Characterizations of the mathematical models of Ultrasound Contrast Agents: a review

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Abstract

The typical contrast agents of ultrasound imaging composed of microbubbles of smaller than 7 µm in diameter this microbubbles consist of gas coated with a protein, lipid or polymer layer it is acting as very powerful scatterers.
There are several models describe the dynamic behavior of these microbubbles under ultrasound filed, the Lord Rayleigh's model is the oldest one and the basis for all other models, this model was modified by plesset by added the driving sound field, resulting in an equation called Rayleigh-Plesset equation which describes bubble oscillating due to the driving sound field in an inviscid and incompressible fluid of constant density, RP model is a second order nonlinear ODE, The RP equation may be modified by Noltingk, Neppiras and Poritsky Whose added the effects of the surrounding field , this led to an equation called the RPNNP equation which is considered the the first step to construct a shelled bubble model. Later researchs Take into account the liquid compressibility effect on the bubble dynamics, the major developments occurred in this area by Keller and Miksis. The microbubbles which used in such contrast agents are normally stabilized by a thin shell ,the stiffness and viscosity of this thin shell add a another foctors to the acoustical behavior of the bubble, several models exist for the encapsulating shell, the common models of encapsulated bubble are Hoff model and Marmottant Model, these models are an extension of the RP equation.

Understanding the behavior of the microbubbles under ultrasound filed gives us a good tool to predict it's dynamic motion, which help in designing a new and good contrast agent. In this article we review the linear and non-linear behavior of the microbubbles and its mathematical models

توصيف النماذج الرياضية لاوساط التباين للموجات فوق الصوتية: استعراض

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الخلاصة:

اوساط التباين النموذجيه المستخدمه في مجال التصوير بالموجات فوق الصوتيه تتألف من فقاعات مايكرويه ذات اقطار اقل من 7 μm وهي مكونة من غاز ومغلفه بقشره بروتينيه ، دهنيه او من البوليمر، تلك الفقاعات توصف بانها ذات استطاره قويه جداً. هناك العديد من النماذج الرياضيه التي تصف السلوك الديناميكي لتلك الفقاعات المايكرويه تحت تاثير الموجات فوق الصوتيه ، يعتبر نموذج Lord Rayleigh اقدم نموذج وهو الاساس لكل النماذج الاخرى وقد تم تعديله من قبل Plesset الذي اضاف اليه تاثير المجال الصوتي فنتج عنه معادله تسمى Rayleigh-Plesset او RP هي معادله تفاضلية غير خطيه من الدرجه الثانية تصف فقاعة تهتز بتاثير مجال صوتي في سائل عديم اللزوجه وغير قابل للانضغاط ذا كثافه ثابتة، تم تعديل هذا النموذج من قبل كل من Noltingk، Neppirasو Poritsky الذين اضافوا تاثير المجال المحيط بالفقاعه وادى ذلك الى معادله تسمى RPNNP والتي تعتبر الخطوه الاولى لبناء نموذج لفقاعه ذات قشرة، بحوث لاحقه اخذت بالاعتبار تاثير انضغاطية السائل على ديناميكية الفقاعة ، والتطور الكبير الذي احدث في هذا المجال كان من قبل Miksis و Keller. الفقاعات المايكروية المستخدمة في اوساط التباين للموجات فوق الصوتية تكون عادة محفوظه بوساطه قشرة رقيقة، الصلابة واللزوجة لهذه القشرة تضيف عوامل اخرى الى السلوك الديناميكي للفقاعة، وهناك عدة نماذج تصف هذه القشرة . ان اكثر نموذجين انتشاراً يصفان الفقاعات المغلفه بقشره هما نموذج Hoff و نموذج Marmottant وهما امتداد لنموذج RP. ان فهم سلوك هذه الفقاعات تحت تاثير الموجات فوق الصوتيه يعطينا وسيله جيده للتنبؤ لحركتها الديناميكيه والتي تساعدنا على تصميم اوساط تباين جديدة وذات كفاءة عالية.

في هذا البحث نستعرض السلوك الخطي وغير الخطي للفقاعات المايكرويه واهم النماذج الرياضية التي تصف ذلك السلوك.

Key words: contrast agent, microbubbles, ultrasound, bubble vibration

Introduction

Ultrasound represents the safest, fastest and least expensive method of several medical diagnosis imaging techniques such as magnetic resonance imaging or x- ray, however, image quality of ultrasound is often inferior, therefore methods for improving image contrast are highly desirable, one of this methods which has growing interest is the contrast agents, usually typical contrast agents of ultrasound imaging composed of microbubbles of smaller than 7 µm in diameter, because it have to pass through capillaries with diameter of about 7µm (through the pulmonary circulation) so this enable them to cross capillary beds, (the diameter of red blood cell is about 7 µm), and giving an upper limit for the particle diameter that is much smaller than the wave length of the sound, these microbubbles if administered intravenously, flood the blood pool and remain within the vascular compartment, it is acting as very powerful scatterers (as secondary sources of ultrasound waves) [1].

Generally, the microbubbles consist of gas coated with a protein, Lipid or Polymer layer [2], protect these bubbles from dissolving in the blood or to coalesce to form large bubbles, when a microbubble subjected to ultrasound it will start to oscillate with the same frequency of the ultrasound waves, but at higher ultrasound intensity the oscillations of the microbubbles become more, extreme and nonlinear behavior will start to appear.

