

Theory of Red Blood Cell Oscillations in an Ultrasound Field

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Manipulating particles in the blood pool with noninvasive methods has been of great interest in therapeutic delivery. Recently, it was demonstrated experimentally that red blood cells can be forced to translate and accumulate in an ultrasound field. This acoustic response of the red blood cells has been attributed to sonophores, gas pockets that are formed under the influence of a sound field in the inner-membrane leaflets of biological cells. In this paper, we propose a simpler model: that of the compressible membrane. We derive the spatio-temporal cell dynamics for a spherically symmetric single cell, whilst regarding the cell bilayer membrane as two monolayer Newtonian viscous liquids, separated by a thin gas void.

When applying the newly-derived equations to a red blood cell, it is observed that the void inside the bilayer expands to multiples of its original thickness, even at clinically safe acoustic pressure amplitudes. For causing permanent cell rupture during expansion, however, the acoustic pressure amplitudes needed would have to surpass the inertial cavitation threshold by a factor 10.

Given the incompressibility of the inner monolayer, the radial oscillations of a cell are governed by the same set of equations as those of a forced antibubble. Evidently, these equations must hold for liposomes under sonication, as well.

Keywords: spatio-temporal cell dynamics; Rayleigh-Plesset equation; spherical cell; red blood cell; erythrocyte; sonophore.

1. Introduction

Manipulating particles in the blood pool with non-invasive methods has been of great interest in therapeutic delivery, about which a review has been published by DELALANDE *et al.* (2012). Ultrasonic equipment is commonly used for noninvasive manipulation, owing to its reliability, safety, availability, and low operating cost. Following numerous nondestructive and destructive experimental studies on microbubbles under sonication near biological cells, *e.g.*, PRENTICE *et al.* (2005), VAN WAMEL *et al.* (2006), KUDO *et al.*

(2009), and DELALANDE *et al.* (2011), it was speculated that cells themselves respond to sound by oscillating (KRASOVITSKI *et al.*, 2011), which might lead to novel ways of noninvasive cell manipulation, filtration, and even eradication (WALTHER, POSTEMA, 2016).

Recently, MAZZAWI *et al.* (2015) demonstrated experimentally that red blood cells can be forced to translate and accumulate in an ultrasound field. This acoustic response of the red blood cells has been attributed to sonophores, gas pockets that are formed under the influence of a sound field in the inner-membrane leaflets of biological cells (KRASOVITSKI

et al., 2011). Under sonication, such trapped gas pockets must oscillate in a similar way as encapsulated gas microbubbles do.

Although the existence of sonophores would explain experimentally observed phenomena, such as the attraction of oscillating microbubbles to fixated cells (DELALANDE *et al.*, 2011) and the occurrence of the transient formation of pores in cell membranes in the absence of microbubbles (BAO *et al.*, 1997), there might be a more straightforward explanation for the behaviour observed.

In this paper, we propose a simpler model: that of the compressible membrane. Initially, we follow the derivation for antibubble dynamics of KOTOPOULIS *et al.* (2015) step by step whilst replacing only few parameters, but from Subsec. 2.4 we deviate by including an outer cell membrane, following the derivation of encapsulated bubbles dynamics by CHURCH (1995).

2. Theory

Let us consider a spherical cell, as schematically represented in Fig. 1. We regard the inner cell structure as an incompressible liquid of radius R_1 . Instead of regarding the surrounding bilayer membrane as one layer, we split it up into three components (BOAL, 2012): an inner monolayer Newtonian viscous liquid membrane of inner radius R_1 and outer radius R_2 , an outer monolayer Newtonian viscous liquid membrane of inner radius R_3 and outer radius R_4 , and a gas void separating both monolayers of inner radius R_2 and outer radius R_3 . Even though actual cells are rarely spherical, we may disregard this fact, as the radial dynamics are predominantly determined by the surface pressure of the surface with the greatest curvature (ISENBERG, 1992).

