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DYNAMICS OF ULTRASOUND CONTRAST AGENTS WITH LIPID COATING

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Abstract

Encapsulated gas microbubbles, known as ultrasound contrast agents, are widely used in ultrasonic medical diagnostics and therapy. Ultrasound contrast agents typically consist of a gas core surrounded by a shell of albumin or lipid. Existing theoretical models of contrast agents assume that the encapsulating coating behaves as an elastic (or viscoelastic) solid. However, experimental data available in the literature for lipid-shelled agents indicate that the lipid coating exhibits properties of a viscoelastic fluid rather than a viscoelastic solid. The present paper proposes a new theoretical model for a lipid-shelled contrast agent microbubble. The model describes the encapsulating coating as a linear viscoelastic fluid and incorporates the translational motion of the bubble. It is shown that theoretical predictions of the new model are in good agreement with experimentally measured translational displacements of lipid-shelled microbubbles exposed to a high-intensity ultrasound field.

INTRODUCTION

Ultrasound contrast agents are micron-sized artificial gas bubbles surrounded by a shell of albumin, lipid, or other biocompatible material [1]. These bubbles are injected into the bloodstream in order to increase blood-tissue contrast during an ultrasonic examination. The function of the shell is to stabilize bubbles against dissolution and coalescence. This technique is effectively used in contrast echocardiography. Targeted imaging and localized drug delivery are examples of other clinical applications of contrast agents [5]. Targeted agents are taken up by specific tissues or adhere to specific sites in the body. By enhancing the acoustic differences between normal and abnormal parts of organs, these tissue-specific agents improve the detectability of abnormalities, such as lesions, inflammatory processes and thrombi. In addition, targeted agents can carry drugs or genes to be delivered to a specific site or tissue, which provides unprecedented possibilities for a highly selective therapeutic action. At the same time, contrast bubbles can induce deleterious bioeffects and damage, such as undesirable destruction of tissues and detrimental production of free radicals in blood [10]. There is therefore increased need for a thorough understanding of the dynamics of contrast agents.

Existing theoretical models of contrast agents assume that the encapsulating coating behaves as an elastic (or viscoelastic) solid [4,7,9,11,13]. However, experimental data available in the literature for lipid-shelled agents indicate that the lipid coating exhibits properties of a viscoelastic fluid rather than a viscoelastic solid [3,6,14]. It is the purpose of the present paper to verify this hypothesis. To this end, a new theoretical model for a lipid-shelled contrast agent microbubble is developed that describes the encapsulating coating as a linear 3-constant Oldroyd fluid. The model also incorporates the translational motion of the bubble. The validation of the model is carried out by comparing its predictions with available experimentally measured translational displacements of lipid-shelled contrast agents.

MODEL FORMULATION

Consider a spherical encapsulated gas bubble immersed in a fluid and undergoing radial oscillation in response to an imposed acoustic field. Assuming that the ambient fluid and the encapsulating layer are incompressible, from the continuity equation it follows that both the fluid velocity and the velocity inside the bubble shell obey the equation:

$$\nabla \cdot \boldsymbol{v} = 0 , \tag{1}$$

where $\boldsymbol{v}$ stands for both of the above velocities. In view of spherical symmetry, from (1) it follows that

$$v(r,t) = \frac{R_1^2(t)\dot{R}_1(t)}{r^2} , \tag{2}$$

where $v(r,t)$ is the radial component of $\boldsymbol{v}$, $R_1(t)$ is the inner radius of the bubble shell, and the overdot denotes the time derivative. If $R_1 \le r \le R_2$, where $R_2(t)$ denotes the outer radius of the bubble, v is the velocity inside the encapsulating layer; if $r > R_2$, v is the velocity of the ambient fluid. Also, the assumption of incompressible shell gives:

$$R_2^3 - R_1^3 = R_{20}^3 - R_{10}^3 , \qquad R_1^2\dot{R}_1 = R_2^2\dot{R}_2 , \tag{3}$$

where R_{10} and R_{20} are respectively the inner and the outer radii of the bubble shell at rest. These equations are used in further calculations.

