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3-D Analyses of Changes in Free Bubble induced Stresses on Blood Vessel Wall in Ultrasound Therapy

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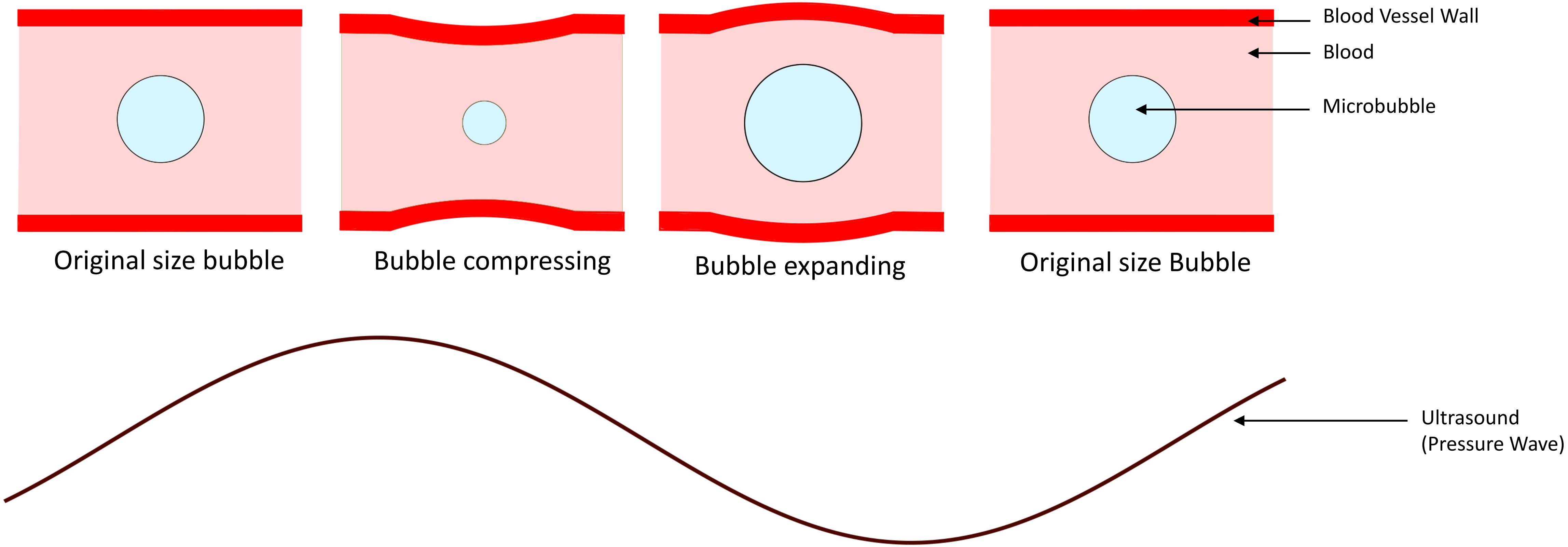
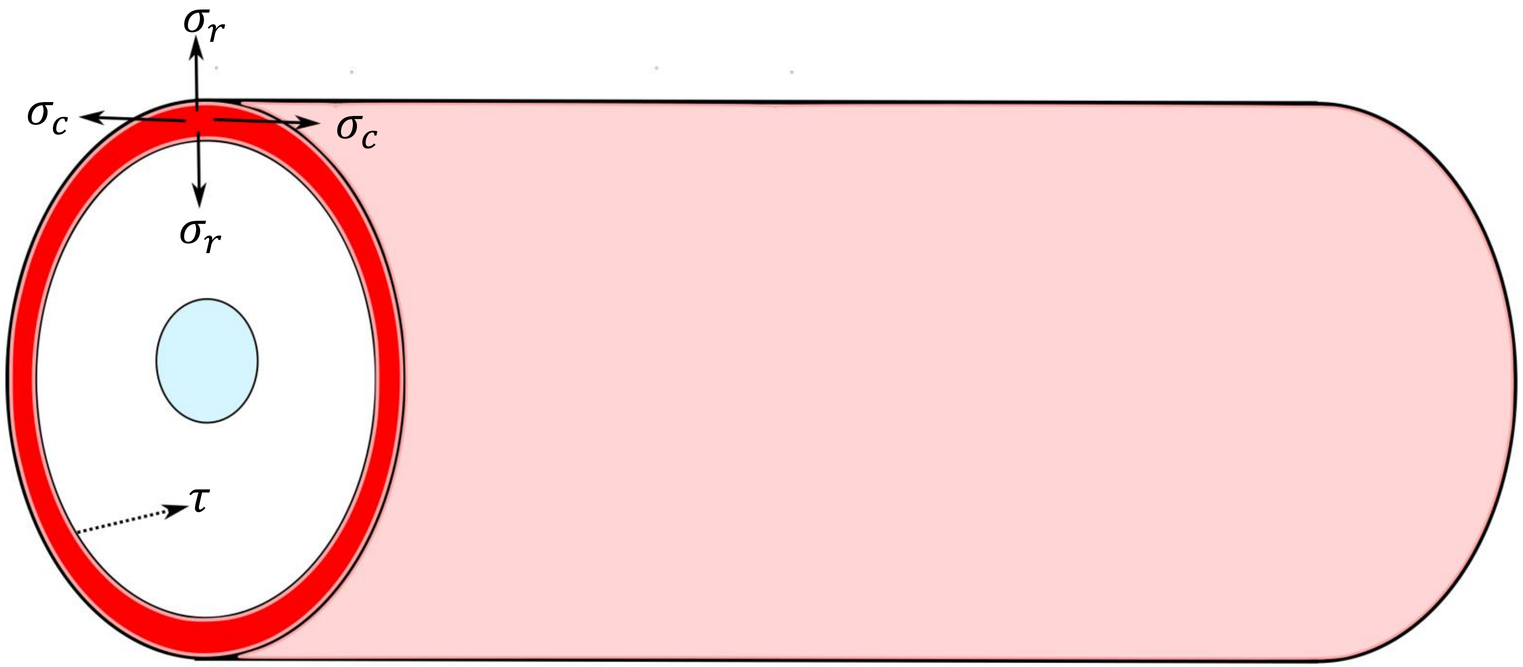
Bubble oscillation inside blood vessel in presence of ultrasound



Applications

- Drug and Gene delivery
- Blood-Brain barrier opening
- Lysis of blood clot and cell membrane

Stresses on blood vessel wall due to bubble oscillation



Stresses:

σ_c is circumferential stress
σ_r is radial stress
τ is shear stress

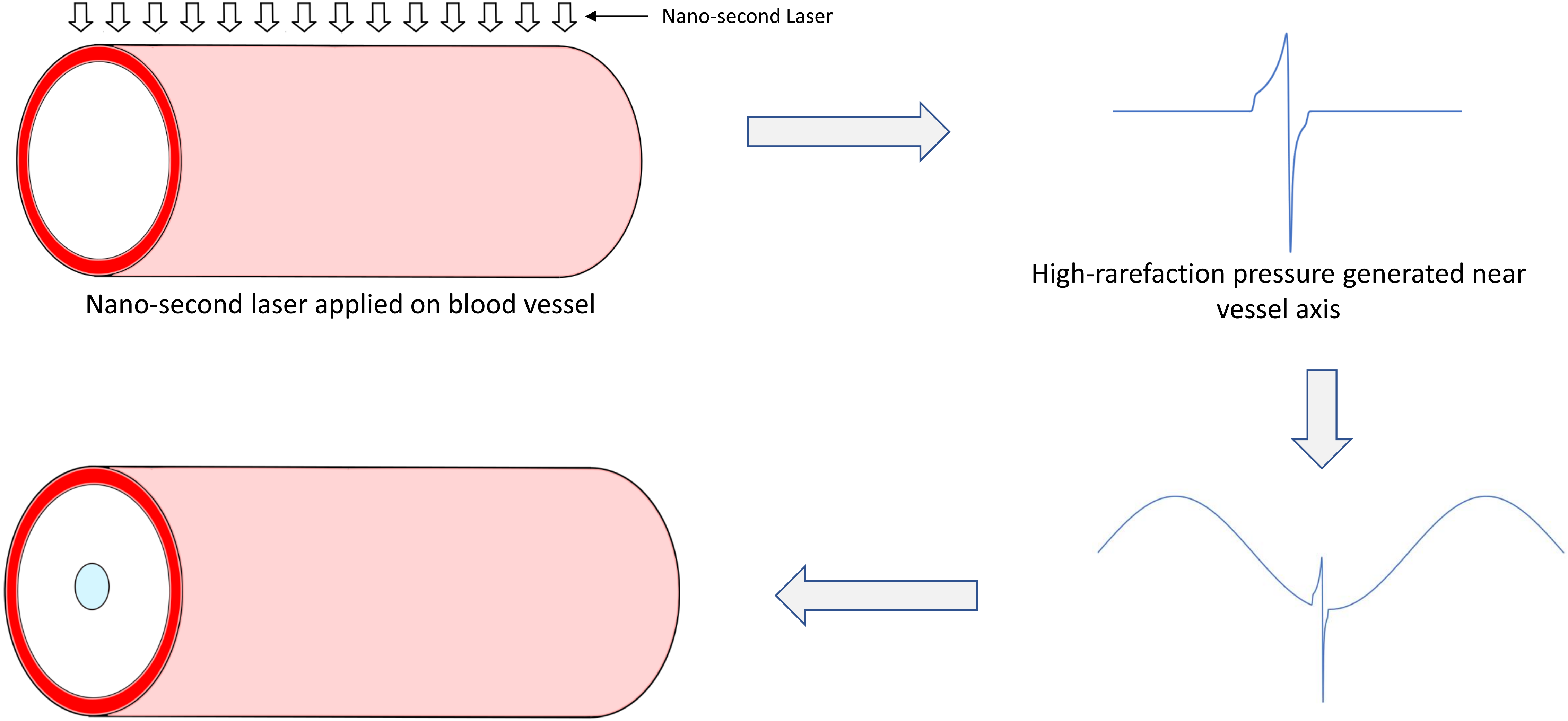
Circumferential Stress

- Responsible for vessel rupture
- Depends upon pressure exerted by blood on the vessel wall

Shear Stress

- Responsible for ion activation, reversible perforation of the membrane, cell detachment and lysis.
- Depends upon blood velocity gradient near to the vessel wall.

Photo-mediated ultrasound therapy (PUT)



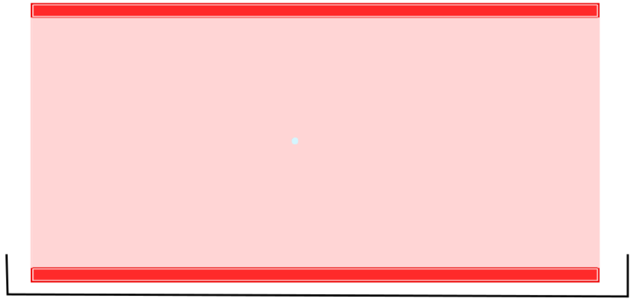
Nano-second laser applied on blood vessel

High-rarefaction pressure generated near vessel axis

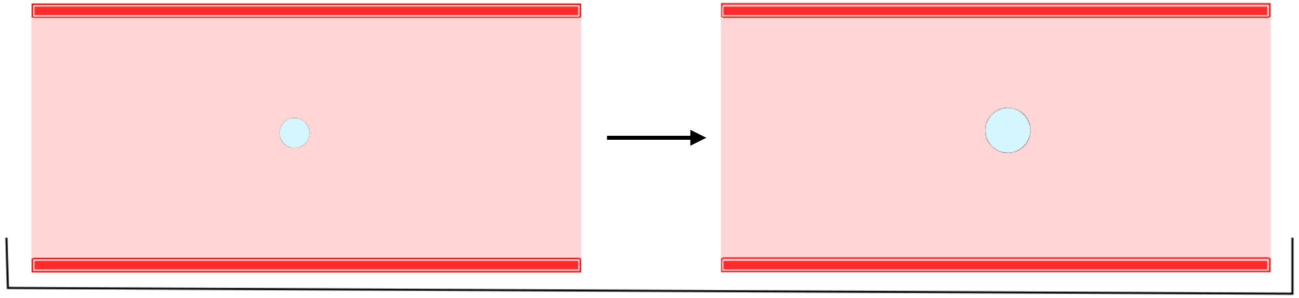
High-rarefaction pressure (due to laser) is superposed on ultrasound peak negative phase

Bubble nucleates due to ultrasound plus laser and then oscillates due to ultrasound wave

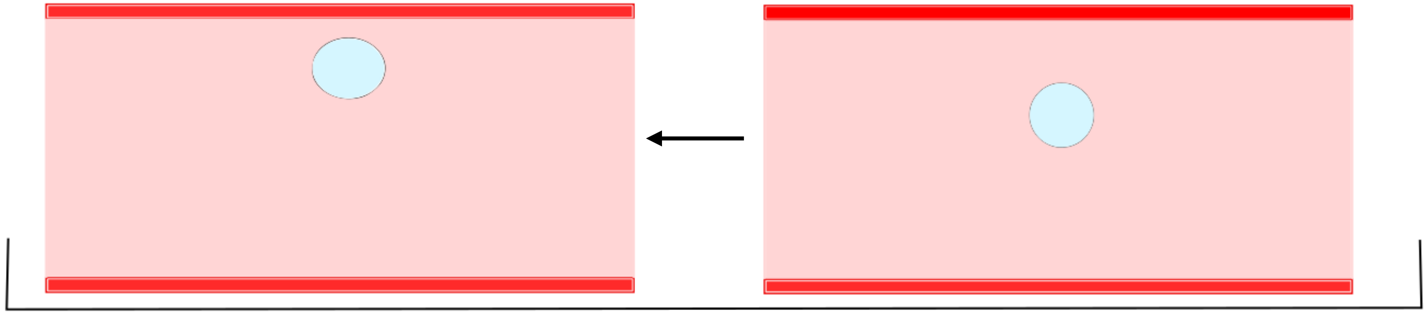
Three phases of PUT



Phase 1:
Bubble nucleation
(Ultrasound + Laser)