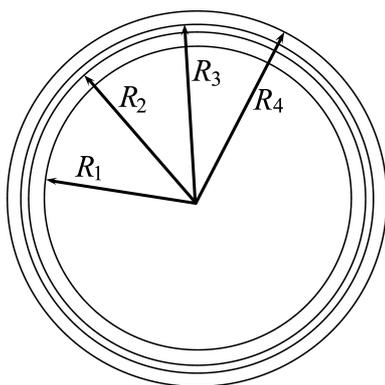


Fig. 1. Schematic representation of a spherical cell consisting of a liquid core of radius R_1 , surrounded by a monolayer Newtonian viscous liquid membrane of outer radius R_2 , a compressible gas void of outer radius R_3 , and a monolayer Newtonian viscous liquid membrane of outer radius R_4 .

Because the monolayer membranes are considered Newtonian viscous liquids, they are incompressible, as is the intracellular liquid. Consequently, the inner membrane radii do not respond to pressure changes. However, the gas void separating the inside and outside membranes must abide by the same thermodynamics that cavitation bubbles do when subjected to a sound field.

2.1. Fundamental equation of cell dynamics

Let us consider a polytropic gas void, surrounding the spherical incompressible liquid core of radius R_2 as presented in Fig. 1. For now, we ignore the outer monolayer membrane.

We are assuming adiabatic conditions. Furthermore, no mass exchange between the respective interfaces is assumed.

Following the derivation for antibubble dynamics of KOTOPOULIS *et al.* (2015) and introducing a driving function $P(t)$, the fundamental equation of cell dynamics becomes:

$$R_3 \ddot{R}_3 + \frac{3}{2} \dot{R}_3^2 = \frac{1}{\rho_L} \left[\left(p_0 + \frac{2\sigma}{R_{30}} \right) \left(\frac{R_{30}^3 - R_2^3}{R_3^3 - R_2^3} \right)^\gamma - \frac{2\sigma}{R_3} - p_0 - P(t) \right], \quad (1)$$

where p_0 is the ambient pressure, R_{30} is the initial outer radius of the gas void, γ is the polytropic exponent of the gas inside the void, ρ_L is the density of the liquid surrounding the cell, and σ is the surface tension.

2.2. Cell dynamics in a Newtonian viscous fluid

The viscosity η_L of a Newtonian viscous fluid is by definition equal to the rate of strain $\Delta\varepsilon/\Delta t$.

Again, following the derivation for antibubble dynamics of KOTOPOULIS *et al.* (2015) and introducing a driving function $P(t)$, the fundamental equation of cell dynamics in a Newtonian viscous fluid becomes:

$$R_3 \ddot{R}_3 + \frac{3}{2} \dot{R}_3^2 = \frac{1}{\rho_L} \left[\left(p_0 + \frac{2\sigma}{R_{30}} \right) \left(\frac{R_{30}^3 - R_2^3}{R_3^3 - R_2^3} \right)^\gamma - \frac{2\sigma}{R_3} - \frac{4\eta_L}{R_3} \dot{R}_3 - p_0 - P(t) \right]. \quad (2)$$

This is the Rayleigh-Plesset-like equation for a cell in a Newtonian viscous fluid, which can only be applied if the surrounding fluid is incompressible and the gas is polytropic. The equation is a second-order nonlinear ordinary differential equation.

2.3. Linear analysis for an unrestrained cell

Let us assume that (2) has a solution of the form

$$R_3(t) = R_{30}[1 + \xi(t)] \quad (3)$$

for small excursions ξ of the outer surface of the void, *i.e.*, $\xi \ll R_{30}$. Then, (2) can be linearised and represented by a mass-spring-dashpot system (POSTEMA, 2011).

The linear natural angular resonance frequency ω_0 of an unrestrained cell is given by:

$$\omega_0^2 = \frac{1}{R_{30}^2 \rho_L} \left[\frac{3\gamma p_{g0}}{1 - \left(\frac{R_2}{R_{30}}\right)^3} - \frac{2\sigma}{R_{30}} \right], \quad (4)$$

where p_{g0} is the initial gas pressure inside the void.

It can be observed that the linear damped resonance frequency of a gas void is increased by the cubic ratio of the inner cell liquid radius and the initial radius compared to that of a regular gas bubble.

