Collapse and jet formation of ultrasound contrast microbubbles near a membrane for sonoporation

Nima Mobadersany, Kausik Sarkar*

The George Washington University, Washington, D.C., USA

Abstract
Contrast agents, in the presence of ultrasound, can help facilitate the uptake of drugs and genes into desired cells through the process called sonoporation. Sonoporation is the temporarily rupture of cell membranes in the presence of ultrasound. In this work, we studied the behaviour of a contrast agent near a rigid wall in the presence of ultrasound using boundary integral equation method. A contrast microbubble forms a high-velocity microjet at the last stage of the collapse phase. The microjet and the adjacent surrounding fluid impinges on the membrane and spreads radially, generating high shear stress resulting in the rupture and perforation of the cell membrane. The encapsulation of the microbubble can be assumed as an interface with an infinitesimal thickness. There are several models to simulate the interface. In this study, the encapsulation is modelled using strain-softening interfacial elastic model called the exponential elasticity model (EEM).

Keywords: sonoporation; ultrasound; microjet; Boundary integral equation; microbubble collapse

Introduction
Ultrasound waves are pressure waves capable of transporting energy inside the body at precise locations as they are absorbed very little by tissues. Their non-invasive, safe and painless transmission through the skin is the reason for their wide use in drug delivery and gene therapy applications [1]. Microbubbles in the presence of ultrasound facilitates the transport of drugs through a process called sonoporation. Sonoporation is the acoustically induced temporary rupture of membranes. With a scanning electron microscope, it has been shown that multiple surface pores are being created on the cell membrane exposed to ultrasound [2]. The induction of sonoporation using targeted microbubbles have been studied both in vitro and vivo [3-5]. Microbubbles were initially developed for enhancing the contrast of the image inside the body due to their high echogenicity. They consist of a gas core encapsulated by a layer of proteins or lipids to prevent them against premature dissolution. The shell reduces the surface tension and stabilizes them. At high amplitude ultrasound excitations, microbubbles implode after a few cycles. If the collapsing microbubbles are in the vicinity of a solid boundary, they generate a high-velocity liquid microjet toward the wall. The impingement of microjet along with its high velocity creates high shear stresses in the cell membrane resulting in sonoporation. This consequently will facilitate uptake of drugs into the desired site [6-8]. The study of non-spherical bubble collapse shows that the dynamics of the jet strongly depends on the distance of the bubble relative to the wall [9]. It is also shown that in addition to the jet speed, jet size can also have a determining factor on the impacting power of collapsing bubble [10]. During the formation of jet, there exists very high pressure fluid on top of the jet pushing the bubble toward the wall [11, 12]. In this work, we do numerical study on the formation of microjet from contrast agent microbubbles in the vicinity of a solid wall to better understand the mechanism of sonoporation. We have assumed the cell membrane as a solid wall for simplification. We have used a zero-thickness interfacial rheology models to simulate the encapsulation of the contrast agent microbubbles as the encapsulation is practically an interface [13]. The boundary integral equation method has been used for the numerical study.

Mathematical equations
In this study, the flow around the bubble is assumed incompressible, irrotatational and inviscid. The surrounding flow is governed by Laplace equation. It is solved using a boundary integral equation method obtained using following Green’s integral formula:

$$c(p)\phi(p) + \int_S \phi(q) \left[ \frac{\partial}{\partial n} \left( \frac{1}{|p-q|} + \frac{1}{|p-q|^2} \right) \right] ds = \int_S \frac{\partial}{\partial n} \left( \phi(q) \right) \left( \frac{1}{|p-q|} + \frac{1}{|p-q|^2} \right) ds . \tag{1}$$

*Corresponding Author, Kausik Sarkar: sarkar@gwu.edu
In equation(1), \( s \) is the boundary of the fluid domain which includes the bubble surface and its image; \( \phi \) is the velocity potential and \( \frac{\partial \phi}{\partial n} \) is the normal velocity; \( p \) is a point in the fluid domain, or on the boundary; \( q \) is a point on the fluid boundary and \( q^\wedge \) is the image point of \( q \) across the plane \( z=0 \) where the cell membrane is located. \( c(p) \) is a coefficient dependent on the location of the point \( p \). The image bubble helps satisfy the impermeability condition on the cell membrane. Figure 1 shows the schematic of the problem. The bubble surface is discretized into \( M \) cubic spline elements. The velocity potential and the normal velocity are assumed to be constant on each element and are located in the middle of the elements. The normal velocity on the boundary of the fluid domain is indicated by \( n \) and is directed outward (directed toward the bubble center). The vertical axis is indicated by \( z \), while \( r \) is the radial axis. The problem is assumed axisymmetric.