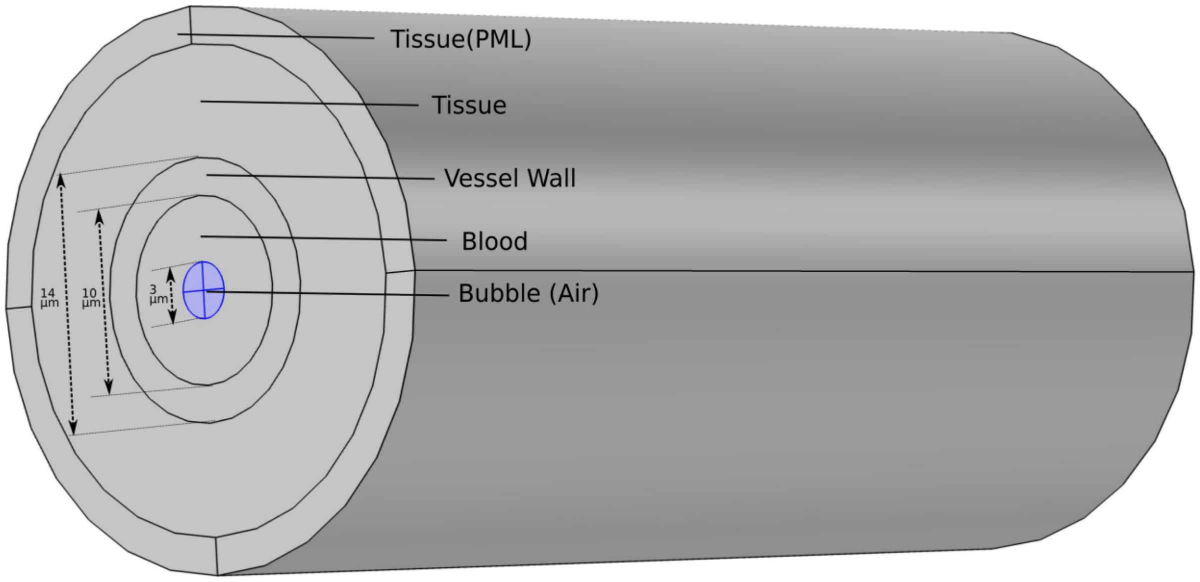


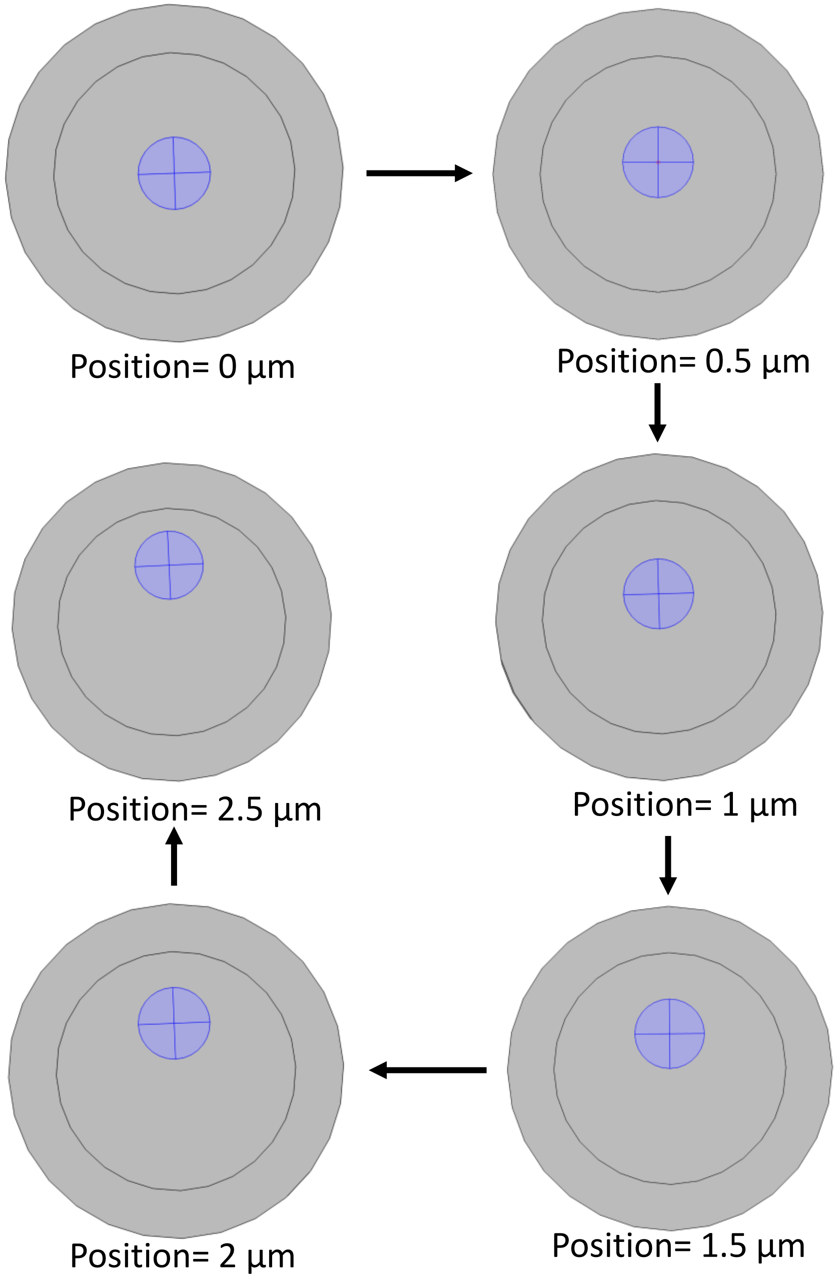
Phase 2:
Equilibrium Bubble size increases due to rectified diffusion
(Ultrasound only)



Phase 3:
Bubble reaches a stable size and drifts towards vessel wall
(Ultrasound only)

Model Setup:

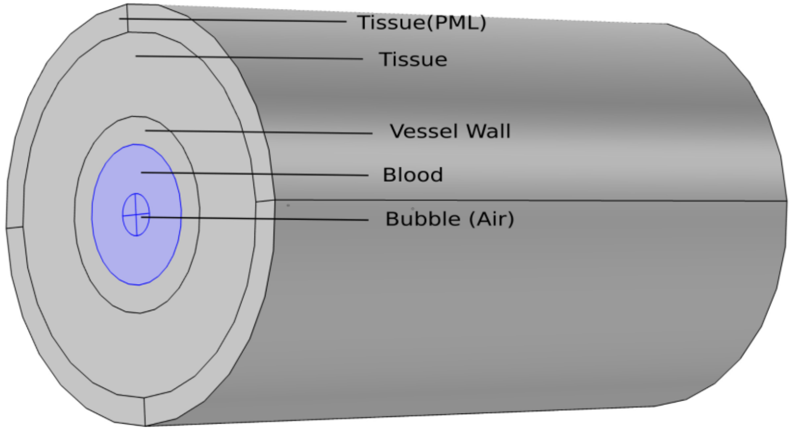




- The changes in the induced circumferential and shear stresses on the vessel wall were calculated for a bubble drifting away from the vessel axis under ultrasound pressure of 150 kPa at 1 MHz.

- The 1.5-µm radius bubble was placed in 6 different positions (0, 0.5, 1, 1.5, 2, 2.5), starting from on the vessel axis to 2.5 µm away from axis in a 5-µm radius vessel.

Fluid Domain:



Variable	**Blood**	**Air**
Density	1055 kg/m^3	Initial=2.3843 kg/m^3 (changes with pressure)
Dynamic Viscosity	0.005 Pa-s	1.814e-5 Pa-s

Table 1. Material Properties of fluid domain

- Blood and bubble (air) domains were solved using Navier-Stokes and continuity equation with blood as Newtonian & incompressible fluid and bubble as Newtonian & compressible fluid.

$$\rho\frac{\partial \boldsymbol{v}}{\partial t}+\rho(\boldsymbol{v}\cdot\nabla)\boldsymbol{v}=\nabla\cdot\left[-pI+\mu(\nabla\boldsymbol{v}+(\nabla\boldsymbol{v})^T)-\frac{2}{3}\mu(\nabla\cdot\boldsymbol{v})I\right]+\boldsymbol{F},$$

