

Perforation of cell membranes using encapsulated microbubbles in the presence of ultrasound

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I. OBJECTIVE

Ultrasound waves are pressure waves capable of transporting energy into the body as they are absorbed relatively little by tissues. Their non-invasive, safe and painless transmission through the skin makes them suitable for use in drug delivery and gene therapy applications. Ultrasound in the presence of microbubbles facilitates transportation of drugs. These FDA approved encapsulated microbubbles (contrast agents) were initially developed for enhancing the contrast of ultrasound image. Contrast agents can carry and transport drugs or genes to the desired site through injection inside the bloodstream. They consist of a gas core encapsulated by a layer of protein or lipid to stabilize them against dissolution. Ultrasound wave excites the microbubbles making them implode (collapse) resulting in the release of drug/gene into the desired tissue. In addition to the role of microbubble as a drug carrier, in this study we aim to show that the collapse of microbubble forms or even increases the size of the small pores in the cell membrane. This can allow the transfer of DNA/RNA into the cell for gene therapy. It can also help to facilitate the uptake of drugs and large molecules into the cells. It can even help delivering drugs to cells with tight junctions like blood brain barrier by increasing the permeability of the cells. We also show that not only the collapse of these bubbles can help perforating the membranes, but their repeated pulsation also creates shear stress on membranes and perforates them. These bubbles will pulsate repeatedly if the excitation ultrasound pressure is not high enough to make them implode.

II. METHODOLOGY

In the presence of high ultrasound waves, contrast agents (encapsulated microbubbles) collapse within a few microseconds in the vicinity of a cell membrane which makes it very difficult to observe the details of the process experimentally. Therefore in this research, we are studying their behavior numerically.

The flow near the bubble collapse has very high velocity and therefore the viscosity effects of the flow can be ignored due to high Reynolds number. It has also been proved that the flow around the bubble can be assumed incompressible. Therefore the surrounding flow can be treated as a potential flow which satisfies Laplace equation. Hence, a boundary element method can be applied for the mathematical modeling of the flow around the encapsulated microbubble. It is a grid-free method and has been widely used in bubble dynamics. To apply it, the Green's integral formula is used for the flow around the bubble:

$$2\pi\phi_p + \int_s \phi_q \frac{\partial}{\partial n} \left(\frac{1}{|p-q|} \right) ds = \int_s \frac{\partial}{\partial n} (\phi_q) \left(\frac{1}{|p-q|} \right) ds \quad (1)$$

S is the surface surrounding the flow including the bubble boundary and the solid boundary, ϕ is the velocity potential and $\partial\phi/\partial n$ is the normal velocity on the surface S. p is the collocation point and q is any point on the surface. As it is shown in figure 1, the bubble boundary and cell membrane is discretized by N elements. The discretization on the cell membrane is extended to a sufficiently long length. The velocity potential and the normal derivative of the velocity potential along each element are assumed to be constant and are located in the middle of each element. Solving (1) along with the kinematic and dynamic boundary conditions on the bubble and solid boundary result in the microbubble evolution over time [1]-[2]-[3]-[4]-[5]. Note that the encapsulation of the bubble affects the dynamic boundary condition.

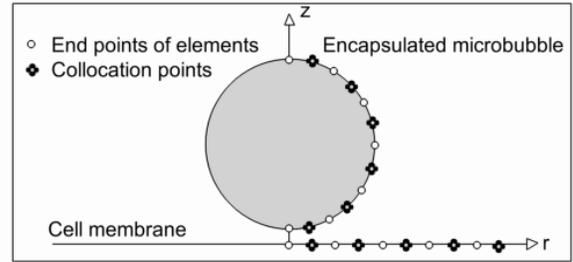


Fig. 1. Schematic of the problem

III. MODELING THE ENCAPSULATION

The encapsulation of the microbubble can be assumed as an interface with an infinitesimal thickness. The surface tension of the encapsulated microbubble is different from that of the free bubble. There are several models to simulate the interface. In this study the encapsulation is modelled using a strain softening model, the exponential elasticity model, developed by our group [4].

IV. RESULTS AND CONCLUSION

In this study we are modeling Sonazoid contrast agent which consists of a high density gas core and a lipid shell. Its average radius is $R_0=1.6 \mu m$.