Conservation of radial momentum yields [12]

$$\rho\left(\frac{\partial v}{\partial t}+v\frac{\partial v}{\partial r}\right)=-\frac{\partial p}{\partial r}+\frac{\partial \tau_{rr}}{\partial r}+\frac{3\tau_{rr}}{r}\,. \tag{4}$$

Here ρ is equal to ρ_S or ρ_F, ρ_S and ρ_F are respectively the equilibrium densities of the shell and the ambient fluid, p is the pressure within the shell, p_S, or the fluid pressure, p_F, and τ_{rr} is the stress deviator in the shell, $\tau_{rr}^{(S)}$, or that in the fluid, $\tau_{rr}^{(F)}$.

The boundary conditions at the two interfaces are given by

$$P_g(R_1,t)=p_S(R_1,t)-\tau_{rr}^{(S)}(R_1,t)+\frac{2\sigma_1}{R_1}\,, \tag{5a}$$

$$p_S(R_2,t)-\tau_{rr}^{(S)}(R_2,t)=p_F(R_2,t)-\tau_{rr}^{(F)}(R_2,t)+\frac{2\sigma_2}{R_2}+P_{ac}(x,t)\,, \tag{5b}$$

where $P_g(R_1,t)$ is the pressure of the gas inside the bubble, σ_1 and σ_2 are the surface tension coefficients for the corresponding interfaces, and $P_{ac}(x,t)$ is the driving acoustic pressure at the location of the bubble. Note that we intend to allow for the translational motion of the bubble at a later time. Therefore the current location of the bubble is indicated by the spatial argument x in $P_{ac}(x,t)$, assuming that the time-dependent position of the bubble centroid in an inertial frame is specified by $x(t)$.

Integrating (4) over r from R_1 to R_2 using the parameters appropriate for the encapsulating layer and from R_2 to ∞ using those appropriate for the ambient fluid, assuming that the fluid pressure at infinity is equal to the hydrostatic pressure P_0, and combining the resulting equation with (5), one obtains

$$R_1\ddot{R}_1\left[1+\beta\frac{R_1}{R_2}\right]+\dot{R}_1^2\left[\frac{3}{2}+\beta\left(\frac{4R_2^3-R_1^3}{2R_2^3}\right)\frac{R_1}{R_2}\right]$$
$$=\frac{1}{\rho_S}\left[P_g(R_1,t)-\frac{2\sigma_1}{R_1}-\frac{2\sigma_2}{R_2}-P_0-P_{ac}(x,t)+3\int_{R_1}^{R_2}\frac{\tau_{rr}^{(S)}(r,t)}{r}\,dr+3\int_{R_2}^{\infty}\frac{\tau_{rr}^{(F)}(r,t)}{r}\,dr\right], \tag{6}$$

where $\beta=\left(\rho_F-\rho_S\right)/\rho_S$.

Assuming that the behavior of the gas core is adiabatic, one has

$$P_g(R_1,t)=P_{g0}\left(\frac{R_{10}}{R_1}\right)^{3\gamma}, \tag{7}$$

where P_{g0} is the equilibrium gas pressure in the bubble and γ is the ratio of specific heats.