There are several models describe the dynamic behavior of the microbubbles, The model which was derived by Lord Rayleigh in 1917 is the oldest, which describes an empty space in the liquid this model was derived from the Navier-Stokes equation for a spherically symmetric bubble located in an incompressible flow liquid with constant external pressure, this modle provides the theoretical basis in develop the models of nonlinear bubble vibration. In the early 1990s, De Jouge et al. was published studies of scatter and transmission of ultrasound from contrast agents [5,6], Fox, Herz field, Medwin had based the theoretical models on bubble models [7,8], this model was extended by Holm et al. in 1994 to give more complete model for the attenuation and scatter from contrast agents in tissue [9], the experimental incorporation of De Jong and Hoff [10] determined elasticity and friction parameters into the Rayleigh–Plesset model. all these models are non-linear, therefore the solutions must be obtained by using the linear approximations for small amplitude oscillations or by using numerical methods, in this article we will address only to the solutions of the linear approximations.

Interactions between ultrasound and microbubbles

Compared to other particles, gas bubbles in liquids are unique as they are highly efficient scatterers of sound, even if the bubble diameter is much smaller than the wavelength of the sound [3]. Because of this strong acoustic scatter, bubbles have many important acoustics applications, one of these applications is the medical ultrasound contrast agents [4], this unique feature results from the high compressibility of the gas in the bubble, This make the microbubbles markedly expand and contract while tissue molecules are moving only a few angstroms as ultrasound compression and rarefaction wave passes [3].

The change in bubble size is determined by the acoustic power applied, but at diagnostic levels they may halve and double in size [4]. Bubble size affect the natural oscillation frequency (resonance frequency),when the frequency of incident ultrasound waves reach the resonance frequency of the bubbles, they become extremely efficient at translating the ultrasound energy from propagating waves into scattered signals.

The non-linear behavior at higher acoustic pressure is another factor that affect the microbubble response, this due to the fact that can expand more easily than they contract, because the increasing pressure at microbubble with smaller volumes opposes further compression due to their stiffness, while less energy is needed for further expansion, In another words the microbubbles diameter change in asymtrical mode about the radius at equilibrium, in the rarefaction phase, the increase in diameter is larger than decrease in diameter during compression phase.

The insolating waves is returned from the bubble as distorted version, this is known as non-linear response, Bubble oscillations become more complex at higher acoustic pressure, this results in diverging from simple spherical change and further increasing the non-linear properties of the scattered ultrasound waves.

For diagnostic ultrasound imaging, contrast agent must composed of particles (microbubble) that are much smaller in size than the ultrasound wavelength but though are highly powerful ultrasound scatters, The ultrasound signals scattered from microbubbles have a characteristic features that distinguish it from ultrasound signals that scattered from tissue, Understanding of these effects can help in optimizing the equipment of diagnostic ultrasound and also help the manufacturers of contrast agents to design the agents which provide as best information as possible.

The bubble vibration and its mathematical models

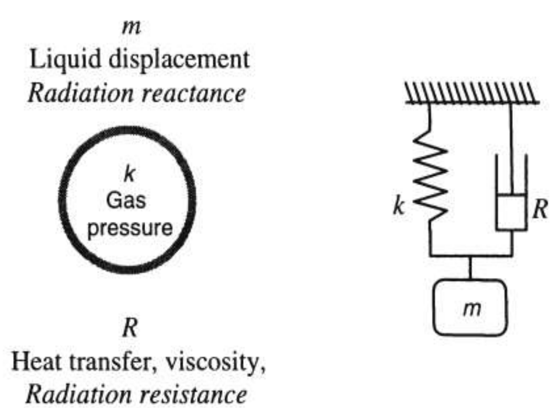
The volume pulsations of the microbubbles in a contrast agent depend on the external oscillating pressure field (Ultrasound waves) and these microbubbles respond in linear or non-linear mode, the radius of the microbubble change linearly in relation with the amplitude of the applied ultrasound wave at low acoustic pressure which result in linear pulsation of microbubble, but at high acoustic pressures, microbubbles pulsation become non-linear, in principle, expansion of bubbles is unlimited unlike the compressibility of the bubble.

At small excitation levels, the bubble wall displacement can be compared to the displacement of a simple one dimensiond mass spring oscillator [6] (figuer 1).

In this case the oscillator is defined by its mass, restoring force, damping, and applied force. This leads to the equation of motion of the bubble, which is expressed as:

$$m\ddot{x} + \beta\dot{x} + S\,x = F_{driv} \qquad (1)$$

where m is the mass of the bubble–liquid system, β is the mechanical resistance related to the dissipation, S is the stiffness of the system, F_{driv} (t) is the driving force, and x (t) is the radial displacement of the bubble wall relative to the initial radius R_0, where x (t) =R(t) - R_0.



Bubble	Mechanical oscillator
Gas pressure	Spring, stiffness
Liquid mass	Mass, inertia
Radiation resistance viscosity, heat transfer	Dash-pot, friction

Figure.1 Analogy between a gas bubble and mechanical oscillators [4].

According to this approximayion ,the motion of the bubble surface (oscillation) almost like the simple harmonic oscillation and the resonance frequency f_r of the bubble for an undamped oscillation is given by:

$$f_r = \frac{1}{2\Pi}\sqrt{\frac{S}{m}} \qquad (2)$$

The stiffness of the gas bubbles in a liquid is that of the enclosed volume of gas that acts like a spring when the bubble is irritated from its equilibrium radius.

The mass of the liquid surrounding the bubble that oscillates with it, result in an inertia. Various frictional mechanisms will damp out the oscillations of the bubble, the damping β in Equation 1 is determined by three important parameters responsible for the damping: ***First***, reradiation damping: In the reradiation damping (resistence), the bubble can act as a secondary source, reradiates the energy of ultrasound, this lead to decrease the energy of the system. ***Second***, damping due to the viscosity of surroundingLiquid: The viscosity of the surrounding fluid, which moves with the bubble wall,also can lead to energy dispersion. ***Third***, thermal damping: the temperature that generated from the expansion and compression of the bubble, which results in a net flow of energy outwards into the surrounding medium, this is another cause to decrease the energy of the system.