Part 1. Collapse of contrast agent:

Figure 2 shows the velocity and pressure around the contrast agent when it is initially located at $3R_0$ from the cell membrane, and excited with pressure and frequency of

500Mpa and 2Mhz. where 2MHz is the damped resonance frequency of Sonazoid at average size. The excitation pressure is high enough to make the bubble collapse. At high excitation pressures, the contrast agent grows spherically to reach a maximum volume. Then it starts to collapse. During the last stage of the collapse phase, the contrast agent forms a jet directed toward the membrane. Figure 2 shows the contrast agent during the collapse phase when it has formed a jet. Also, it is observed that at the last stage of the collapse phase of the contrast agent, the fluid has a very high velocity near the jet of the bubble.

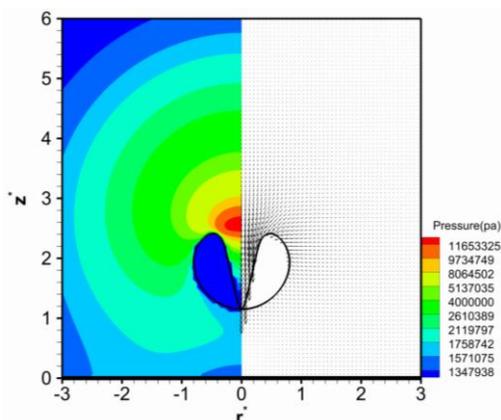


Fig. 2. Velocity and pressure surrounding the contrast agent in the vicinity of cell membrane excited with ultrasound

The collapse time from the start of the jet formation to the end of the bubble collapse is very short (about $0.92\mu s$). As it is observed in figure 2, the microjet of the contrast agent and the adjacent surrounding fluid are moving toward the cell membrane with a very high velocity (jet velocity reaches 300 m/s). Note that the magnitude of velocity vectors in the figure is relative to other particles in the same sub-figure, and they do not show the actual magnitude of fluid velocity. This high velocity fluid impinges the membrane and spreads radially along it. This will generate high velocity gradient on the tissue, and therefore it will generate shear stress resulting in the temporarily perforation and rupture of cell membrane. To have an understanding of the shear stress, in figures 3 we have plotted the shear stress on the cell membrane. This mechanism increases the permeability of cell membrane allowing drugs and DNA pass through the membrane and reach the tissue for treatment. At low excitation pressures.

Part 2. Repeated pulsation of contrast agent:

At low excitation pressures, the contrast agent will pulsate repeatedly instead of collapsing. When the bubble is pulsating, it creates fluctuations in the fluid. The time average of these fluctuations is non zero gives rise to steady vortices near the cell membranes. These vortices creates shear stress on the membrane, and helps perforating the membrane and facilitating drug delivery and gene therapy.

Figure 4 shows the generation of a ring vortex near the cell membrane created due to the repeated pulsation of contrast agent, and figure 5 shows the vortex-induced shear stress along

the cell membrane. The shear stress perforates the cell membrane, helps drug and large molecules pass through the pores of membrane and reach the cancerous cells.

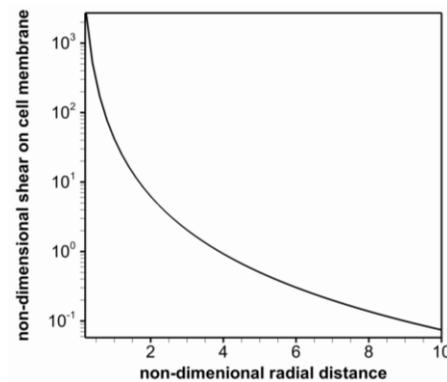


Fig. 4. Non-dimensional shear stress on the cell membrane due to jet velocity of the bubble at different radial distances from the center of the bubble

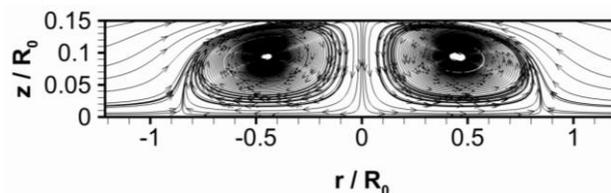


Figure 5. Steady vortices near the cell membrane (contrast microbubble is not visible in the figure and it is located at $z=1.2R_0$)

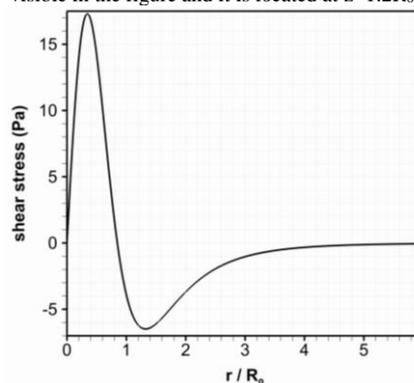


Figure 6. Shear stress along the cell membrane induced by the vortices due to pulsation of contrast agent

V. REFERENCES

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