If a cell is suspended in a Newtonian viscous fluid, it resonates with a linear damped natural angular resonance frequency ω_d , given by (2.2.7) in KOTOPOULIS *et al.* (2015):

$$\omega_d^2 = \frac{1}{R_{30}^2 \rho_L} \left[\frac{3\gamma p_{g0}}{1 - \left(\frac{R_2}{R_{30}}\right)^3} - \frac{2\sigma}{R_{30}} - \frac{4\eta_L^2}{R_{30}^2 \rho_L} \right]. \quad (5)$$

It can be observed from (5) that the linear damped resonance frequency decreases when the viscosity of the surrounding fluid increases.

2.4. Presence of the outer cell membrane

Now let us take into account that the gas void is surrounded by a restraining layer. Both the liquid composing the membrane and the outer surrounding liquid are assumed to be viscous and incompressible. Assuming no mass exchange between the respective interfaces, the radial velocity $v(r, t)$ in the membrane and in the surrounding fluid at a distance r from the centre of the cell can be expressed as (LEIGHTON, 1994):

$$v(r, t) = \frac{R_3^2}{r^2} \dot{R}_3, \quad (6)$$

If $R_3 < r < R_4$, $v(r, t)$ denotes the velocity inside the membrane. If $r > R_4$, $v(r, t)$ denotes the radial velocity of the surrounding liquid. From the assumption of an incompressible membrane it can be shown that

$$R_4^3 - R_3^3 = R_{40}^3 - R_{30}^3 \quad (7)$$

and

$$R_3^2 \dot{R}_3 = R_4^2 \dot{R}_4, \quad (8)$$

where R_{40} is the initial cell radius.

From conservation of radial momentum (LANDAU, LIFSHITZ, 1986), it follows that

$$\rho_M \left(\frac{\partial v}{\partial t} + v \frac{\partial v}{\partial r} \right) = -\frac{\partial p}{\partial r} + \frac{\partial \tau_{rr}^M}{\partial r} + \frac{3\tau_{rr}^M}{r} \quad (9)$$

and

$$\rho_L \left(\frac{\partial v}{\partial t} + v \frac{\partial v}{\partial r} \right) = -\frac{\partial p}{\partial r} + \frac{\partial \tau_{rr}^L}{\partial r} + \frac{3\tau_{rr}^L}{r}, \quad (10)$$

where ρ_M is the the density of the membrane, ρ_L is the density of the surrounding liquid, p is the pressure in the membrane or the liquid, τ_{rr}^M is the viscous stress tensor in the membrane, and τ_{rr}^L is the viscous stress in the liquid. Equation (9) is integrated from R_3 to R_4 , and (10) is integrated from R_4 to infinity, substituting (6) for v . It is here assumed that the contribution to the radial momentum from the gas inside the void can be neglected. Combining these two integrals, the result can be expressed as

$$\begin{aligned} & \rho_L R_3 \ddot{R}_3 \left[1 + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \frac{R_3}{R_4} \right] \\ & + \rho_L \dot{R}_3^2 \left[\frac{3}{2} + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \left(\frac{4R_4^3 - R_3^3}{R_4^3} \right) \right] \\ & = P_M(R_3, t) - P_M(R_4, t) + P_L(R_4, r) \\ & + \tau_{rr}^M(R_4, t) - \tau_{rr}^M(R_3, t) - \tau_{rr}^L(R_4, t) \\ & + 3 \int_{R_3}^{R_4} \frac{\tau_{rr}^M}{r} dr + 3 \int_{R_4}^{\infty} \frac{\tau_{rr}^L}{r} dr, \end{aligned} \quad (11)$$

where $P_M(R_1, t)$ and $P_M(R_2, t)$ are the pressures in the membrane at the inner and outer interfaces, respectively, $P_L(R_2, t)$ is the pressure in the liquid at the outer interface, $\tau_{rr}^M(R_1, t)$ and $\tau_{rr}^M(R_2, t)$ are the stresses at the inner and outer interfaces, respectively, and $\tau_{rr}^L(R_2, t)$ is the stress in the liquid at the outer interface (CHURCH, 1995).