The damping coefficients depend on the frequency of the acoustic field and the bubble size. At low frequencies, the damping from liquid viscosity dominates for the smallest bubbles, while thermal damping dominates for the larger bubbles, at high frequencies the radiation damping takes over and becomes the dominating damping mechanism for all bubble sizes[4].The damping coefficients are in the order of 0.1 for bubbles with a diameter between 1 and 10 μm [11].

The basic mathematical models known applied to contrast agents were originally developed for modelling cavitation bubbles which observed on ship's propellers [4], Lord Rayleigh pioneered research on the motion of bubbles by studying inertial cavitation, who studied the collapse of vapor-filled cavities around ship propellers, nearly 60 years after the earliest studies done by Besant on the collapse and growth of a spherical cavity within a continuous liquid medium [12],the model which was derived by Lord Rayleigh is dating from 1917 (equation 3) known as Rayleigh model, all mathmatical models of nonlinear bubble vibration are adopted this model as its basis [13].

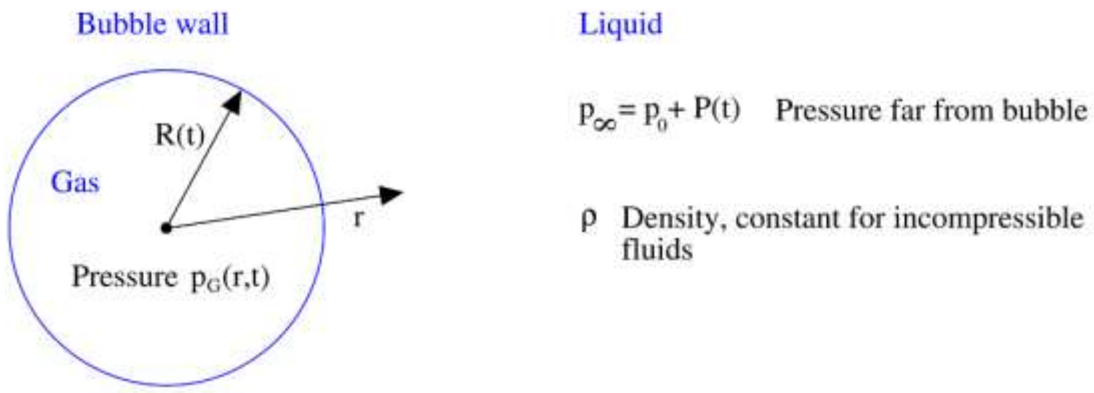


***Figure. 2 Schematic diagram showing the bubble with radius** R(t) **fluid pressure at the bubble wall** pL**, the fluid pressure far from the bubble** P_∞**, the fluid density** ρ **and the gas pressure** P_G*

It describes an empty space in the water, influenced by a constant external pressure. Rayleigh's assumption of an empty space led to the name cavity still used, the Rayleigh equation was derived from the Navier-Stokes equation for a spherically symmetric bubble located in an incompressible flow liquid with constant external pressure[14].

$$\rho_l\left[R\ddot{R}+\frac{3}{2}\dot{R}^2\right]=P_l-\ P_\infty \qquad (3)$$

Here the radius of bobble is a function changing with the time, this relates the radius R (t), velocity $\dot{R}$ (t), acceleration of the bubble surface $\ddot{R}$ (t) (the left side of equation (3) represents inertia, the right side represents restoring stiffness forces), ρ_l is the fluid density, P_l is the fluid pressuer at the bubble surface and P_∞ is the pressuer far from the bubble as shown in figure 2.

A driving acoustic field was included in 1949 by *Plesset* he lett the background pressure P_∞ vary with time as $P_\infty = P_0 + P_{i(t)}$. Here, P_0 is the static background pressure and $P_{i(t)}$ is the driving sound field ($P_{i(t)} = A\sin 2\Pi f t$) [14].

$$\rho_l\left[R\ddot{R}+\frac{3}{2}\dot{R}^2\right]=P_{l(t)}-P_0-P_{i(t)} \qquad (4)$$

This is commonly called the Rayleigh-Plesset equation for the oscillating bubble, It is based on the work by Lord Rayleigh [13]. The Rayleigh-Plesset equation is a second order nonlinear ODE, it is models a bubble oscillating in an inviscid and incompressible fluid of constant density ρ_l.

The surface tension, and liquid viscosity of the surrounding field that shows in (Figure 3) are not included in (equations 4). Noltingk, Neppiras and Poritsky had added the effects of the surrounding field to the expression in equation (4), as this expansion describes the motion of the surrounding field only, with the pressure $\boldsymbol{P_{l(t)}}$ at the bubble surface as a boundary condition [15], they combining the Rayleigh–Plesset equation with the effects of the surrounding field, they obtained the following expression[14].

$$\rho_l\left[R\ddot{R}+\frac{3}{2}\dot{R}^2\right]=P_{\boldsymbol{G}(\boldsymbol{t})}-P_{0}-P_{i(t)}-\left(\frac{2\sigma}{R}+\frac{4\mu\dot{R}}{R}\right) \qquad (5)$$

The effects of the gas inside the bubble are not included in (equation 5). The bubble oscillations change the state of the gas within the bubble, a model of the gas is therefore required.

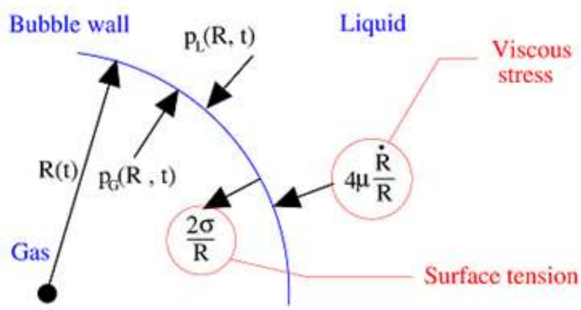


Figure 3: Diagram showing the forces on the bubble surface.

