Permeabilization of Cell Membrane in the Presence of Encapsulated Microbubbles for Drug Delivery into Tissue

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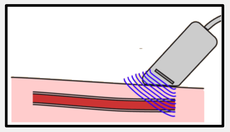
Objective

Understand sonoporation (transient perforation of cell membrane with ultrasound) induced by coated 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

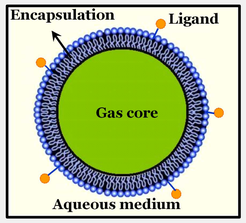
Ultrasound waves :

- Medically in MHz range
- Drug delivery, gene therapy
- Ultrasound imaging

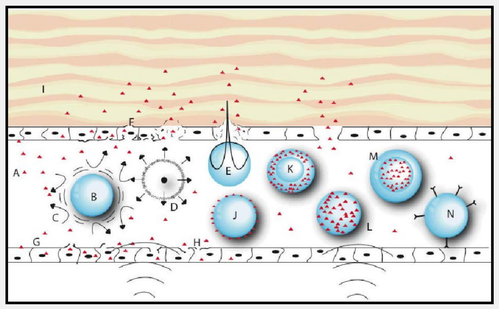


Encapsulated microbubble:

- Encapsulation prevents bubble against dissolution in blood



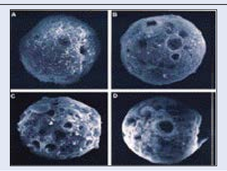
Drug delivery by encapsulated microbubbles:



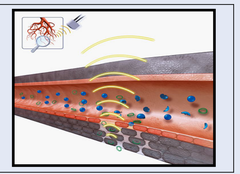
Microbubbles inside the vessel under ultrasound

- **J, K, L, M :**
  - Microbubbles carry drugs on or within their shells (red triangular marks are drugs)
  - Limits toxicity of drug to healthy tissues
- **N:**
  - Attaching ligands to the bubble surface helps bind to receptors on cell surface
- **B, D, E :**
  - Interactions of ultrasound with microbubles
    - ✓ It excites the microbubbles
    - ✓ Microbubbles oscillate over many cycles
    - ✓ Or they implode after few oscillations
    - ✓ Microbubbles release the drug into tissue

- Scanning electron microscopic images of cells exposed to ultrasound showed multiple surface pores [1]



- Transient pores on cell membrane due to ultrasound (sonoporation) facilitates the uptake of drugs into cells



Numerical study

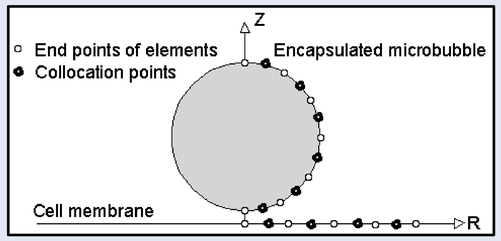
To find the shape of the encapsulated microbubble near tissue:

- Axisymmetric geometry
- Boundary element method
  - ❑ Microbubble is discretized to M cubic spline elements
  - ❑ Cell membrane is discretized to N linear elements
  - ❑ Green's integral formula: (N+M equations)

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

Velocity potential of elements

Velocity of elements



- ❑ Unsteady Bernoulli Equation:

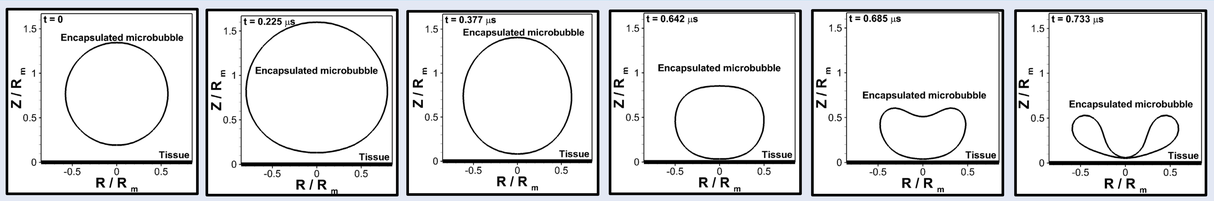
$$\rho\left(\frac{D\phi}{Dt} - \frac{1}{2}|\nabla\phi|^2\right) + \rho g(z-h) = P_\infty - P_{bubble\,wall}$$