The rheological behavior of the bubble shell will be approximated by the linear 3-constant Oldroyd model which can be expressed as [2]

$$\tau_{rr}^{(S)} + \lambda_{S1} \frac{\partial \tau_{rr}^{(S)}}{\partial t} = 2\eta_S \left(v_{rr} + \lambda_{S2} \frac{\partial v_{rr}}{\partial t} \right), \tag{8}$$

where $v_{rr} = \partial v / \partial r$ is the radial component of the rate-of-strain tensor, λ_{S1} is the relaxation time of the shell, η_S is the shear viscosity of the shell, and λ_{S2} is the retardation time of the shell. Substitution of (2) into (8) yields

$$\tau_{rr}^{(S)} + \lambda_{S1} \frac{\partial \tau_{rr}^{(S)}}{\partial t} = -\frac{4\eta_S}{r^3} \left[R_1^2 \dot{R}_1 + \lambda_{S2} \left(R_1^2 \ddot{R}_1 + 2R_1 \dot{R}_1^2 \right) \right]. \tag{9}$$

Equation (9) suggests that $\tau_{rr}^{(S)}(r,t)$ can be written as

$$\tau_{rr}^{(S)}(r,t) = -\ 4\eta_S \frac{D_S(t)}{r^3}\ . \tag{10}$$

Substituting (10) into (9) shows that the function $D_S(t)$ obeys the equation

$$D_S + \lambda_{S1} \dot{D}_S = R_1^2 \dot{R}_1 + \lambda_{S2} \left(R_1^2 \ddot{R}_1 + 2R_1 \dot{R}_1^2 \right). \tag{11}$$

Using (10) and (3), the first integral term in (6) is calculated as

$$3 \int_{R_1}^{R_2} \frac{\tau_{rr}^{(S)}(r,t)}{r}\ dr = -\ 4\eta_S \frac{D_S(t) \left(R_{20}^3 - R_{10}^3 \right)}{R_1^3 R_2^3}\ . \tag{12}$$

The ambient fluid will also be described by a linear 3-constant Oldroyd model

$$\tau_{rr}^{(F)} + \lambda_{F1} \frac{\partial \tau_{rr}^{(F)}}{\partial t} = 2\eta_F \left(v_{rr} + \lambda_{F2} \frac{\partial v_{rr}}{\partial t} \right). \tag{13}$$

Note that for $\lambda_{F1} = \lambda_{F1} = 0$, (13) reduces to the ordinary equation that describes a viscous Newtonian fluid so that equations derived below can also be applied if the ambient fluid is water, which is usually the case in laboratory experiments. Substituting (2) into (13) and representing $\tau_{rr}^{(F)}(r,t)$ as

$$\tau_{rr}^{(F)}(r,t) = -\ 4\eta_F \frac{D_F(t)}{r^3}, \tag{14}$$

one has

$$D_F + \lambda_{F1}\dot{D}_F = R_1^2\dot{R}_1 + \lambda_{F2}\left(R_1^2\ddot{R}_1 + 2R_1\dot{R}_1^2\right). \tag{15}$$

The second integral term in (6) takes the form

$$3\int_{R_2}^{\infty} \frac{\tau_{rr}^{(F)}(r,t)}{r}\ dr = -\ 4\eta_F \frac{D_F(t)}{R_2^3}. \tag{16}$$

Substitution of (7), (12), and (16) into (6) yields

$$R_1\ddot{R}_1\left[1+\beta\frac{R_1}{R_2}\right] + \dot{R}_1^2\left[\frac{3}{2}+\beta\left(\frac{4R_2^3-R_1^3}{2R_2^3}\right)\frac{R_1}{R_2}\right]$$
$$= \frac{1}{\rho_S}\left[P_{g0}\left(\frac{R_{10}}{R_1}\right)^{3\gamma} - \frac{2\sigma_1}{R_1} - \frac{2\sigma_2}{R_2} - 4\eta_F\frac{D_F(t)}{R_2^3} - 4\eta_S\frac{D_S(t)\left(R_{20}^3-R_{10}^3\right)}{R_1^3R_2^3} - P_0 - P_{ac}(x,t)\right]. \tag{17}$$