The polytropic law assumes the gas pressure to be uniform within the bubble. This is equivalent to saying that the velocity of the bubble surface is smaller than the speed of sound in the gas. At large radial oscillation amplitudes the surface velocity can reach very high velocities during the compressional phase of the oscillation, violating this assumption, these high velocities will occur in a very small fraction of the oscillation cycle. In the following, the gas is always assumed to follow the polytropic law.

$$p_G(t)\,V^{\gamma}(t) = \text{constant} \qquad (6)$$

Where $p_G(t)$ is the gas pressur, $V(t)$ is the time dependent volume and γ is called the polytropic exponent (for adiabatic processes the γ is the ratio of specific heats, for air γ = 1.4, If the process is isothermal γ = 1) [4].

The gas pressure may be determined by assuming the bubble is initially in equilibrium at time (t_0).
This relating the gas pressure to the undisturbed fluid pressure far from the bubble at time (t) = 0
So,the pressure inside the bubble at time (t) will be

$$p_G(\text{t})\, R^{3\gamma} = p_G(0)\, R_0^{\ 3\gamma} \tag{7}$$

Initially the bubble was in equilibrium, so that the initially gas pressure in sied the bubble have to be the static background pressure P_0 adding to the surface tension effect as in figure *3* i.e.

$$P_{\boldsymbol{G(0)}} = P_0 + \frac{2\sigma}{R_0} \tag{8}$$

$$p_G(\text{t})\, R^{3\gamma} = (P_0 + \frac{2\sigma}{R_0})\, R_0^{\ 3\gamma} \tag{9}$$

$$p_G(\text{t}) = (P_0 + \frac{2\sigma}{R_0}) \left[\frac{R_0}{R}\right]^{3\gamma} \tag{10}$$

By adding the polytropic gas law with the boundary condition to (equation 5), result in the following expression which describes the motion of an ideal gas bubble.

$$\rho_l \left[R\ddot{R} + \frac{3}{2}\dot{R}^2\right] = \left[P_0 + \frac{2\sigma}{R_0}\right]\left[\frac{R_0}{R}\right]^{3\gamma} - \frac{2\sigma}{R} - \frac{4\mu\dot{R}}{R} - P_0 - P_{i(t)} \tag{11}$$

The left-hand side of this ODE for the bubble radius R(t) consists of dynamical pressure terms (inertia) already known to Rayleigh (where R , $\dot{R}$ and $\ddot{R}$ represent the radius, velocity and acceleration of the bubble), (ρ_l) is the density of the liquid. The right-hand side represents restoring stiffness and damping viscous forces which comes from the surface tension at the bubble $(\sigma)$and the liquid viscosity (μ), P_0 is the constant ambient pressure and $P_{i(t)}$ the ultrasound driving, modelled as $(P_{i(t)} = A\cos wt$) with a fixed frequency, and $\boldsymbol{\gamma}$ is the ratio of spesific heats (for air $\boldsymbol{\gamma}$ =1.4 , if the process is isothermal $\boldsymbol{\gamma}$ =1)

This expression commonly called Rayleigh–Plesset–Noltingk–Neppiras–Poritsky (RPNNP) equation [16], which is describes the unshelled bubble oscillating in a viscid and incompressible fluid with fluid constant density ρ_l.

A limiting condition for arriving at a demarcation between compressible flow and incompressible flow is based on the comparison of flow velocity with the velocity of an infinitesimal pressure pulse in the fluid medium (i.e. velocity of sound in the medium). The flow consider incompressible if the ratio of the flow velocity to velocity of the sound in the medium (defined as Mack number) is less than 0.3, if the ratio is greater than 0.3 then the flow is consider as a compressible flow [17], In other words the compressibility effect of surrounding field comes from the hiegh velocity of the bubble wall $\dot{R}$ which coused by the driving sound field, and Equation (11) did not account for liquid compressibility, which becomes a dominant factor as the bubble wall velocity $\dot{R}$ becomes greater than 0.3 of the sonic velocity in the medium [17].

Later researchs in this area addressed this fact of bubble dynamics, Gilmore proposed the first model for cavitation bubble dynamics accounting for liquid compressibility effect (The Gilmore model is suitable for large amplitude bubble oscillations with high Mach numbers)[18]. during the subsequent years major developments occurred in this area by Keller and Kolodoner [19], more precise forms of models for radial motion of cavitation bubbles were resulted by Keller and Miksis [20] and Prosperetti and Lezzi [21].

Two common models for cavitation bubble dynamics in a compressible fluid among scientific community in bubble dynamics are:

1. Keller and Miksis equation [20,22], which considers a compressible liquid.

$$\left(1-\frac{\dot{R}}{c}\right)R\ddot{R}+\left(1-\frac{\dot{R}}{3c}\right)\frac{3}{2}\dot{R}^2=\frac{1}{\rho_l}\left(1+\frac{\dot{R}}{c}\right)\left(P_{G(t)}-P_{\circ}-P_{i(t)}\right)+\frac{\dot{R}}{\rho_l c}\dot{P}_{G(t)}-\frac{4\mu\dot{R}}{\rho_l R}-\frac{2\sigma}{\rho_l R} \quad (12)$$

The factors of type $\left(1\mp\frac{\dot{R}}{c}\right)$ in this model change the inertia due to the compressibility of the liquid, but can cause the solution to become unstable for high Mach-numbers. this model is only meaningful for acoustic Mach-numbers much smaller than one [4].

As the bubble oscillates, it radiates acoustic energy which result in oscillation damping, The term which contians $\dot{\boldsymbol{P}}_{\boldsymbol{G}(t)}$ can predict acoustic radiation damping of the bubble and this term gives an important improvement of the this model, where c is the speed of sound in the liquid [23].

