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

**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)

\[ 2\pi \phi + \frac{1}{2} \sum_{m=1}^{N} \frac{\phi_m}{\int_{-1}^{1} \frac{1}{p_i - q_i} ds} = \sum_{m=1}^{N} \int_{-1}^{1} \frac{1}{p_i - q_i} ds \]

Velocity potential of elements Velocity of elements

- Unsteady Bernoulli Equation:

\[ \rho \left( \frac{D\phi}{Dt} + \frac{1}{2} \nabla \phi^2 \right) + \rho g(z - h) = \mathbf{P}_p \cdot \mathbf{n} \]  

\[ \mathbf{P}_{\text{bubble wall}} = \mathbf{P}_p + \mathbf{V}_r \cdot \mathbf{V} \cdot (\mathbf{V} + \mathbf{N}) \]

Evolution of encapsulated microbubble near tissue with \( f = 3\text{MHz}, P_p = 500\text{kPa}, h = 4\mu m, R_m = 3\mu m \)

- 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

**Results**

- 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

**Conclusion**

- With high intensity ultrasound exposure
  - Forms a jet impinging on the tissue
  - Jet has high velocity
  - Fluid near jet has high velocity
  - Creates holes on cell membrane
  - Generates high shear
  - Permeabilizes and perforates cell membrane
  - Facilitates uptake of drug into tissue

**References**