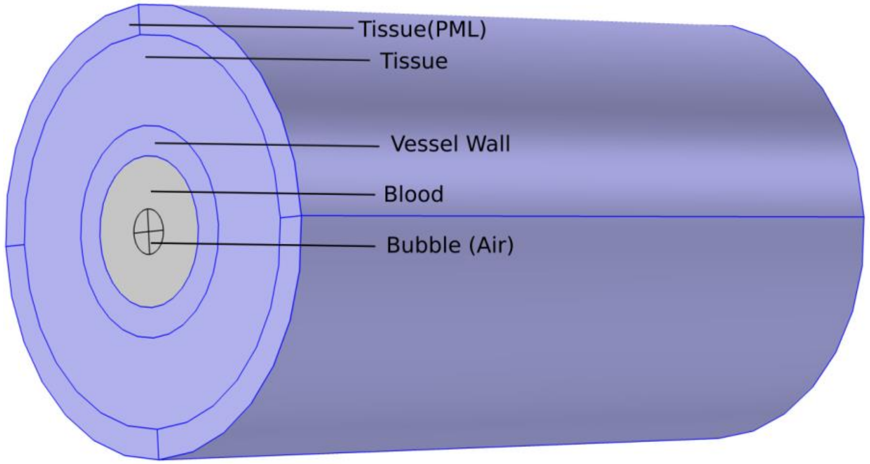
$where\ \rho\ is\ fluid\ density, v\ is\ velocity\ vector, p\ is\ pressure,$

$$\frac{\partial\rho}{\partial t}+\nabla\cdot(\rho\boldsymbol{v})=0$$

$\mu\ is\ fluid\ viscosity\ and\ F\ is\ volume\ force\ vector$

- The bubble and blood boundary was given fluid-fluid interface with surface tension of 0.072 N/m.
- The bubble was given Laplace Pressure equivalent to 2*0.072/R Pa to balance the surface tension. (R=bubble radius)

Solid Domain:



Variable	**Vessel**	**Tissue**
Density	1070 kg/m^3	1050 kg/m^3
Young's Modulus	1.5 MPa	0.5 MPa
Poisson's Ratio	0.49	0.49

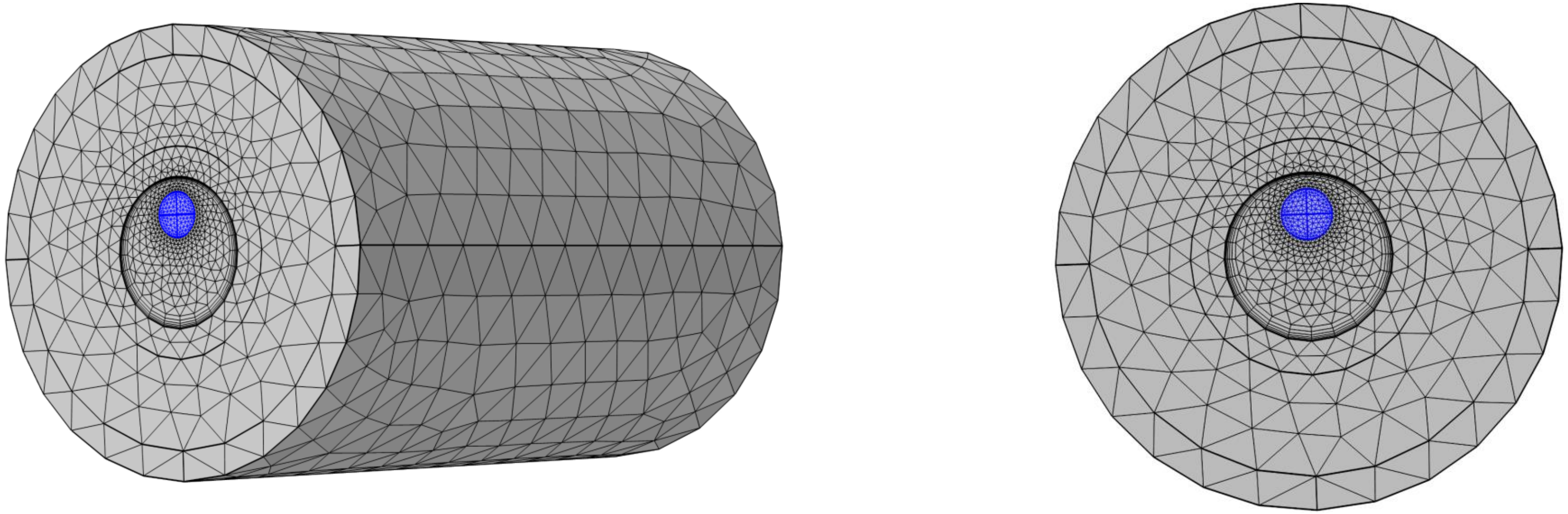
Table 1. Material Properties of solid domain

- The vessel and tissue were assumed as linear elastic solid and deformation was solved using below equation.

$$\rho_s \frac{\partial^2 \boldsymbol{u}}{\partial t^2} = \nabla . \sigma + \boldsymbol{F}_v, \qquad where\ \rho_s\ is\ solid\ density, u\ is\ displacement\ vector, \sigma\ is\ stress\ tensor\ and\ F_v\ is\ volume\ force\ vector$$

- A perfectly matched layer (PML) was given to outer boundary of tissue to absorb the oscillations and prevent reflections.

Mesh:

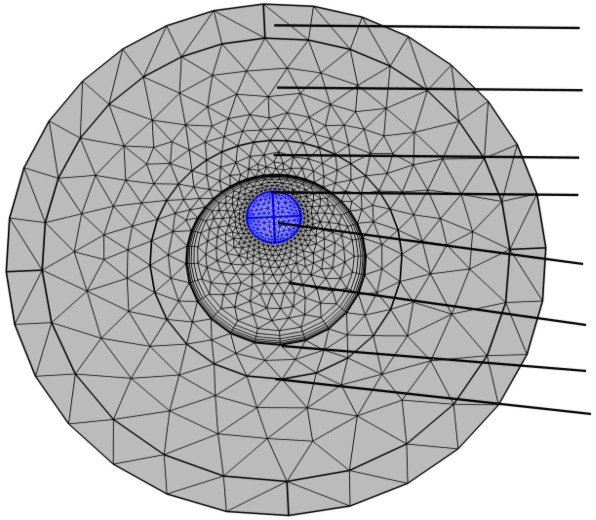


- Tetrahedral element were used for meshing with linear interpolation for velocity and pressure in fluid domain and quadratic Lagrange interpolation for displacement in solid domain.

- An ALE (Arbitrary Lagrangian Eulerian) based moving mesh was used for fluid domain to account for deformation at vessel-blood interface and bubble-blood interface.

- The total mesh have around 45000 elements with very fine mesh on bubble-blood interface and boundary layer mesh on blood-vessel interface.

Boundary Conditions & Time Step:



- The ends of the solid and fluid domain were given symmetry boundary condition to assume the model as infinitely long.
- The ultrasound wave was applied to the outer side of vessel using the boundary load condition.
- A fully coupled fluid structure interaction along with no slip was applied at blood-vessel interface.
- A free time step with maximum time step of 3 nanosecond was used for all cases. The model was solved till 4.5 µs.

Stress Calculation and Model Verification:

- The circumferential stress (CS) on the vessel wall due to pressure exerted by blood was calculated by assuming the vessel as a thick cylinder using below equation.

$$(CS)\quad \sigma_{cr} = \frac{P_i r_i^2}{r_o^2 - r_i^2} + \frac{r_i^2 r_o^2}{r^2}\left(\frac{P_i}{r_o^2 - r_i^2}\right),$$

where Pi is the pressure on the inner side of vessel, r_i *and* r_o *are the inner and outer vessel radius*

- The shear stress(SS) on the vessel wall due to blood velocity gradient near the wall is calculated using below equation.

$$(SS)\quad \tau_{xz} = \mu\left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x}\right),$$

where μ *is the blood viscosity,* u *is the blood velocity in x direction and* w *is the blood velocity in z direction*