2. Another important variant of the bubble dynamics equation is the model poroposed by Lofstedt et al. and Barber et al. [24,25,26], in this model all

prefactor parentheses containing $\dot{R}/c$ in the Keller and Miksis model are deleted. This leads to the equation:

$$R\ddot{R}+\frac{3}{2}\dot{R}^2=\frac{P_{G(t)}-P_0-P_{i(t)}}{\rho_l}+\frac{\dot{R}}{\rho_l c}\dot{P}_{G(t)}-\frac{4\mu\dot{R}}{\rho_l R}-\frac{2\sigma}{\rho_l R} \qquad (13)$$

It is recommended to express P_l instead of P_G in the equation ١3, where P_l is the pressure at the bubble surface.

Where

$$P_{l(t)}=P_{G(t)}-\frac{4\mu\dot{R}}{R}-\frac{2\sigma}{R} \qquad (14)$$

So we can rewrite equation 14 as follow

$$R\ddot{R}+\frac{3}{2}\dot{R}^2=\frac{P_{l(t)}-P_0-P_{i(t)}}{\rho_l}+\frac{\dot{R}}{\rho_l c}\dot{P}_{G(t)} \qquad (15)$$

This second order nonlinear ODE describes the unshelled bubble oscillating in a viscid and compressible fluid of constant density ρ_l and with acoustic radiation damping, this expression commonly called (modified Rayleigh-Plesset equation)

Coated bubble vibration

The gas bubbles used in ultrasound contrast agents are normally stabilized by a thin shell. The shell can influence the mechanical properties of the bubble by increasing its stiffness and by introducing added viscous damping.The stiffness and viscosity of the shell of the encapsulated bubble add a another foctors to the acoustical behavior of the bubble, the shell stiffness causes an increase in resonance frequency of the bubble and the viscosity of the shell causes an increase in the bubble damping [4].

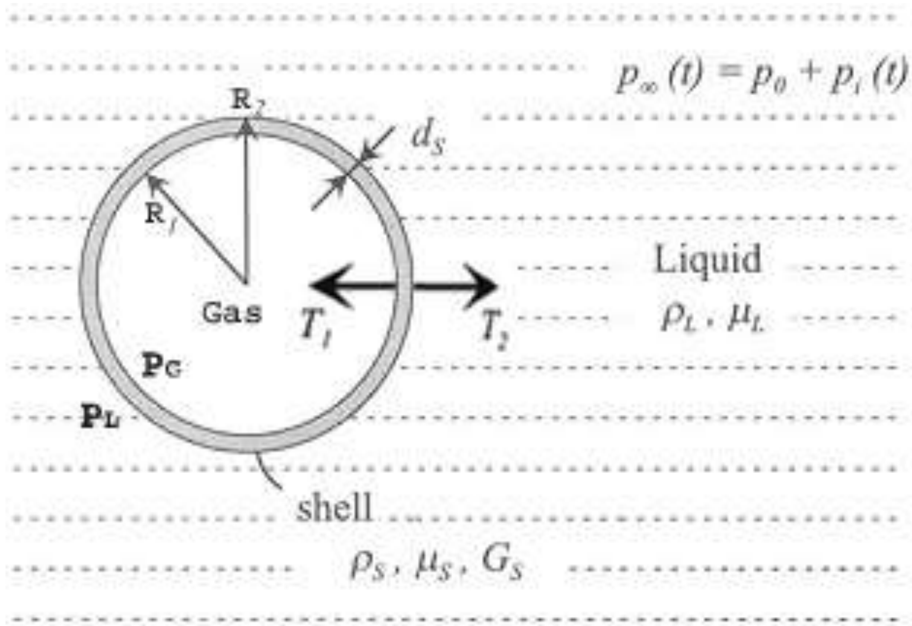


Figure 4:* *Definition of the radial stress and pressures on the bubble shell, Where $T_1$and T_2 are the stresses at the inner and outer surfaces of the shell, $d_s = d_s(t)$ is the instantaneous shell thickness, The shell is thin compared to the bubble radius (d_s << R) and it may vary as the bubble radius R = R(t) oscillates, The outer shell radius is $R = R_{outer}\ (t)$, The inner shell radius R_{inner} is expressed as $R_{inner} = R - d_s$ [4].

In other words for coated bubble the tension across the thin shell due to elasticity and viscosity (the difference in radial stress between the inner and outer shell surface) gives the pressure difference across the shell , So a new foctors will add to the pressure $P_{l(t)}$ at the surface of the bubble in equations (14) and this pressure can be found by calculate the difference in radial stress across the shell $(T_2 - T_1)$ due to elastic and viscous forces in the shell, and the gas pressure inside the bubble $P_{G(t)}$ which calculated from a polytropic gas model.

The first model of the encapsulated microbubbles were modeled by De Jong et al. [5], the experimental incorporation of De Jong and Hoff [10] determined elasticity and friction parameters into the Rayleigh–Plesset model, Linear visco-elastic constitutive equations used by Church [27] to describe the shell, since then many models have been determined to investigate the effect of the shell on the bubble's vibration, e.g [28,29].

The pressures and stresses are illustrated in figure 4, the boundary conditions require continuity in radial stress at the shell-liquid and shell-gas interfaces.

These boundary conditions are:

$$\left.\begin{array}{ll} T_l = T_2 & \text{Continuity at outer shell surface.} \\ p_G = -T_1 & \text{Continuity at inner shell surface.} \end{array}\right\} \quad (16)$$

The expressions for the stresses involved are:

$$T_l = -p_l - \frac{4\mu_l \dot{R}}{R} \quad \text{Stress at the bubble-liquid surface.}$$

$$T_2 - T_1 \quad \text{Stress difference across the shell.}$$

$$P_G = P_0\left(\left[\frac{R_0}{R}\right]^{3\gamma}\right) \quad \text{Gas pressure inside the bubbel}$$

These equations are combined with the boundary conditions (16), giving an
expression for the pressure $P_{l(t)}$ at the bubble surface.

$$p_l = P_0\left(\left[\frac{R_0}{R}\right]^{3\gamma}\right) - \frac{4\mu_l \dot{R}}{R} - (T_2 - T_1) \quad (17)$$

Where μ_l is the viscosity of fluid. The effect of surface tension has not been included here, where it is assumed that the shell reduces the surface tensions of both the gas-shell and the shell-liquid interfaces, so that these can be neglected [4].