The boundary conditions from conservation of radial momentum can be stated as

$$p_g(R_3, t) + \tau_{rr}^M(R_3, t) = P_M(R_3, t) + \frac{2\sigma_3}{R_3} \quad (12)$$

and

$$\begin{aligned} P_M(R_4, t) - \tau_{rr}^M(R_4, t) &= P_L(R_4, t) - \tau_{rr}^L(R_4, t) \\ &+ \frac{2\sigma_4}{R_4} + P(t), \end{aligned} \quad (13)$$

where $P_g(R_1, t)$ is the instantaneous pressure inside the void, and σ_3 and σ_4 are the surface tensions at the two respective interfaces of the outer membrane. Combining (11) with the boundary conditions in (12) and (13) yields

$$\begin{aligned} & \rho_L R_3 \ddot{R}_3 \left[1 + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \frac{R_3}{R_4} \right] \\ & + \rho_L \dot{R}_3^2 \left[\frac{3}{2} + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \left(\frac{4R_4^3 - R_3^3}{R_4^3} \right) \right] \\ & = p_g(R_3, t) - \frac{2\sigma_3}{R_3} - \frac{2\sigma_4}{R_4} - p_0 - P(t) \\ & + 3 \int_{R_3}^{R_4} \frac{\tau_{rr}^M}{r} dr + 3 \int_{R_4}^{\infty} \frac{\tau_{rr}^L}{r} dr, \end{aligned} \quad (14)$$

It now remains to determine the two integrals in (14). Where the first integral describes the rheological properties of the membrane, and the latter integral describes the damping from the surrounding fluid.

Assuming the void is surrounded by a Newtonian viscous liquid, the shear viscous stress can be expressed as

$$\tau_{rr}^L = 2\eta_L \frac{\partial v}{\partial r}, \quad (15)$$

The last integral in (14) can now be determined using (6), yielding an expression for the effect of a viscous surrounding liquid:

$$3 \int_{R_2}^{\infty} \frac{\tau_{rr}^L}{r} dr = -4\eta_L \frac{R_3^2}{R_4^3} \dot{R}_3. \quad (16)$$

The general Rayleigh-Plesset-like equation for a cell with a finite membrane and surrounded by a Newtonian viscous liquid is obtained by substituting

$$p_g = p_{g0} \left(\frac{R_{30}^3 - R_2^2}{R_3^3 - R_2^2} \right)^\gamma \quad (17)$$

for $p_g(R_1, t)$ and (16) for the last integral in (14):

$$\begin{aligned} & \rho_L R_3 \ddot{R}_3 \left[1 + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \frac{R_3}{R_4} \right] \\ & + \rho_L \dot{R}_3^2 \left[\frac{3}{2} + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \left(\frac{4R_4^3 - R_3^3}{R_4^3} \right) \right] \\ & = p_{g0} \left(\frac{R_{30}^3 - R_2^2}{R_3^3 - R_2^2} \right)^\gamma - \frac{2\sigma_3}{R_3} - \frac{2\sigma_4}{R_4} - p_0 - P(t) \\ & - 4\eta_L \frac{R_3^2}{R_4^3} \dot{R}_3 + 3 \int_{R_3}^{R_4} \frac{\tau_{rr}^M}{r} dr. \end{aligned} \quad (18)$$

2.5. Newtonian viscous liquid outer cell membrane

Now let us assume that the outer monolayer membrane of a cell can be regarded as a Newtonian viscous liquid, where the viscous stress in the membrane τ_{rr}^M is related to the membrane viscosity η_M by (DOINIKOV, DAYTON, 2007):

$$\tau_{rr}^M = 2\eta_M \frac{\partial v}{\partial r}. \quad (19)$$

The remaining integral in (18) describes the shear viscosity in the Newtonian liquid membrane, which dampens the radial response from the void as it is excited by an acoustic pulse. Substituting (19) and using both (7) and (8), the integral can be written in terms of radial displacement:

$$3 \int_{R_3}^{R_4} \frac{\tau_{rr}^M}{r} dr = -4\eta_M \frac{R_4^3 - R_3^3}{R_3 R_4^3} \dot{R}_3. \quad (20)$$

Substituting (20) into (18) gives a Rayleigh-Plesset-like equation for a cell with a Newtonian membrane of finite thickness surrounded by a Newtonian viscous liquid:

$$\begin{aligned} & \rho_L R_3 \ddot{R}_3 \left[1 + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \frac{R_3}{R_4} \right] \\ & + \rho_L \dot{R}_3^2 \left[\frac{3}{2} + \left(\frac{\rho_L - \rho_M}{\rho_M} \right) \left(\frac{4R_4^3 - R_3^3}{R_4^3} \right) \right] \\ & = p_{g0} \left(\frac{R_{30}^3 - R_2^2}{R_3^3 - R_2^2} \right)^\gamma - \frac{2\sigma_3}{R_3} - \frac{2\sigma_4}{R_4} - p_0 - P(t) \\ & - 4\eta_L \frac{R_3^2}{R_4^3} \dot{R}_3 - 4\eta_M \frac{R_4^3 - R_3^3}{R_3 R_4^3} \dot{R}_3. \end{aligned} \quad (21)$$

