Perforation of cell membranes using contrast agent microbubbles in the presence of ultrasound

Nima Mobadersany and Kausik Sarkar

Department of Mechanical & Aerospace Engineering

THE GEORGE WASHINGTON UNIVERSITY WASHINGTON, DC

School of Engineering & Applied Science THE GEORGE WASHINGTON UNIVERSITY

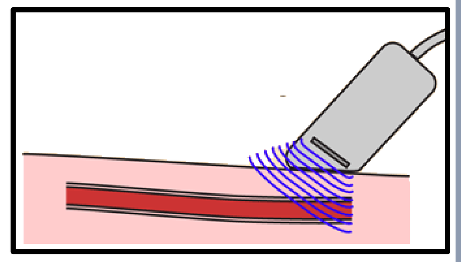
Objective

Understanding sonoporation (transient rupture of cell membrane with ultrasound) induced by contrast agent microbubbles. It facilitates drug delivery in tissues, i.e. cancerous tissues and blood brain barrier. Currently the process is difficult to observe experimentally. Simulation will help design for efficient drug delivery.

Background

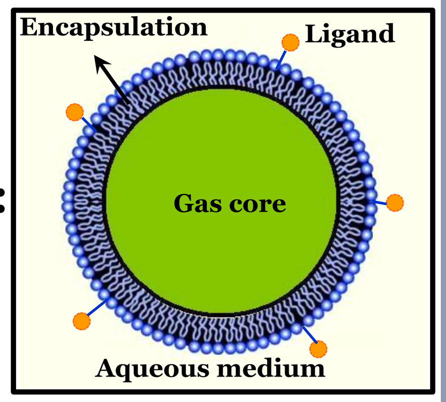
Ultrasound waves :

- Pressure waves with f > 20KHz
- Medically in MHz range
- Drug delivery, gene therapy
- Ultrasound imaging

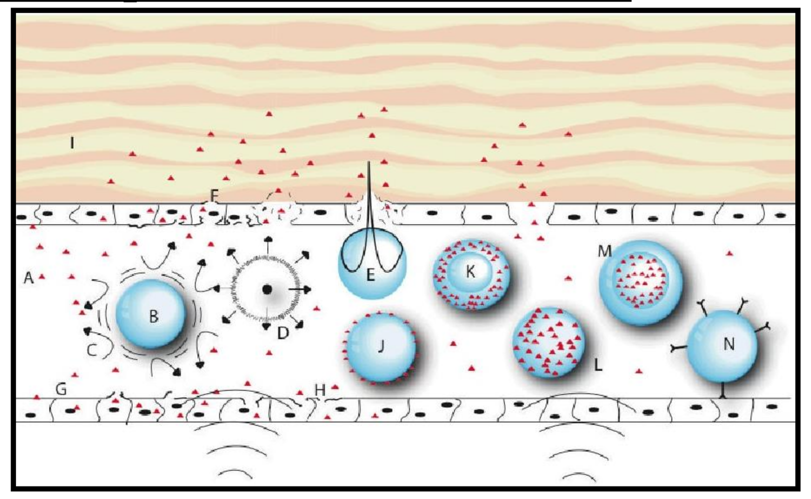


Contrast agent (Coated microbubble):

- Encapsulation prevents bubble against dissolution in blood



Drug delivery by encapsulated microbubbles:



Microbubbles inside the blood vessel as a drug carrier

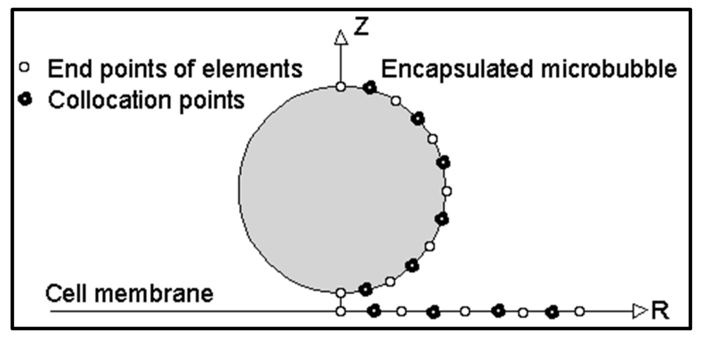
- Bubbles oscillate and implode under ultrasound
- Release drugs
- Generate shear stress
- Ruptures vessel wall
- Increases drug delivery