The common models for tension across the thin shell $(T_2 - T_1)$ due to elasticity and viscosity are summarized in the following four different models, the thin shell in these models is described as a visco-elastic solid (using the Lame coefficients and shear viscosity) [4] .

- Linear material - nonlinear geometry

$$T_2 - T_1 = 12\frac{d_{se}}{R_0}\left(\frac{1}{1+x}\right)^4 (G_s x + \mu_s \dot{x}) \quad (18)$$

This model is nonlinear relation, the nonlinearity in this equation comes from the geometry of the system (in other words from $\left(\frac{1}{1+x}\right)^4$), assuming that the material properties stay linear, the validity of this combination of linear material and nonlinear geometry is questionable [4,30].

- Fully linearized model

$$T_2 - T_1 = 12\frac{d_{se}}{R_0}(G_s x + \mu_s \dot{x}) \qquad (19)$$

This model is linear relation and it is appealing as a first order model. It predicts that the shell is equally stiff no matter how much it is expanded or contracted. This
models gives no softening of the shell as it expands, and it is suspected to overestimate the shell stiffness in expansion [4].

- Intermediate model

$$T_2 - T_1 = 12\frac{d_{se}}{R_0}\left(\frac{1}{1+x}\right)^2(G_s x + \mu_s \dot{x}) \qquad (20)$$

This model is a compromise between the two assumptions, the factor $\left(\frac{1}{1+x}\right)^2$ adds some softening to the shell as it expands, but not so much as in equation (20) [4].

- Exponential shell

$$T_2 - T_1 = 12\frac{d_{se}}{R_0}(G_s(1 - e^{-x/x_0})x + \mu_s\, e^{-x/x_1}\ \dot{x}) \qquad (21)$$

This model is an exponential relation between pressure and radial strain, which has been found successful in describing the elasticity of blood vessel walls,It was suggested used on the shell of contrast agents by *Angelsen et al.* [31]. This model is appealing as it gives softening in shell expansion, in addition, it gives a monotonic decrease in pressure as the shell is expanded.

Where μ_s is shear viscosity in the shell (Its an equivalent viscosity of the shell and gas which represents both visous and thermal losses [32]) , G_s is shear modulus of the shell, d_{se} is the shell thickness at equilibrium, R_0 is the bubble radius at equilibrium, $x = \frac{R-R_0}{R_0}$, $\dot{x} = \frac{\dot{R}}{R_0}$, x_0 and x_1 are two constants respectively $\frac{1}{8}$, $\frac{1}{4}$ [32], in the equations (18 to 21) the terms which contain G_s represent the shell stiffness and the terms which contain μ_s represent the bubble damping due the viscosity of the shell [4].

By choosing and the Exponential shell model (equation (21)) and compensation with the equation (17) which describes the pressure $P_{l(t)}$ at the shell bubble surface, substituting the result into equation (15), result in the folloing expration :

$$R\ddot{R} + \frac{3}{2}\dot{R}^2 = \frac{P_0\left(\left[\frac{R_0}{R}\right]^{3\gamma} - 1\right) - P_{i(t)}}{\rho_l} - \frac{4\mu_l \dot{R}}{\rho_l R} - \frac{1}{\rho_l}\left[12\frac{d_{se}}{R_e}\left(G_s\left(1 - e^{-\frac{R-R_0}{x_0 R_0}}\right)\frac{R-R_0}{R_0} + \mu_s \frac{\dot{R}}{R_0} e^{-\frac{R-R_0}{x_1 R_0}}\right)\right] + \frac{R}{\rho_l c}\dot{P}_{G(t)} \quad (22)$$

This model is usually called Hoff's model, Hoff et al. in 2000 derives their model from Church's model 1995 which adopted on the modified Rayleigh-Plesset model,and due to the experimental incorporation of De Jong and Hoff [4].

Hoff et al. model depend on viscosity and shear modulus of the shell substance, the shear modulus and viscosity of the shell are in general frequency dependent, but in this modle it is assumed that they are constant for the frequency range of the medical ultrasound imaging.

Another approach takes into account the physical properties of the monolayer of the bubble's shell, sach model was suggested by Marmottant et al. equation (23) [34] .

$$\rho_l\left[R\ddot{R} + \frac{3}{2}\dot{R}^2\right] = \left[P_0 + \frac{2\sigma(R_0)}{R_0}\right]\left[\frac{R_0}{R}\right]^{3\gamma}\left[1 - \frac{3\gamma}{c}\dot{R}\right] - \frac{2\sigma(R)}{R} - \frac{4\mu_l \dot{R}}{R} - \frac{4\mu_s \dot{R}}{R^2} - P_0 - P_{(t)} \quad (23)$$

Marmottant model is identical to a unshelled bubble model (equation 15), except from the shell viscosity term $\frac{4\mu_s \dot{R}}{R^2}$ and the effective surface tension term $2\sigma_{(R)}$ the characteristic of this model, is a variable effective surface tension, the effective surface tension at the bubble wall varies along three linear regimes and these regimes depend on the bubble area, in other words, during the oscillation, the dynamical surface tension will vary, since it is a function of the bubble area, therefore the effective surface tension write as $\sigma_{(R)}$ to emphasize this dependence, so the elasticity of the shell is vary with the bubble radius [33] .Marmottant's model only needs three parameters to describe the effective surface tension: the buckling area of the bubble A_{buckling} below which the surface buckles, an elastic compression modulus