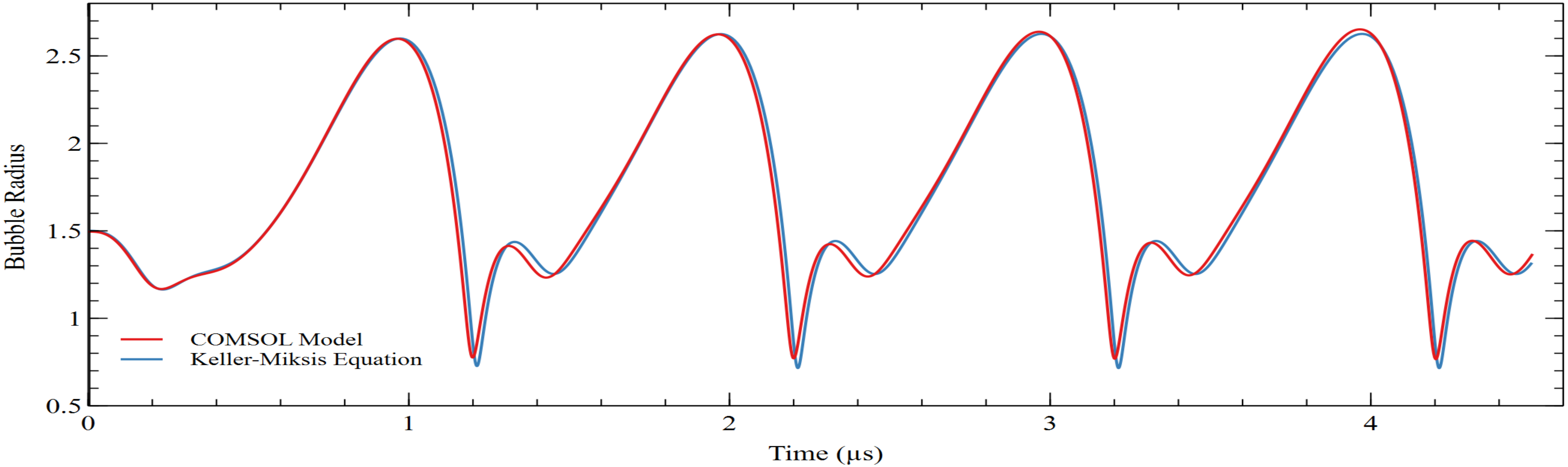
- The model was verified by solving the model with large vessel radius (10 times of bubble radius) to reduce the vessel confinement effect and comparing the obtained results with Keller-Miksis(KM) equation's results.

$$(\mathrm{KM})\quad \left(1 - \frac{\dot{R}}{\mathrm{c}}\right) R\ddot{R} + \frac{3}{2}\left(1 - \frac{\dot{R}}{3\mathrm{c}}\right)\dot{R}^2 = \frac{\mathrm{R}}{\rho \mathrm{c}}\frac{d}{dt}(P_b) + \frac{1}{\rho}\left(1 + \frac{\dot{R}}{\mathrm{c}}\right)\left(P_b - P_\infty - p\left(t + \frac{R}{c}\right)\right)$$

$$P_b = \left(P + \frac{2\sigma}{\mathrm{R}_o}\right)\left(\frac{\mathrm{R}_o}{\mathrm{R}}\right)^{3k} - \left(\frac{2\sigma}{\mathrm{R}}\right) - \left(\frac{4\mu\dot{R}}{\mathrm{R}}\right)$$

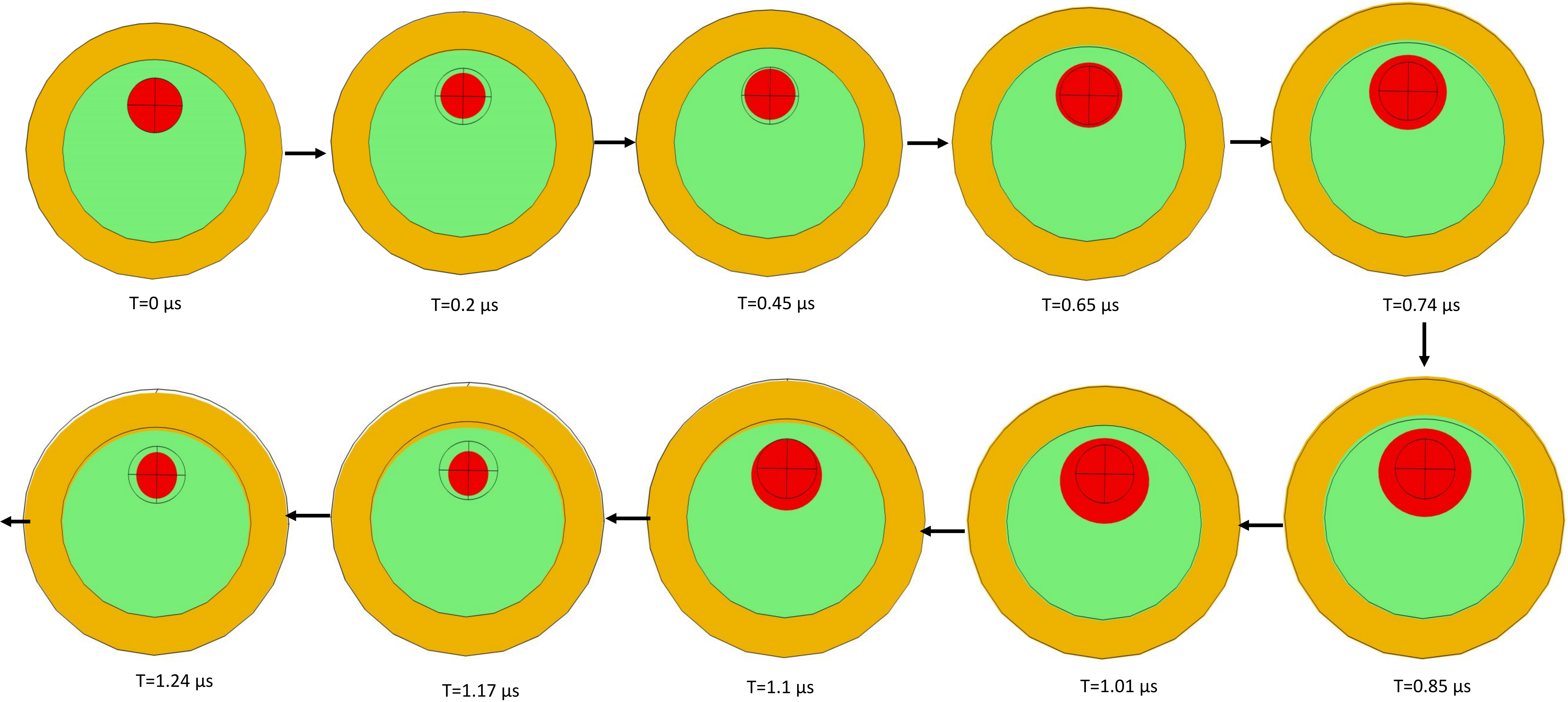
where R *is the bubble radius,* c *is the speed of sound in blood,* ρ is the density of surrounding medium, P_b *is the pressure in the surrounding medium side at the bubble and medium interface,* P_∞ *is the pressure in the surrounding medium at infinity,* σ *is the surface tension coefficient,* μ *is the viscosity of the medium and* k *is the polytropic index.*

Model Verification with Keller-Miksis Equation:

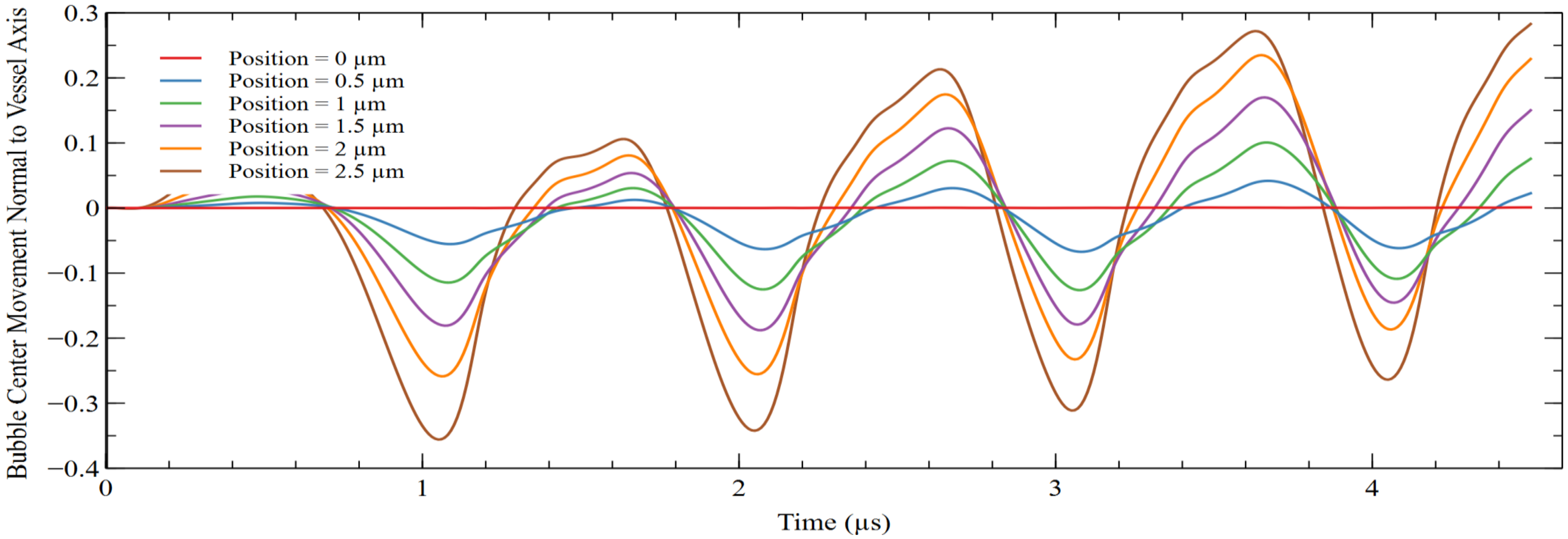


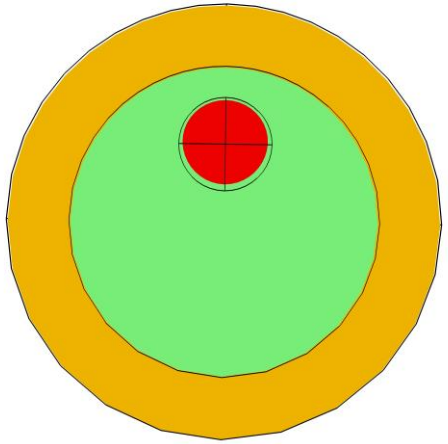
- The COMSOL model was solved with bubble radius of 1.5 µm inside vessel of 15 µm with application of ultrasound of 150 kPa amplitude and 1 MHz frequency.
- The Keller Miksis equation meant for bubble surrounded by infinite fluid was used to solve for initial bubble radius of 1.5 µm and ultrasound amplitude of 150 kPa and frequency of 1 MHz. The polytropic index of 1 (isothermal) was used as our model does not involve heat exchange between bubble and fluid.
- The result obtained from COMSOL model matched very well with Keller-Miksis equation result.

Bubble (position=2.5 μm) oscillation with time:

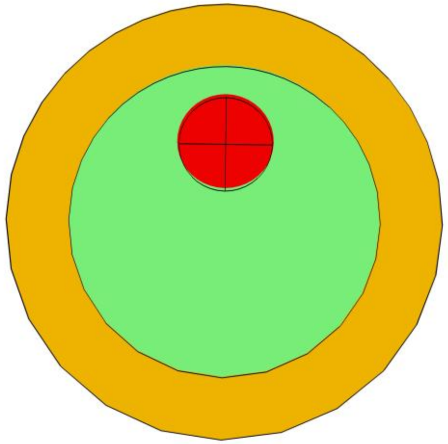


Bubble Center movement with time:

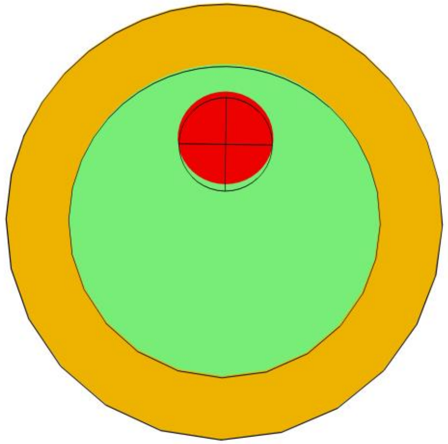




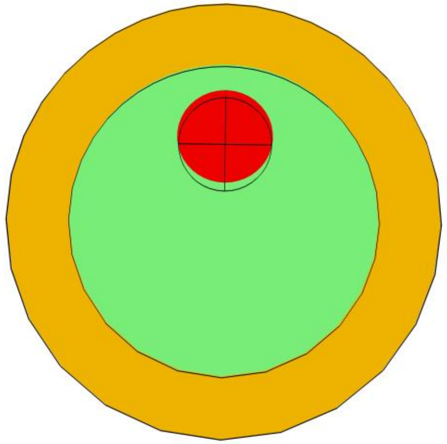
T=1.42 µs



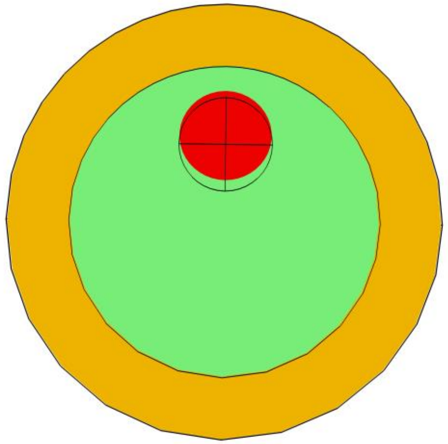
T=1.6 µs



T=2.6 µs

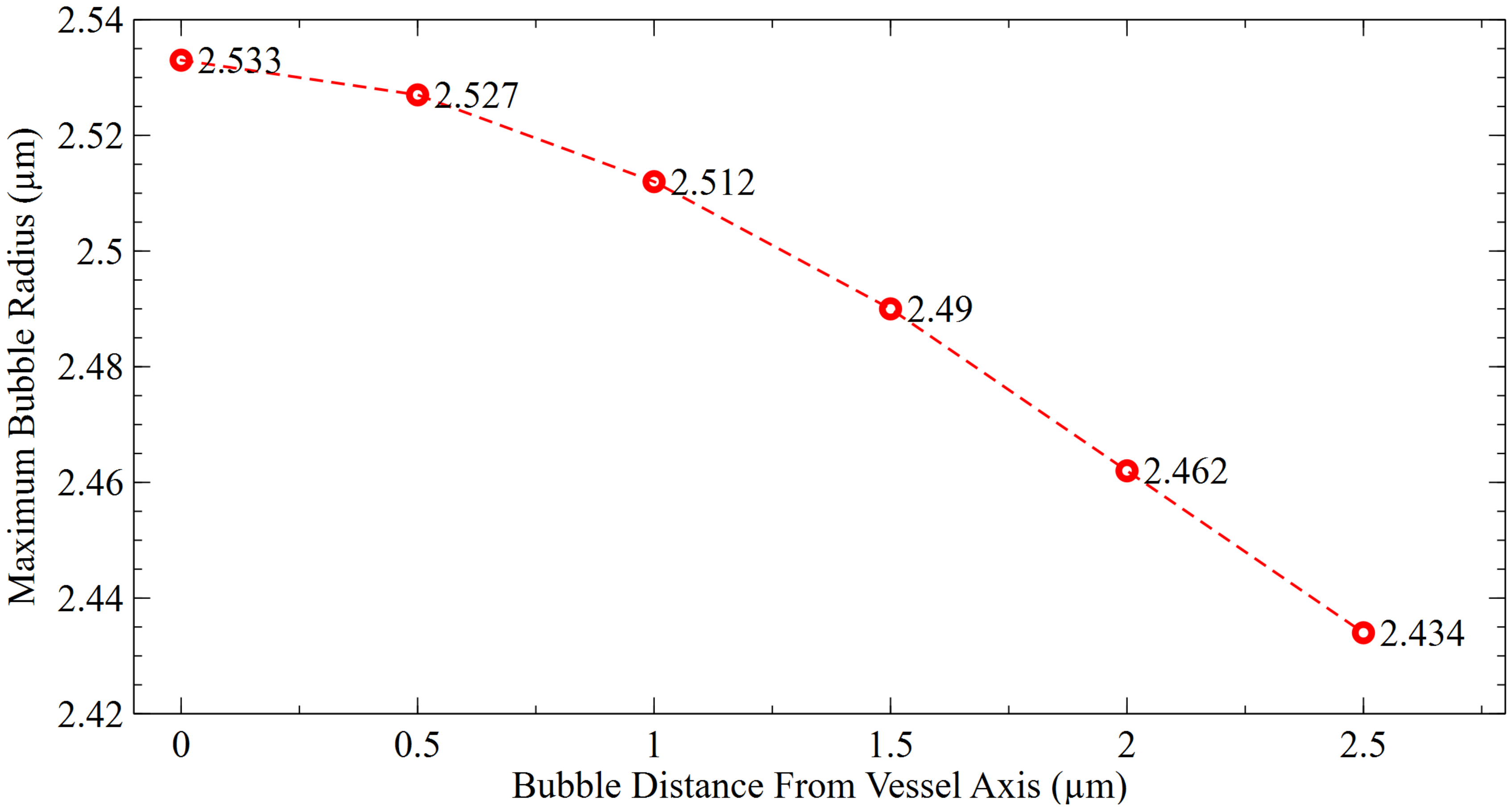


T=3.57 µs

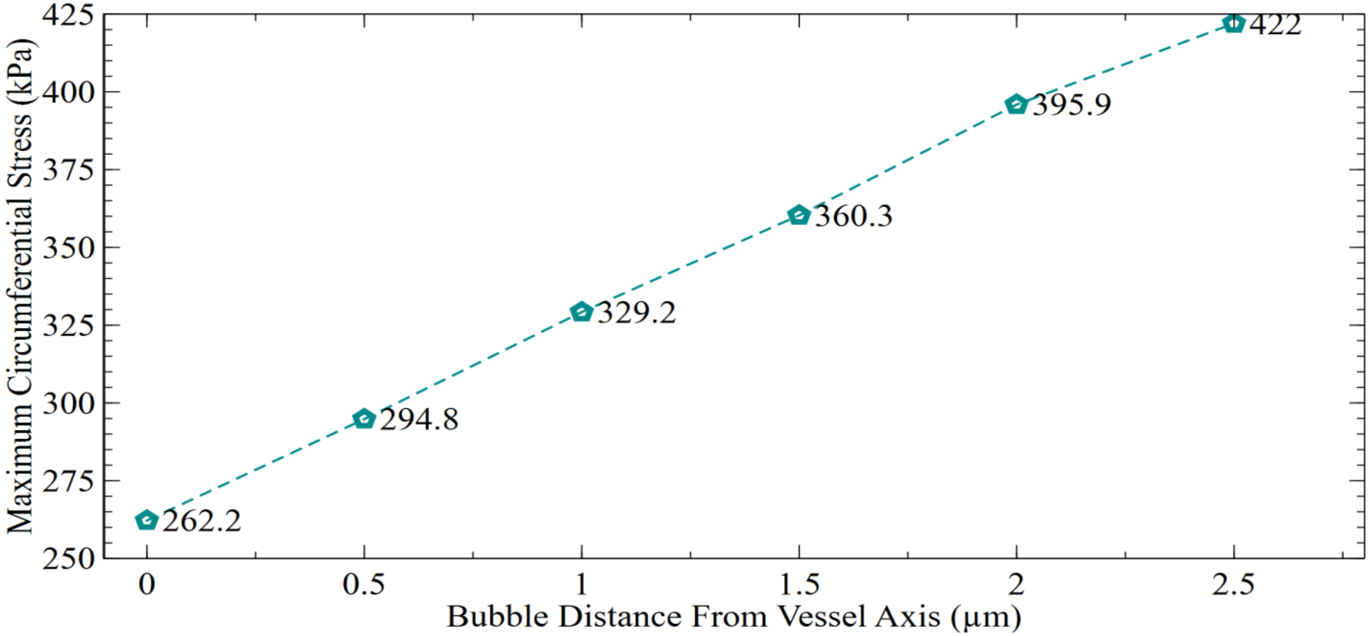


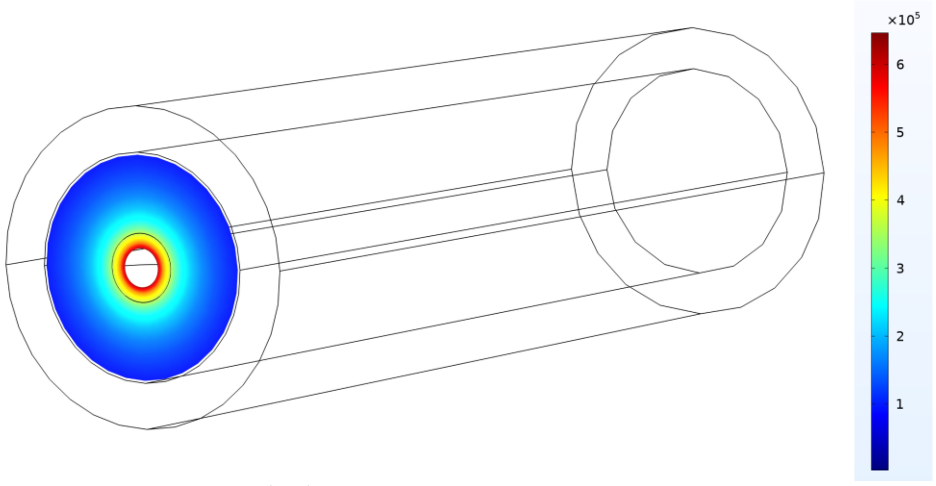
T=4.5 µs

Maximum Bubble Radius :

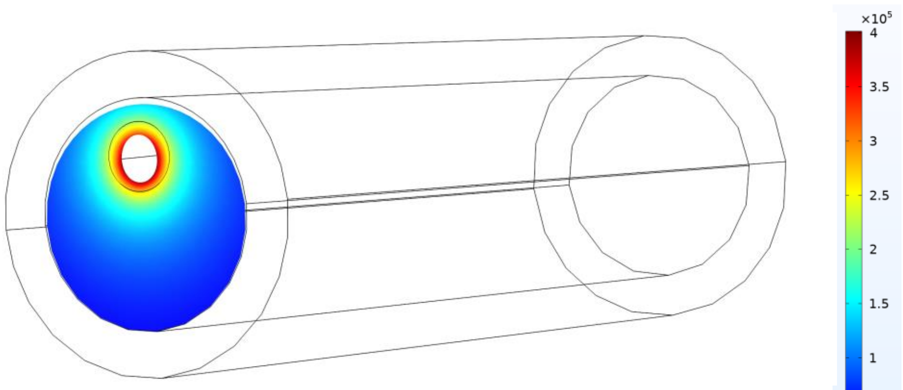


Circumferential Stress:

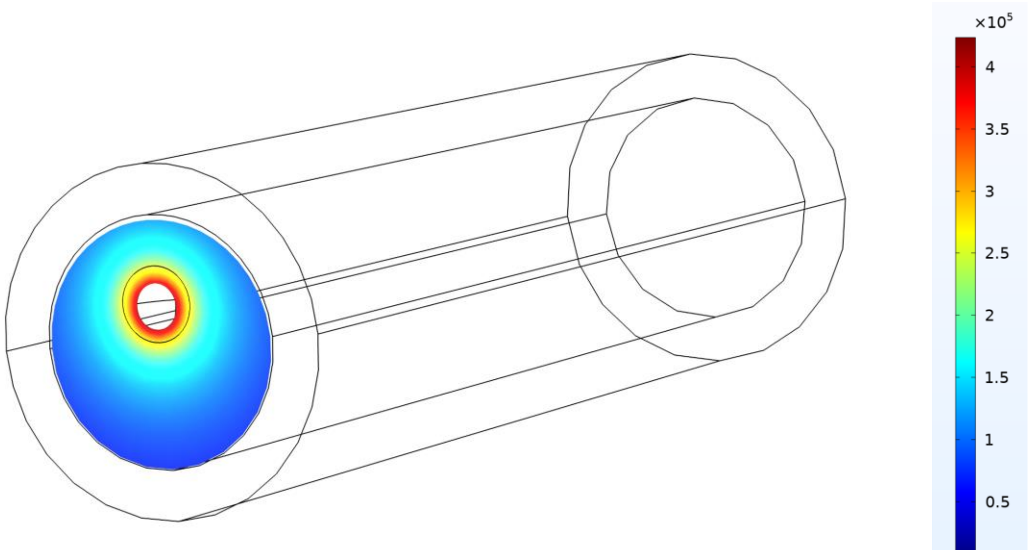




Pressure(Pa) for position=0 µm at t=1.20 µs above bubble center

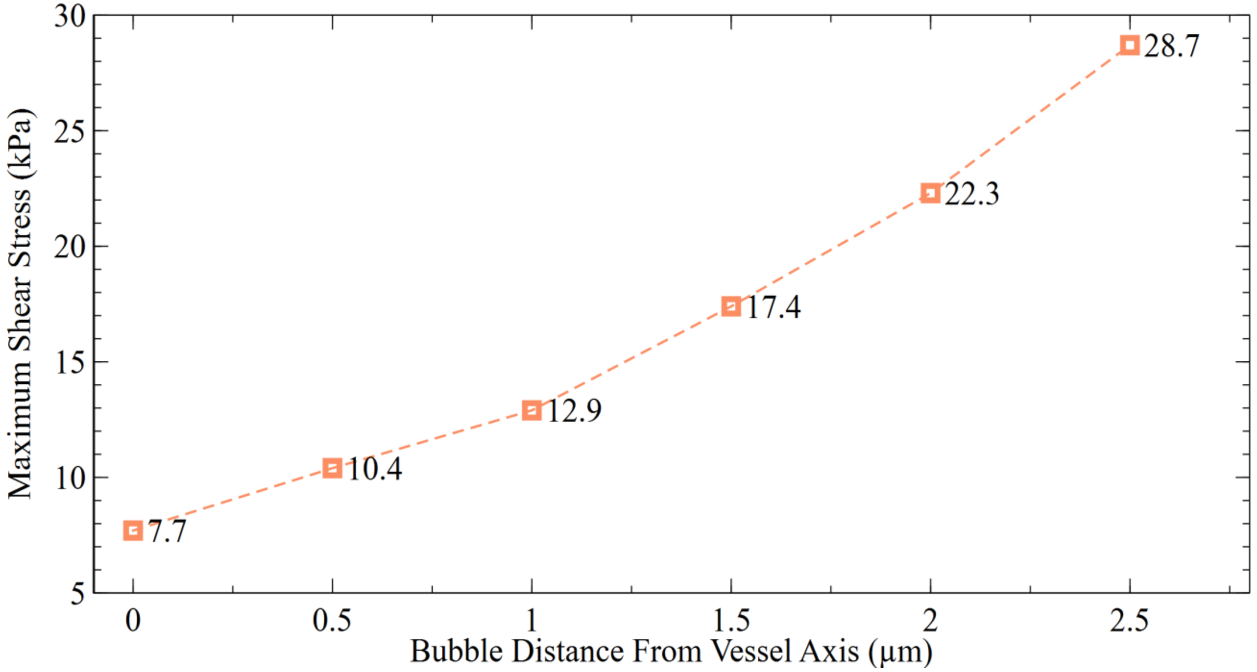


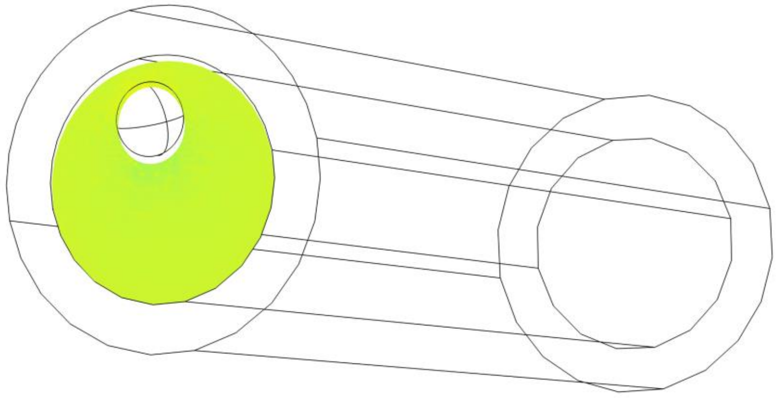
Pressure(Pa) for position=2.5 µm at t=1.20 µs above bubble center



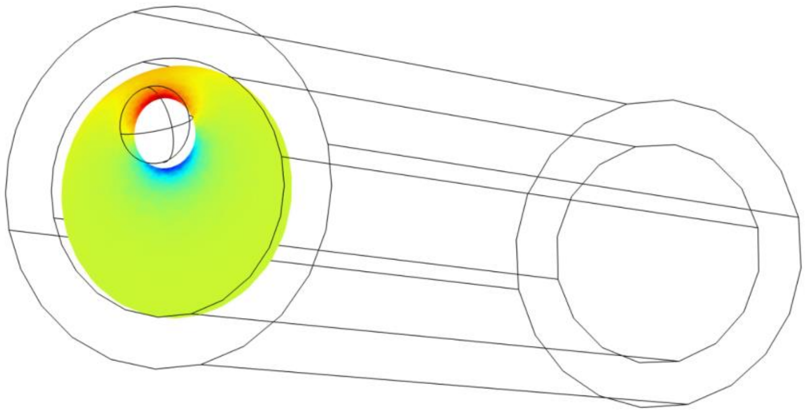
Pressure(Pa) for position=1.5 µm at t=1.20 µs above bubble center

Shear Stress:

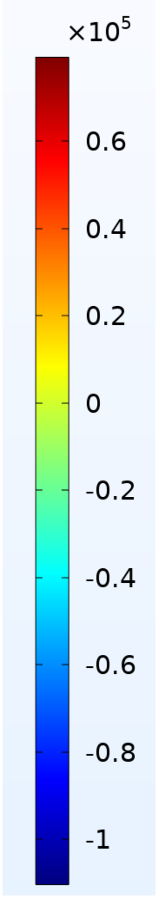




Shear Stress for position=2.5 μm at t=1.13 μs above bubble center.



Shear Stress for position=2.5 μm at t=1.13 μs for 1.5 μm away from bubble center.



Conclusions:

- The overall bubble oscillation amplitude was decreased as it moves closer to the vessel wall and away from the vessel axis.
- The asymmetricity in bubble oscillation increases for bubble placed closer to the vessel wall.
- The circumferential and shear stress on the vessel wall surface nearest to bubble surface were increased as bubble is moved closer to the vessel wall.
- The circumferential and shear stress were not uniform across the vessel surface when bubble is placed closer to the vessel wall.
- The stresses were uniform across the vessel surface initially when the bubble is in center and later concentrate such that higher stresses were on vessel surface near to the bubble surface and lower stresses were on vessel surface away from bubble surface.
- The results obtained are valid for photo-mediated ultrasound therapy (PUT) as well other ultrasound therapies.