Numerical study

To find the shape of the encapsulated microbubble:

- Boundary element method
  - ❑ Microubble is discretized to cubic spline elements
  - ❑ Cell membrane is discretized to linear elements
  - ❑ Green's integral formula
  - ❑ Unsteady Bernoulli Equation

Schematic of the problem



Green's Integral Formula:

$$2\pi\phi_i + \sum_{j=1}^{N+M}\phi_j \int_{S_j} \frac{\partial}{\partial n}\left(\frac{1}{|p_i-q_j|}\right)ds = \sum_{j=1}^{N+M}\frac{\partial}{\partial n}(\phi_j)\int_{S_j}\left(\frac{1}{|p_i-q_j|}\right)ds$$

velocity potential of elements (ϕ_j); velocity of elements ($\frac{\partial}{\partial n}(\phi_j)$)

Unsteady Bernoulli Equation:

$$\rho\left(\frac{D\phi}{Dt}-\frac{1}{2}|\nabla\phi|^2\right)+\rho g(z-h)=P_\infty - P_{bubble\,wall}$$

Ultrasound:

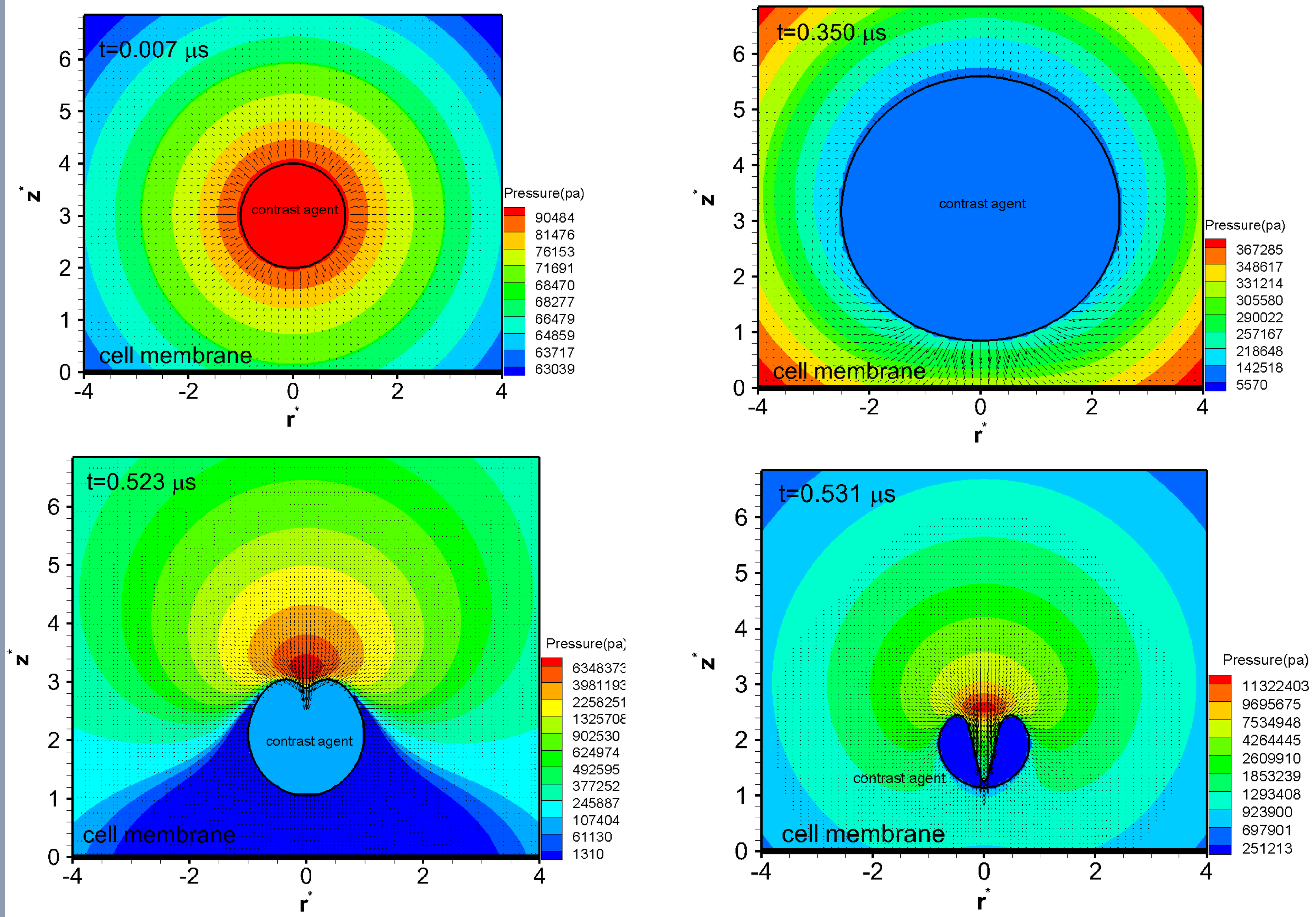
$$P_\infty = P_{atm} - P_{ex}\sin(2\pi f t)$$