Y that gives the slope of the elastic regime and a critical break-up tension $\sigma_{\text{break-up}}$, which predicts for which bubble area the coating ruptures (figure 5), with the result that the effective surface tension saturates at σ_{Liquid} [33] . These three regimes can be expressed as follows:

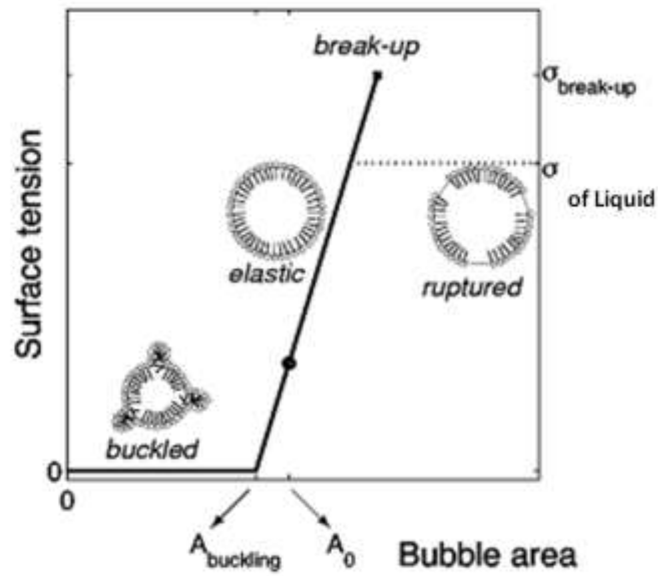


Figure 5: Model for the dynamic surface tension of a monolayer coated bubble (continuous line). The shell has a fixed number of lipid molecules, which corresponds to a monolayer at equilibrium (when area is A_0). The effective surface tension saturates to the liquid value $\sigma_{(Liquid)}$ (broken line) after the break-up effective surface tension has been reached $\left(\sigma_{(break-up)} > \sigma_{(Liquid)}\right)$[34]

$$\sigma_{(R)} = \begin{cases} zero\ \ if\ R \le R_{buckling} \\ Y\left(\frac{R^2}{R_{buckling}^2} - 1\right)\ if\ R_{buckling} \le R \le R_{breakup} \\ \sigma_{(Liquid)}\ if\ R \ge R_{\text{ruptured}} \end{cases} \qquad (24)$$

Marmottant’s model extends the oscillation to unbounded, so its suitable to describe the coated bubble osculation with large amplitudes

In general the aim of using the contrast agent is enhancement the ultrasound diagnostic imaging, to reach this goal the transducer should operate at the resonance frequency of the microbubbles which are composing the contrast agent, This permits to get the best echo at the fundamental mode and at the second-harmonic mode, so knowledge of resonant frequencies of contrast microbubbles is important for the optimization of ultrasound contrast imaging and therapeutic techniques, estimates the resonance frequencies of contrast microbubbles for the linear oscillation regime is useful and best method, even though the resonant frequency of the bubble practically influenced by the amplitude of driving sound which may causes nonlinear behavior [36], to get the resonant frequencies of the microbubbles we linearize the nonlinear ordinary differential equation of the microbubble oscillation, this lead to the general linear ODE form like equation (1)

$$m\ddot{x} + \beta\dot{x} + S\,x = -4\Pi R_0\, P_{\boldsymbol{i(t)}}$$

Where $(-4\Pi R_0^2\ P_{i(t)})$ is the driving force due to the driving acoustic pressure $P_{\boldsymbol{i(t)}}$.

Linearization

1- Hoff’s model

To make this linearisation assume that the applied pressure $P_{\boldsymbol{i(t)}}$ has low amplitude and causes the radius displacement of the bubble wall relative to the initial radius R_0, according to $x(t) = R(t) - R_0 \Rightarrow R(t) = R_0(1 + x(t))$ where $x << 1$ and retain only first order terms in x, Recall equation (10) and substitute these assumptions in it.

$$P_{\boldsymbol{G(t)}} = P_0\left[\frac{R_0}{R}\right]^{3\gamma} = P_0\left(\left[\frac{1}{1+x}\right]^{3\gamma}\right) \qquad (25)$$

(The effect of surface tension has not been included here. It is assumed that the shell reduces the surface tensions of both the gas-shell and the shell-liquid interfaces, so that these can be neglected [4].)

By using the binomial theorem to simplified the pressure term in equatoin (25)

$$\left[\frac{1}{1+x}\right]^{3\gamma} \approx (1-3\gamma x)$$

Which result in (26)

$$P_G(R.t) \approx P_0(1-3\gamma x)$$

$$\dot{P}_G(R.t) \approx -3\gamma P_0 \dot{x}$$

substitute equations (26) in equation (22)

$$R_0^2(1+x)\ddot{x}+\frac{3}{2}\dot{x}^2=\frac{P_0(1-3\gamma x)-P_0-P_{i(t)}}{\rho_l}-\frac{3\gamma P_0 R_0}{\rho_l c}\dot{x}-\frac{4\mu}{\rho_l}\dot{x}-\frac{1}{\rho_l}\left[12\frac{d_{se}}{R_0}(G_s(1-e^{-x/x_0})x+\mu_s e^{-x/x_1}\dot{x})\right] \quad (27)$$

retaining only the linear terms in x, and comper it with the generl linear ODE form (equation (1))

$$\ddot{x}+\frac{3}{\rho_l R_0^2}\left[\frac{P_0\gamma R_0}{c}+\frac{4}{3}\mu_l+4\frac{d_{se}}{R_0}\mu_s\right]\dot{x}+\frac{3}{\rho_l R_0^2}\left[P_0\gamma+4\frac{d_{se}}{R_0}G_s\right]x=-\frac{P_{i(t)}}{\rho_l R_0^2}$$