3. Solution

To simulate a spherically oscillating cell, parameters measured on living blood cells were used. B-layer cell membranes are 20 nm in thickness, whereas the void separating the individual monolayers is only 2 nm in thickness (BOAL, 2012). The shear viscosity of red blood cell membranes is in the order of 10^3 Pa·s (TRAN-SON-TAY *et al.*, 1984). The sizes of cells greatly vary. Red blood cells have in axial view an outer radius of 3 μ m.

Equation (21) was solved numerically using the ode45 algorithm of MATLAB[®] (The MathWorks, Inc., Natick, MA, USA). The parameters chosen were: $\rho_M \approx \rho_L = 10^3$ kg·m⁻³, $R_{40} = 3$ μ m, $(R_{40} - R_{30}) = 9$ nm, $(R_{30} - R_2) = 2$ nm, $\rho_{g0} = 1$ kg·m⁻³, $\gamma = 1.4$, $\sigma_3 = \sigma_4 = 0.025$ N·m⁻¹, $p_0 = 10^5$ Pa, $\eta_L = 10^{-3}$ Pa·s, and $\eta_M = 10^3$ Pa·s.

The driving pulse consisted of a 10-cycles sinusoid wave, with a centre frequency of 1 MHz or 3 MHz. The number of cycles chosen is typical for the upper pulse duration in commercial ultrasound equipment, whereas the centre frequencies are typical for those used in clinical cardiac and gastroenterologic ultrasonic imaging. Acoustic amplitudes ranged from 300 kPa to 20 MPa. The low acoustic pressures were chosen to simulate clinically safe ultrasound, the higher pressures to investigate under what conditions ultrasound-induced cell damage should be permanent.

4. Results and discussion

Figures 2–4 show expansion-time curves of red blood cells under sonication. In all these figures, it can be observed, that all oscillations of the void are highly asymmetric, *i.e.*, greater expansive excursions than contractive excursions. This is a direct result of the incompressibility of the cellular content and of the nonlinearity of (21). It may be interesting to mention, that if the density of the outer membrane were different from the density of the surrounding fluid, more asymmetry should have occurred: According to (18),

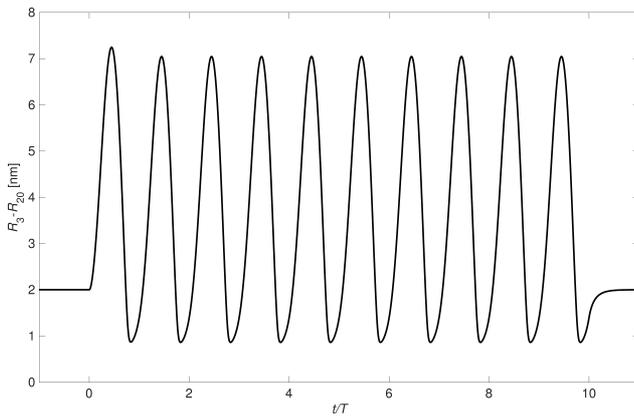


Fig. 2. Expansion-time curve of a red blood cell under 1-MHz sonication. The acoustic amplitude is 300 kPa. Time t has been normalised by period T .

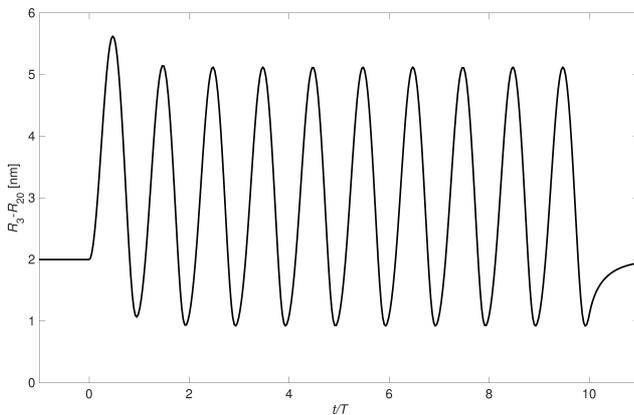


Fig. 3. Expansion-time curve of a red blood cell under 3-MHz sonication. The acoustic amplitude is 500 kPa. Time t has been normalised by period T .