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

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

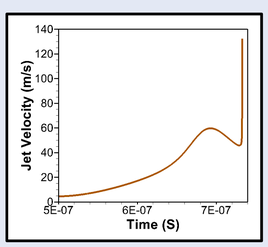
- P_{gas}: gas pressure inside the coated microbubble [2]
- γ: surface tension of the coated microbubble using EEM model for simulating shell [2]
- κ_s: dilatational viscosity of the shell [2]
- $\nabla_s \cdot \mathbf{n}$: Curvature of elements on bubble

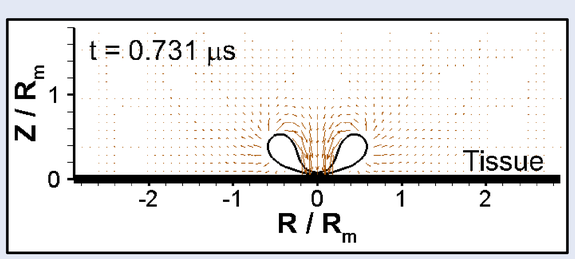
Results



Evolution of encapsulated microbubble near tissue with $f = 3MHz,\ P_A = 500KPa,\ h = 4\mu m, R_0 = 3\mu m$

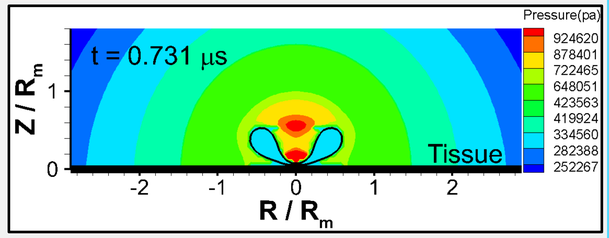
- Microbubble moves toward tissue (radial force), it helps to better release of drug
- Forms a jet directed toward the tissue, jet impinges the cell membrane (130 m/s)
- Creates transient holes on membrane, facilitates uptake of drug into tissue





Velocity vectors of fluid:

- High velocity fluid hits the cell membrane
- Creates velocity gradient, and high shear stress
- Perforates cell membrane, facilitates uptake of drug



Pressure contours of fluid:

- High pressure in the fluid on top of microbubble generates jet directed toward the tissue [3-5]

Conclusion

Encapsulated microbubble in the bloodstream near tissue

↓ With high intensity ultrasound exposure

Forms a jet impinging on the tissue

- Jet has high velocity → Creates holes on cell membrane
- Fluid near jet has high velocity → Generates high shear

→ Permeabilizes and perforates cell membrane

↓

Facilitates uptake of drug into tissue

References

1. *K. Tachibana, T. Uchida, K. Ogawa, N. Yamashita, K. Tamura, (1999) Induction of cell-membrane porosity by ultrasound, THE LANCET Vol 353*
2. *S. Paul, A. Katiyar, K Sarkar, (2010) Material characterization of the encapsulation of an ultrasound contrast microbubble and its subharmonic response: Strain-softening interfacial elasticity model. J Acoust Soc Am 127:3846-57.*
3. *Mohammad Shervani-Tabarabar, Nima Mobadersany, (2011) Velocity field and pressure distribution around a collapsing cavitation bubble during necking and splitting. J Engineering mathematics. 71:349–366.*
4. *Mohammad Shervani-Tabarabar, Nima Mobadersany, (2013) Numerical study on the hydrodynamic behavior of the dielectric fluid around an electrical discharge generated bubble in EDM. Theor. Comput. Fluid Dyn. 27:701–719.*
5. *Mohammad Shervani-Tabarabar, Nima Mobadersany, (2013) Numerical study of dielectric liquid around electrical discharge generated vapor bubble in ultrasonic assisted EDM, Ultrasonics. 53(5):943-55.*