(28)

This equation represent the oscillation of the encapsulated bobble with linear acoustic radiation damping which have total damping :

$$\beta=\frac{3}{\rho_l R_0^2}\left[\frac{P_0\gamma R_0}{c}+\frac{4}{3}\mu_l+4\frac{d_{se}}{R_0}\mu_s\right] \quad (29)$$

Or

$$\beta=\beta_c+\beta_l+\beta_s \quad (30)$$

$\beta_c=\frac{3P_0\gamma}{\rho_l c R_0}$ which represent the damping due to acoustic radiation

$\beta_l=\frac{4\mu_l}{\rho_l R_0^2}$ which represent the damping due to liquid viscosity (31)

$\beta_s=12\frac{d_{se}}{\rho_l R_0^3}\mu_s$ which represent the damping due to shell viscosity

And the resonant frequency will be as follow:

$$f_r = \frac{1}{2\Pi R_0}\sqrt{\frac{3}{\rho_l}\left[\gamma P_0 + 4\frac{d_{se}}{R_0}G_s\right]} \quad (32)$$

2-Marmottant's model

For small vibration amplitudes, i.e. $|R - R_0| \ll R_0$ the shell is in elastic state and the radius of the bubble is in the regime of $R_{buckling} \le R \le R_{breakup}$ Within this regime the surface tension is a linear function of the R_0^2.

So from equation (24) the surface tension can be linearized around a constant value [37] as follow:

$$\sigma_{(R)} = Y\left(\frac{R^2}{R_0^2} - 1\right) \approx +2Y\left(\frac{R}{R_0} - 1\right) \quad (33)$$

The effective surface tension term in equation (23) can be written as follow:

$$-\frac{2\sigma_{(R)}}{R} = -4Y\left[\frac{1}{R_0} - \frac{1}{R}\right] \quad (34)$$

Where Y is the elastic compression modulus, for most shell used in contrast agent usualy $Y \gg \sigma_{(R_0)}$ of the surrounding liquid therefor The term $\frac{2\sigma_{(R_0)}}{R_0}$ can be neglected, Substitute equation (34) into equation (23) lead to

$$\rho_l\left[R\ddot{R} + \frac{3}{2}\dot{R}^2\right] = P_0\left[\frac{R_0}{R}\right]^{3\gamma}\left[1 - \frac{3\gamma}{c}\dot{R}\right] - 4Y\left[\frac{1}{R_0} - \frac{1}{R}\right] - \frac{4\mu_l\dot{R}}{R} - \frac{4\mu_s\dot{R}}{R^2} - P_0 - P_{\boldsymbol{i(t)}} \quad (35)$$

To linearize equation (33) assume that the applied pressure $P_{i(t)}$ has amplitude and causes the radius displacement of the bubble wall relative to the initial radius R_0, according to $x(t) = R(t) - R_0 \Rightarrow R(t) = R_0(1 + x(t))$ where $x << 1$ and retain only first order terms in x, Substitute these assumptions in (35) and using the binomial theorem as in equation (26), with retaining the linear terms in x only, and comper the result with the generl linear ODE form (equation (1)), this leade to :

$$\ddot{x}+\frac{1}{\rho_l}\left[\frac{3\gamma P_0}{cR_0}+\frac{4\mu_l}{R_0^2}+\frac{4\mu_s}{R_0^3}\right]\dot{x}+\frac{1}{\rho_l R_0^2}\left[3\gamma P_0+\frac{4Y}{R_0}\right]x=-\frac{P_{i(t)}}{\rho_l R_0^2} \qquad (36)$$

This equation represent the oscillation of the encapsulated bobble with linear acoustic radiation damping which have a damping :

$$\beta=\frac{1}{\rho_l}\left[\frac{3\gamma P_0}{cR_0}+\frac{4\mu_l}{R_0^2}+\frac{4\mu_s}{R_0^3}\right] \qquad (37)$$

And resonant frequency

$$f_r=\frac{1}{2\Pi R_0}\sqrt{\frac{3\gamma P_0}{\rho_l}+\frac{4Y}{R_0\rho_l}} \qquad (38)$$

For unshelld bubble, equations (32 & 38) are provide the resonant frequency as expected whereas the shear modulus G_s in equation (32) and the elastic compression modulus Y in equation (38) are vanish, therefore the resonant frequency for such bubble is:

$$f_r=\frac{1}{2\Pi R_0}\sqrt{\frac{3\gamma P_0}{\rho_l}} \qquad (39)$$

Conclusion

The microbubbles have strong acoustic scatter, the non-linear behavior at higher acoustic pressure is influential factor that affect the microbubble response.

It is possible to predict the dynamic behavior for the motion of the bubble under the action of ultrasound, There are many models describe the dynamic behavior of the microbubbles, the bubble size, the rheological properties of the surrounding filed and of the shell of the bubble are the domain factors in any useful models.

When the bubble wall velocity $\dot{R}$ becomes greater than 0.3 of the sonic velocity in the medium, the compressibility of the liquid will change the inertia of the bubble, so this fact of bubble dynamics should be take into consideration

The gas bubbles used in ultrasound contrast agents are normally stabilized by a thin shell, there are some models which nearly have different parameters such as the different between Hoff model and Marmottant Model, one of them depend on viscosity and elasticity of the shell substance and the other depend on the viscosity and physical properties of the monolayer microbubbles shell, despite that we can see clearly in equations (28 & 36) the stiffness and viscosity of the shell of the encapsulated bubble add a another foctors to the acoustical behavior of the bubble, the shell stiffness causes an increase in resonance frequency of the bubble and the viscosity of the shell causes an increase in the bubble damping.

The results of many research proves that the results of Hoff's model and Marmottant's model are almost identical together and there are a good matching between their theoretical results and practical results for most contrast agents with frequencies range of the medical ultrasound imaging [34, 35].

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