Equation (17) can be modified to take account of the translation motion of the bubble and radiation losses due to the compressibility of the ambient fluid. The modification can be performed by directly adopting necessary corrections from the equations of motion obtained in [8]. The result is

$$R_1\ddot{R}_1\left[1+\beta\frac{R_1}{R_2}\right] + \dot{R}_1^2\left[\frac{3}{2}+\beta\left(\frac{4R_2^3-R_1^3}{2R_2^3}\right)\frac{R_1}{R_2}\right] - \frac{1}{c}\frac{\rho_F}{\rho_S}H = \frac{\rho_F}{\rho_S}\frac{\dot{x}^2}{4}$$
$$+ \frac{1}{\rho_S}\left[P_{g0}\left(\frac{R_{10}}{R_1}\right)^{3\gamma} - \frac{2\sigma_1}{R_1} - \frac{2\sigma_2}{R_2} - 4\eta_F\frac{D_F(t)}{R_2^3} - 4\eta_S\frac{D_S(t)\left(R_{20}^3-R_{10}^3\right)}{R_1^3R_2^3} - P_0 - P_{ac}(x,t)\right], \tag{18}$$

where

$$H = \left[1+\beta\frac{R_1}{R_2}\right]^{-1}\left\{R_1\frac{dG}{dt} + 2R_1\dot{R}_1\ddot{R}_1\left[1+\beta\frac{R_1^4}{R_2^4}\right] + 2\dot{R}_1^3\left[1+\beta\frac{R_1^4\left(2R_2^3-R_1^3\right)}{R_2^7}\right]\right\}, \tag{19}$$

c is the sound speed in the ambient fluid, and G denotes the right-hand side of (18). The compressibility correction is given by the last term on the left-hand side of (18), while the first term on the right-hand side of (18) provides the coupling with the translational equation. This latter is given by

$$m_b \ddot{x} + \frac{2\pi}{3}\rho_F \frac{d}{dt}\left(R_2^3 \dot{x}\right) = -\frac{4\pi}{3} R_2^3 \frac{\partial}{\partial x} P_{ac}(x,t) + F_d , \tag{20}$$

where m_b is the mass of the bubble, the second term on the left-hand side of (20) is the added mass force, the first term on the right-hand side is the acoustic radiation force, and F_d is the viscous drag force which can be taken, for example, in the form of Oseen’s law [12]:

$$F_d = -\frac{1}{4}\pi\eta_F R_2 \dot{x}\left(24 + 9\rho_F R_2 |\dot{x}|/\eta_F\right). \tag{21}$$

Finally, for $D_S(0) = D_F(0) = 0$, from (18) it follows that P_{g0} is given by

$$P_{g0} = P_0 + \frac{2\sigma_1}{R_{10}} + \frac{2\sigma_2}{R_{20}}. \tag{22}$$

It is also worth noting that in the general case $\dot{x}$ in (18) and (20) should be considered as the velocity of the bubble with respect to the velocity of the surrounding liquid. That is, if there is a stream in the bulk liquid, due to the propagation of the acoustic wave and so forth, $\dot{x}$ should be replaced with $\dot{x} - v_{ex}$, where v_{ex} denotes the liquid velocity unrelated to the presence of the bubble.

MODEL VALIDATION

To validate the proposed model, experimental data obtained for the contrast agent MP1950 in [6] were used. MP1950 is a phospholipid-shelled microbubble with a decafluorobutane core. The ambient fluid used in [6] was water, i.e., $\lambda_{F1} = \lambda_{F1} = 0$. MP1950 was insonified with a single 20-cycle acoustic pulse with a pressure amplitude of 180 kPa and a center frequency of 2.25 MHz. To evaluate the shell parameters λ_{S1}, λ_{S2}, and η_S, theoretical radius-time curves obtained from the model were fitted to experimental curves measured in [6] by the least squares method. The other gas and shell parameters were chosen to be $\gamma = 1.07$, $\rho_S = 1100$ kg/m^3, $\sigma_1 = 0$ N/m, $\sigma_2 = 0.033$ N/m, and $R_{20} - R_{10} = 2$ nm. The estimated values for λ_{S1}, λ_{S2}, and η_S were then used to calculate expected translational displacement for bubbles of different size. The obtained results are depicted in Figure 1. Shown by circles is experimental data obtained in [6]. The solid line corresponds to the best-fit values of the shell parameters $\lambda_{S1} = 1.5 \cdot 10^{-8}$ s, $\lambda_{S2} = 10^{-10}$ s, and $\eta_S = 1.33$ Pa s, which were obtained by fitting theoretical and experimental radius-time curves for a 0.79-μm radius bubble. For comparison, the dashed line reproduces the theoretical curve obtained in [6] assuming that the lipid coating behaves as a viscoelastic solid. It is seen that the new (Oldroyd) model provides a much better agreement between theory and experiment.