![Figure 1. Schematic of the problem](image)

Equation (1) gives a set of linear equations for evaluating \( \frac{\partial}{\partial n}(\phi) \) on each segment on the bubble surface. To find the velocity potential in the next time steps, the normalized form of the unsteady Bernoulli equation is applied for the flow along the surface of the contrast agent:

\[
\frac{D\phi^*}{Dt^*} = \frac{1}{2} |\nabla^* \phi^*|^2 + \frac{(P_{\omega} - P_{bw})}{P_{atm}},
\]

where \( \phi^* \), \( t^* \) and \( \nabla^* \) are the non-dimensional velocity potential, time and gradient respectively (with respect to ambient pressure, density and initial radius). \( P_{bw} \) is the pressure in the fluid on the bubble surface. \( P_{atm} \) is the pressure in the far field including the static ambient pressure (here atmospheric pressure) and excitation ultrasound pressure:

\[
P_{\omega} = P_{atm} - P_{ex} \sin(\omega t).
\]

\( P_{ex} \) and \( \omega \) are the excitation pressure and excitation radial frequency due to the ultrasound wave. The gas inside the contrast agent is assumed to be an ideal gas that follows a polytropic law:

\[
P_g = P_{g0} \left( \frac{V_0}{V} \right)^K.
\]

\( P_g \) is the gas pressure inside the microbubble when its volume is \( V \). \( P_{g0} \) is the initial gas pressure inside microbubble when the bubble is in its initial volume of \( V_0 \), and \( K \) is the polytropic constant.

**Modelling the encapsulation of the microbubble**

The pressure inside and outside the microbubble are related by the normal stress balance. The effect of the encapsulation is considered on the normal stress balance:

\[ P_g - P_{bw} = \left( \sigma_{eff} + \kappa_s (\nabla_s \cdot V) \right) (\nabla_s \cdot n) . \]  

(5)

In equation (5), \( \sigma_{eff} \) and \( \kappa_s \) are the effective surface tension and dilatation viscosity of the contrast agent due to the encapsulation respectively, \( \nabla_s \cdot V \) is the surface divergence of velocity, and \( \nabla_s \cdot n \) is the curvature of the contrast agent [14]. Applying the dilatation viscosity term in the normal jump condition gives rise to instability which could not be removed by smoothing. Therefore in the current research, we neglect the dilatation viscosity for simplicity, and we will study its effect in future studies. Various different interfacial rheology models \( \sigma(R) \) have been proposed. In the present study we are using exponential elasticity model (EEM) [15] to calculate the effective surface tension.

\[
\begin{align*}
\sigma_{eff} (R) &= \sigma_0 + \beta E' , & \text{where } E' = E_0' \exp(-\alpha' \beta) \text{ and } \beta = (\frac{R^2}{R_E^2} - 1), \\
\sigma_{eff} (R) &= 0, & \text{for } \sigma(R) < 0
\end{align*}
\]

(6)

\( \sigma_{eff} (R) \) is the effective interfacial tension, \( E' \) is the elasticity of the shell, \( E_0' \) is elasticity constant and \( \beta \) is the area fraction. \( R_E \) is the equilibrium radius of the contrast agent. Equilibrium radius equals to the radius of the bubble where elastic stress is zero.

\[ R_E = R_0 \left[ 1 + \left(1 + \frac{2 \gamma_0 \alpha'}{E_0'} \right)^{1/2} \right] . \]

(7)