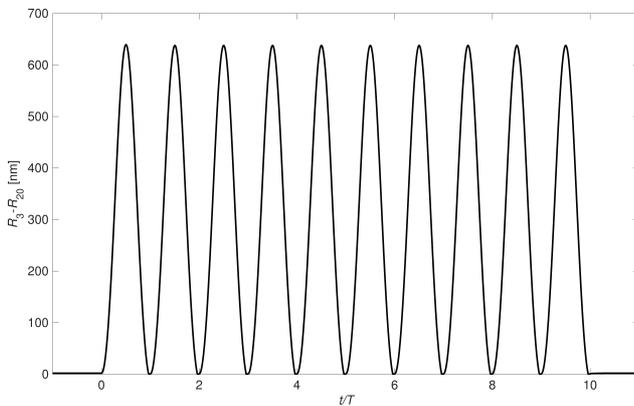


Fig. 4. Expansion-time curve of a red blood cell under 1-MHz sonication. The acoustic amplitude is 20 MPa. Time t has been normalised by period T .

it follows from the first term on the left-hand side that the acceleration increases if $\rho_L > \rho_M$, and the acceleration decreases if $\rho_L < \rho_M$. The ratios of the densities effects the second term on the left-hand side in a similar way, decreasing and increasing the degree of nonlinearity. The first term on the right-hand side is

a different form of a Rayleigh-Plesset-like equation, describing the radial pulsation of a gas bubble. The pressure inside a cell is larger than in a gas bubble under the same conditions.

Figures 2 and 3 both demonstrate a maximum void expansion of more than 5 nm, *i.e.*, more than $2.5\times$ the initial void thickness, despite the high viscosity ($\eta_M = 10^3 \text{ Pa}\cdot\text{s}$) of the outer monolayer membrane. The acoustic amplitudes in both computations were chosen to correspond to a mechanical index of 0.3 (APFEL, HOLLAND, 1991): At a transmit frequency of 1 MHz, acoustic amplitudes of pulsed ultrasound below 300 kPa are considered safe in neonatal scans, whereas at a transmit frequency of 3 MHz, acoustic amplitudes of pulsed ultrasound below 500 kPa are considered safe in neonatal scans (POSTEMA, 2011).

Hence, even at low acoustics amplitudes, the void inside the bilayer membrane oscillates to multiple times its initial thickness. These excursions are not enough to permanently damage a red blood cell.

Recently, LI *et al.* (2013) measured that red blood cells need to be stretched to an area corresponding to 20% increase of their resting radius. Figure 4 shows that such excursions can be achieved during sonication at 1 MHz with an acoustic pressure amplitude of 20 MPa. This pressure amplitude corresponds to $10\times$ the threshold of inertial cavitation (APFEL, HOLLAND, 1991). Hence, permanent cell damage caused by the oscillating bilayer void can be neglected in clinical situations. However, diffusive processes into the void have not been accounted for in our model. Such processes might inflate the void over multiple cycles.

The purpose of this paper was to propose a model with less unknown parameters than the sonophore. Introducing compressible membranes, bulk viscosity and thermal conductivity would, albeit representing a more realistic situation, complicate the model with unknown material properties. However, real excursion amplitudes should be even lower due to these additional damping terms.

It can be noted that, given the incompressibility of the inner monolayer, the radial oscillations of a cell are governed by the same set of equations as those of a forced antibubble (KOTOPOULIS *et al.*, 2015).

5. Conclusions

We derived the spatio-temporal cell dynamics for a spherically symmetric single cell, whilst regarding the cell bilayer membrane as two monolayer Newtonian viscous liquids, separated by a thin gas void.

Given the incompressibility of the inner monolayer, the radial oscillations of a cell are governed by the same set of equations as those of a forced antibubble. Evidently, these equations must hold for liposomes under sonication, as well.

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