$$P_{bubble\,wall} = P_{gas} - [\gamma + \kappa_s \nabla_s \cdot V](\nabla_s \cdot n)$$

- P_{gas}: gas pressure inside the coated microbubble [1]
- γ: surface tension of the coated microbubble using EEM model for simulating shell [1]
- κ_s: dilatational viscosity of the shell [1]
- $\nabla_s \cdot n$: curvature of elements on bubble

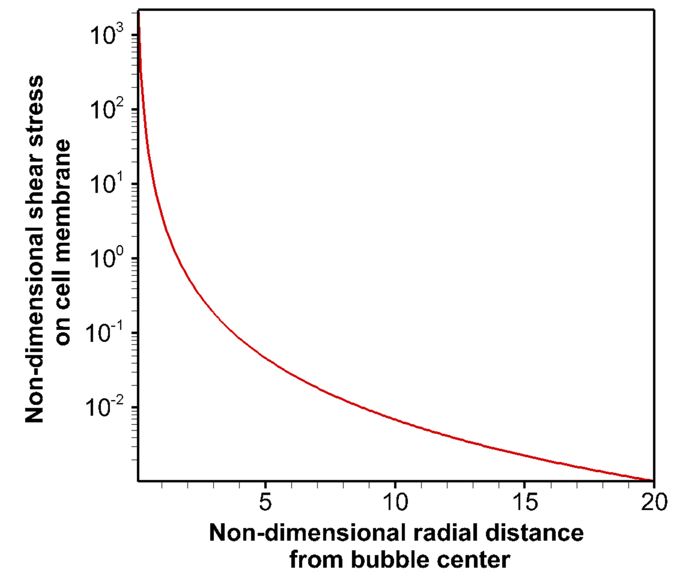
Results

- High ultrasound pressures excites contrast agent
- Contrast agent expands and collapses due to excitation
- During the expansion, it remains nearly spherical
- During the collapse, it forms a high velocity jet directed toward the tissue (jet velocity reaches 310 m/s) [2-4]

