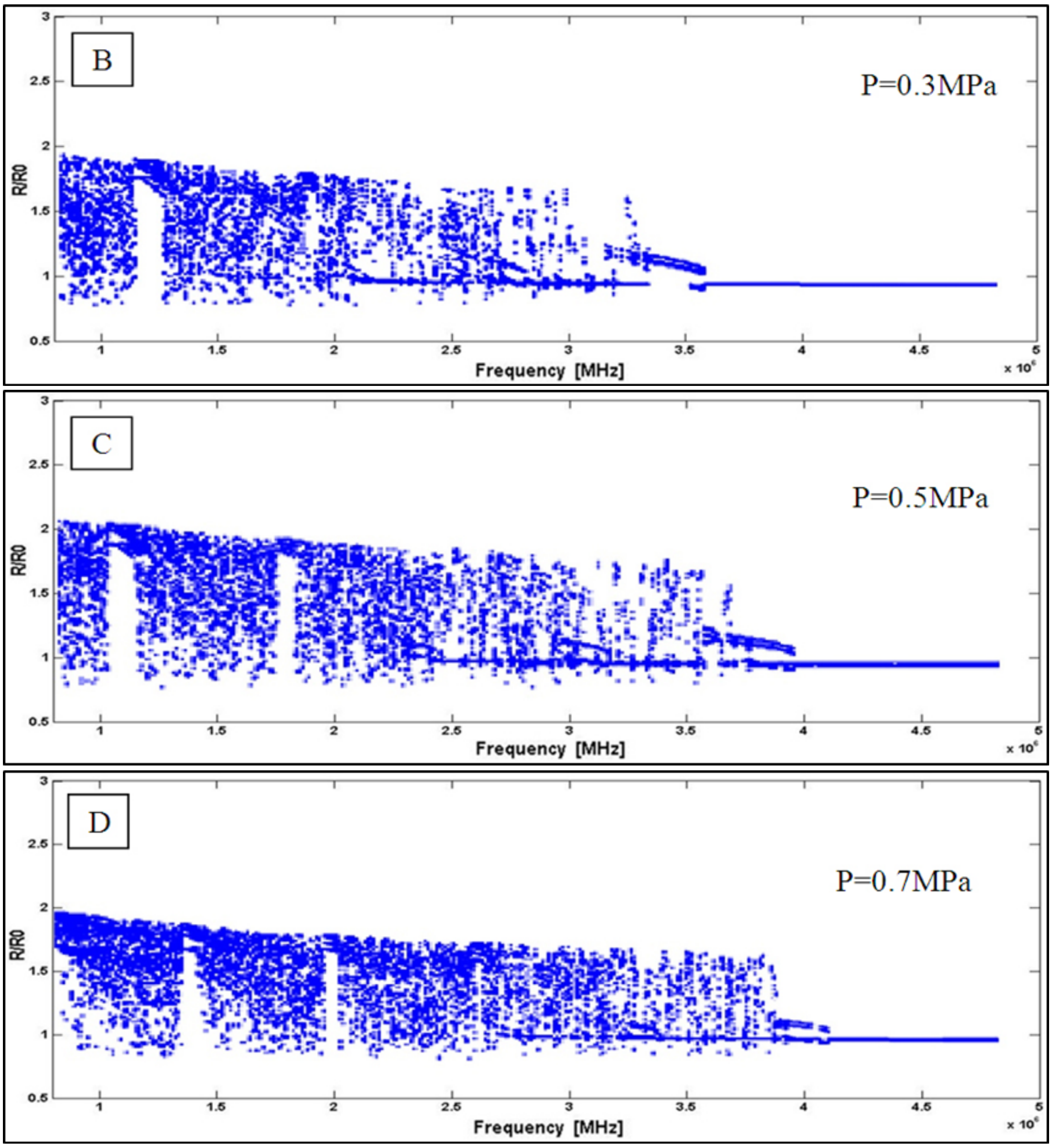


Figure 2: Bifurcation diagrams of normalized bubble radius which has resonant frequency 1.847 MHz, versus frequency with acoustc pressure of (A) 100 KPa, (B) 300 KPa, (C) 500 KPa, and (D) 700 KPa.

6. Conclusion

The dynamics of the ultrasound contrast agents were studied for a wide range of system control parameters (acoustic pressure, and frequency). The discussion of the above results confirmed that the oscillations of the microbubbles are pressure and frequency dependent, this is consistent with the previous study [3, 14, 15, 16]. As it is known, in conventional subharmonic imaging, the bubbles insonated with a frequency of approximately twice their natural resonance frequency. If the pressure amplitude of the incident ultrasound is sufficient, the bubble will exhibit subharmonic oscillations at half the driving frequency. According to these results, in addition to the generation the subharmonics at half of the driving frequency, it is possible to force the bubbles to exhibit higher order of subharmonics. This study demonstrated theoretically that the generation the higher order of subharmonic oscillations is possible to result when high driving frequencies with low and appropriate pressures amplitudes are used, especially when these frequencies are multiples of the resonant frequency of the bubble, this is considered a useful information in subharmonic imaging. On the other hand, This study showed the possibility of using the bifurcation theory in simulation the behavior of bubbles. Moreover, it is considered an useful tool during designing and manufacturing the new microbubbles contrast agents by simulations the effects of driving pressure and frequency on durability of these microbubbles and their ability limits in generation the harmonic and subharmonic.

7. References

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دراسة محاكاة لتغيرات الضغط والتردد على سلوك الفقاعات المايكرويه لعوامل التباين

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الخلاصة

ان الفرق بين كثافة الغاز داخل الفقاعه المايكرويه والوسط المحيط بها هو ما يسبب التصرف اللاخطي المعقد لفقاعات اوساط التباين المستخدمه في مجال التصوير بالموجات فوق الصوتية. بالإضافة إلى ذلك، هنالك العديد من العوامل الاخرى تؤثر على سلوك تلك الفقاعات بعضها يرتبط ارتباطا وثيقاً بشكل هيكل الفقاعه والماده المكونه لقشرتها مثل نصف قطر الفقاعه، سمك القشره، وخصائص المرونه واللزوجه لماده القشره. والبعض الاخر يرتبط بالموجه فوق الصوتية المسلطه عليها مثل التردد وسعه الضغط الصوتي. في هذه الدراسه سيتم محاكات سلوك الفقاعات المايكرويه عند تعرضها لمدى واسع من التغيير في عاملي التردد و الضغط الصوتي وتحليل التغيرات الحاصله في سلوكها باستخدام نظريه التشعب ووصف تاثير ذلك على استقرارها. من ناحيه اخرى اوضحت نتائج هذه الدراسه نظريا ان يمكن الحصول على رتب عاليه من التوافيات والتوافقيات المرافقه اذا ما كان التردد المسلطه على الفقاعه عالي نسبياً حتى وان كان وسعه الضغط الصوتي قليله.