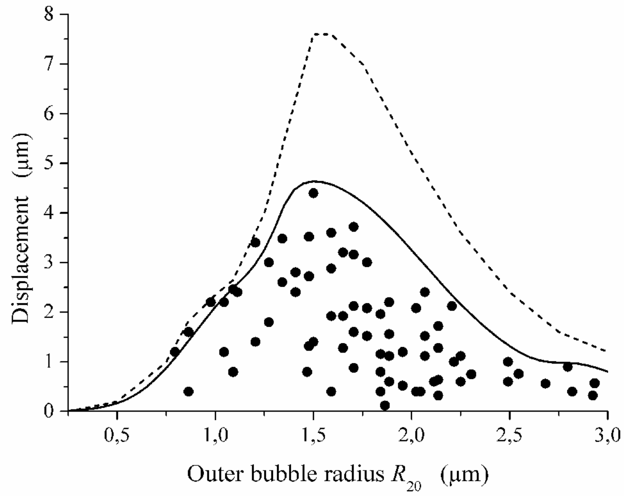

Figure 1. Experimental and theoretical translational displacement as a function of equilibrium bubble radius. Circles indicate experimental results. Bubbles are set in motion by a 20-cycle, 2.25 MHz, 180 kPa acoustic pulse. The ambient fluid is water.

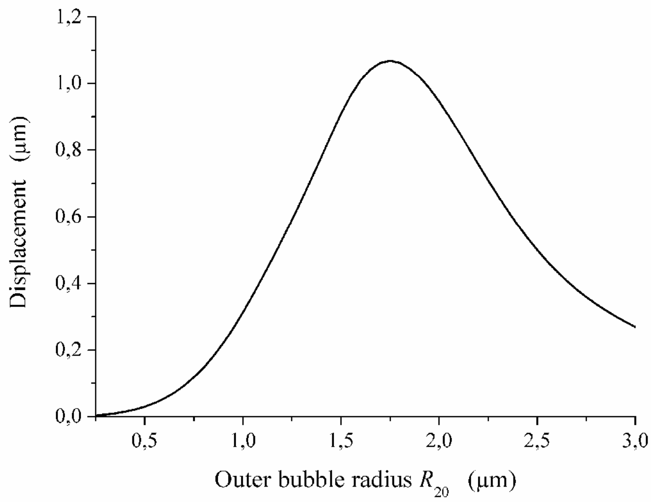

Figure 2. Simulated translational displacement in blood.

Figure 2 shows the simulated translational displacement in the case that the ambient fluid is a non-Newtonian liquid with blood characteristics [11]: $\lambda_{F1} = 10^{-8}$ s, $\lambda_{F2} = 0$, and $\eta_F = 0.004$ Pa s. The other parameters are the same as in Figure 1. As could be expected, distances travelled by bubbles in blood are considerably shorter.

SUMMARY

The present paper proposes a model that describes the spatio-temporal dynamics of a lipid-shelled contrast agent microbubble in a strong ultrasound field. Unlike previous studies, the behavior of the lipid coating is approximated by the 3-constant Oldroyd model. Comparison of theoretical results with experimental values of translational displacement available in the literature for lipid-shelled contrast agents shows that the proposed model provides good agreement between theory and experiment.

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