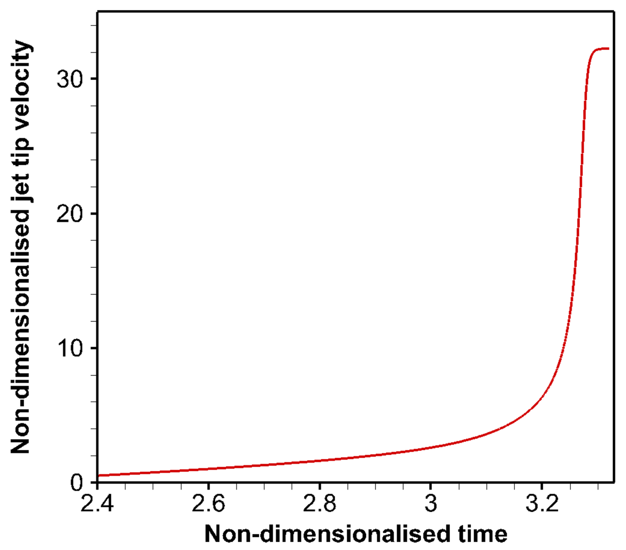


Velocity and pressure around contrast agent during the growth and collapse phase at different times when it is excited at 500 kPa and 2MHz (the contrast agent is initially located at 3R0 where R0 is the initial radius of contrast agent)

- The fluid near the jet has high velocity
- High velocity fluid impinges the cell membrane and spreads radially along it
- High velocity gradient, and hence high shear stress is being generated on the cell membrane [5]
- Cell membrane is perforated due to shear stress resulting in better uptake of drug into tissues



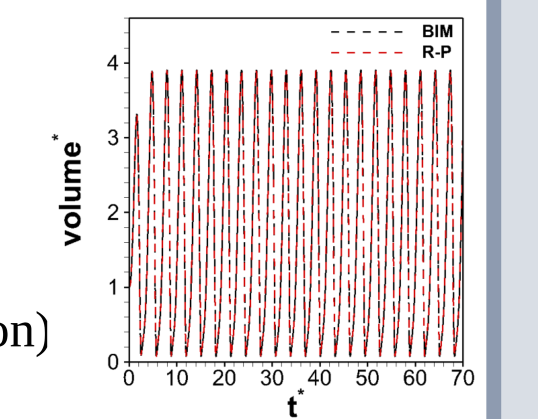
Shear stress on the cell membrane due to the collapse of contrast agent



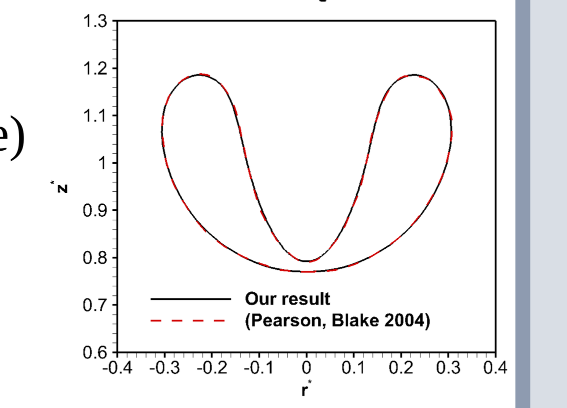
Non-dimensional velocity of the jet of the contrast agent

Validation of Numerical Results

Agreement of encapsulated microbubble oscillation in our code with the Rayleigh-Plesset equation in the absence of tissue (R-P is only for spherical oscillation)



Comparison of final stage of free bubble collapse (uncoated bubble) in the vicinity of a wall due to high initial pressure [6]



Conclusion

- Contrast agent microbubbles (coated microbubbles) are excited in the presence of high pressure ultrasound waves
- They expand and collapse due to the excitation
- During the collapse, they form a jet directed toward the cell membrane
- The jet and the adjacent fluid particles have a very high velocity (jet velocity reaches 310 m/s)
- This high velocity fluid generates high shear stress on the cell membrane
- High shear stress temporarily rupture and perforates the cell membrane
- Drugs and large molecules can pass through the perforated cell membrane easily

References

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5. ***N. Mobadersany,** K. Sarkar, 'Jet fromation of contrast microbubble in the vicinity of a vessel wall," J. Acoust. Soc. Am. 139, 2029 (2016).*
6. *A Pearson, JR. Blake, SR. Otto (2004) Jets in bubbles. J Eng Math 48:391-412.*