Results and discussion

In this study, we are using Sonazoid contrast agent as an example. Accordingly, the bubble radius is 1.6 \( \mu m \). The excitation frequency is assumed to be 2 MHz same as the average damped resonance frequency of Sonazoid. Figure 2 shows the contrast microbubble and the surrounding velocity and pressure when \( h^* = 4.0, P_{ex}^* = 5.0, f = 2 MHz \). \( h^* \) is the non-dimensional (with respect to the initial radius) initial distance of the bubble center from the cell membrane, \( P_{ex}^* \) is the non-dimensional (with respect to the atmospheric pressure) excitation pressure and \( f \) is the excitation frequency. Note that the magnitude of velocity vectors in the figure is relative to other particles in the same figure, and they do not show the actual magnitude of fluid particles velocity. Figure 2(a) shows the contrast agent at the early stages of the growing phase of the bubble with a higher pressure inside. Figure 2(b) shows the contrast microbubble when it reaches the maximum size at \( t^* = 2.1888 \) where \( t^* \) is the non-dimensional time. Bubble expands nearly spherically to reach the maximum volume. During the last stage of the collapse phase, the microbubble forms a jet directed toward the membrane. Figure 2(c) shows the beginning of the collapse phase when the bubble starts to form a jet at \( t^* = 3.2697 \). There exists a high-pressure region on top of the contrast agent pushing the high velocity jet [16]. Figure 2(d) shows the last stage of the collapse phase of the contrast agent at \( t^* = 3.3214 \). The collapse time from the start of the jet formation to the end of the collapse is very short.
Figures 2(c-d) show that the microjet and the adjacent surrounding fluid are moving toward the cell membrane with a very high velocity. This high velocity fluid impinges the membrane and spreads radially along it. This will generate a high velocity gradient on the tissue and therefore a shear stress resulting in the rupture and perforation of cell membrane. To calculate the shear stress generated on the wall, we consider the flow field induced from the jet of the contrast agent spreading outward radially along the tissue [17]. We assume a jet flow impacting vertically on the tissue with a constant velocity equal to the averaged vertical velocity of the elements on the jet at each time. Glauret wall jet flow has been used to estimate the shear on the tissue [18] to compute the wall shear stress $\tau$:

$$\tau = \rho v \left( \frac{\partial u}{\partial y} \right)_{y=0} = \rho \left( \frac{125F^3}{216
u x^4} \right)^{\frac{1}{4}}.$$  \hspace{1cm} (8)

The constant $F$ is the momentum flux of the incoming jet:

$$F = \frac{1}{128} U_{jet}^3 d_{jet}^4.$$  \hspace{1cm} (9)

$U_{jet}$ is the average jet velocity, and $d_{jet}$ is the jet diameter. Figure 3 shows the shear stress along the wall due to the impingement of the jet.
Figure 3. Corresponding shear stress on the rigid boundary with respect to non-dimensional time when $h^* = 4$, $P_{ex}^* = 5$ using EEM model for the encapsulation

Figures 4 (a-c) show the non-dimensional volume, volume centroid and jet tip velocity of the contrast microbubble at the conditions shown in figure 2. As shown in figures 4(a), the maximum growth of the contrast microbubble decreases with the increase of shell elasticity, as the higher elasticity makes the contrast agent stiffer. Figure 4(b) shows the motion of volume centroid. Microbubbles with higher shell elasticity experiences less excursion towards the cell membrane. The life time of the contrast agent decreases with the increase of shell elasticity. Therefore, contrast agent with higher shell elasticity, has less time to move toward the cell membrane. Figure 4(c) shows that the velocity of the jet tip is higher with higher shell elasticity. In contrast to coated bubbles, free bubbles experience more expansion, more translation toward the cell membrane and less jet velocity.

Figure 4. Non-dimensional volume, non-dimensional volume centroid and non-dimensional jet tip velocity of microbubble with respect to non-dimensional time when $h^* = 4.0$, $P_{ex}^* = 5.0$ using EEM model for the encapsulation

Conclusion

The behaviour of contrast microbubble near a rigid wall in the presence of ultrasound have been studied using boundary integral equation method. During the last stage of the collapse, the contrast agent forms a high-velocity microjet towards the wall. The microjet impinges the wall with high velocity and exerts a high shear stress. The shear stress induced by the jet may lead to sonoporation. An exponential elasticity model (EEM) has been used to simulate the interfacial rheology of the microbubble encapsulation.

References


