Cavitation in Models of Wave Propagation Through Tissue Under High-Intensity Focused Ultrasound

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- High-Intensity Focussed Ultrasound (HIFU) offers an effective and non-invasive way of treating cancerous tumours through ablation with to contributions from
  - mechanical

  and
  - thermal

- Cavitation may occur during treatment and, like diagnostic applications, be used for monitoring

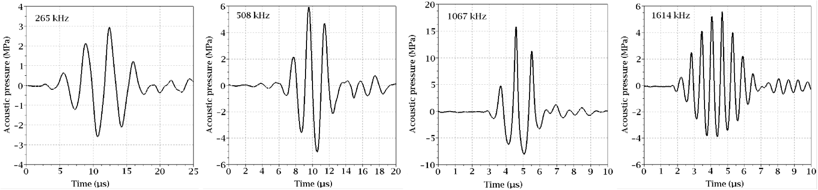
- However, it is believed that cavitation activity is more than just an indicator of the pressure and temperature fields: cavitation can enhance or inhibit heat deposition.

Essentially there are two methods of treatment

pressure wave compression of tissue due to peak positive pressure of ultrasonic wave

or

cavitation enhanced heating from oscillations of bubbles caused by peak negative pressure of ultrasonic wave



In addition to profile of the wave propagating through tissue, there is frequency dependence on the bubbles stability

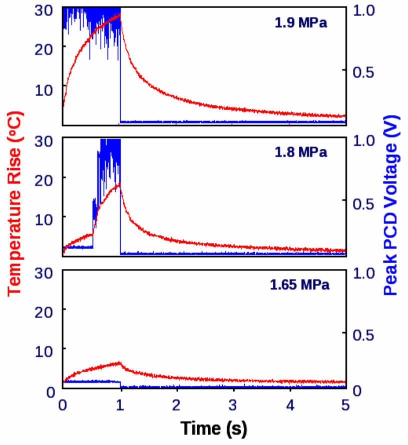


Figure: A dramatic increase in the observed rate of heating that is coincident with the onset of inertial cavitation activity[1].

[1] C. C. Coussios, C. H. Farny, G. Ter Haar, and R. A. Roy. *Role of acoustic cavitation in the delivery and monitoring of cancer treatment by high-intensity focused ultrasound*, Int. J. Hyperthermia **23**, (2007) pp. 105–120.

Shielding of the ultrasonic beam by clouds of cavitation bubbles will cause

(i) Healthy tissue to be damaged

(ii) Cancerous tissue to remain

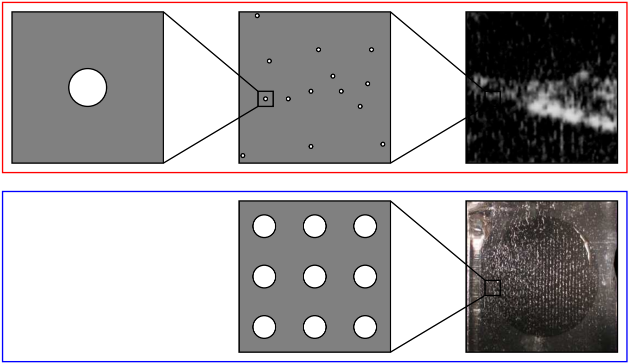
Boiling

Frequency dependence

Typically, during HIFU exposure effective medium models incorporate the oscillations of many bubbles which are assumed to equally sized and independent into propagation equations to predict:

- Attenuation
- Dispersion
- Pressure
- Temperature

In general there are two types of propagation models derived from a two-phase model.



- If bubble clouds are sufficiently dense (void fraction $\sim$1%) then hetrogeneous multiscale methods can be applied, else matched asymptotic analysis applied

Does cavitation occur in all situations? The problem of nucleation is a challenging one

Single Bubble Cavitation Models

The oscillations of a bubble can be modeled by an

Enhanced Single Bubble Rayleigh-Plesset Equation

$$\rho\left(\ddot{R}R+\frac{3}{2}\dot{R}^2\right)=p_g\left(R\right)+p_v-p_\infty-p\left(t\right)-\frac{2\sigma}{R}-\frac{4\mu\dot{R}}{R}+\int_a^b\frac{\tau_{rr}}{r}\,\mathrm{d}s+\frac{R}{c}\frac{\mathrm{d}}{\mathrm{d}t}\left(p_g-p\right) \quad (1)$$

with

$$p_g\left(R\right)=\frac{\widetilde{G}}{R^{3\kappa}} \quad \text{where} \quad \widetilde{G}=\left(p_\infty-p_v+\frac{2\sigma}{R_0}\right)R_0^{3\kappa}$$

Multi-Bubble Cavitation Models

The (secondary Bjerknes) interaction leads to an

Enhanced *Multi*-Bubble Spherical Rayleigh-Plesset Equation

$$\rho \left(\ddot{R}_i R_i + \frac{3}{2} \dot{R}_i^2 + \sum_{\substack{j=1,\\ j \neq i}}^{N} \frac{R_j}{D_{ij}} \left(R_j \ddot{R}_j + 2 \dot{R}_j^2 \right) \right) = p_g \left(R_i \right) + p_v - p\left(t\right) - \frac{2\sigma}{R_i} - \frac{4\mu \dot{R}_i}{R_i} + \int_a^b \frac{\tau_{rr}}{r} \, \mathrm{d}s + \frac{R_i}{c} \frac{\mathrm{d}}{\mathrm{d}t} \left(p_g - p \right) \tag{2}$$

Delay Differential Equations

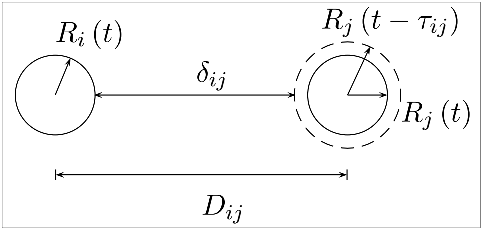
Due to fluid compressibility bubble interactions are no longer considered to be instantaneous. The interaction, given in equation (2), is now modelled as a

Delayed Multi-Bubble Spherical *Keller-Miksis* Equation

$$\begin{aligned} &\frac{R_j\left(t\right)}{D_{ij}}\left(R_j\left(t\right)\ddot{R}_j\left(t\right)+2\dot{R}_j^2\left(t\right)\right)\mapsto \\ &\quad\frac{R_j\left(t-\tau_{ij}\right)}{\delta_{ij}}\left(R_j\left(t-\tau_{ij}\right)\ddot{R}_j\left(t-\tau_{ij}\right)+2\dot{R}_j^2\left(t-\tau_{ij}\right)\right) \end{aligned} \tag{3}$$

for a multi-bubble Keller-Miksis system.

Exact delay is $\tau_{ij} = \delta_{ij}/c$ where $\delta_{ij} = D - \left(R_i\left(t\right) + R_j\left(t - \tau_{ij}\right)\right)$



Approximated as

$$\begin{aligned} & \delta_{ij} \approx D - \Big(R_i\left(t\right) + R_j\left(t\right) - \tau_{ij}\dot{R}_j\left(t\right)\Big) \\ \Rightarrow \quad & \tau_{ij} \approx \big(D - \left(R_i\left(t\right) + R_j\left(t\right)\right)\big)/\big(c + \dot{R}_j\left(t\right)\big) \end{aligned}$$

Note:

- No symmetry: $\delta_{ij} \neq \delta_{ji}$ and $\tau_{ij} \neq \tau_{ji}$
- No natural frequency attainable in closed form
  - infinite number of solutions to transcendental equation ...

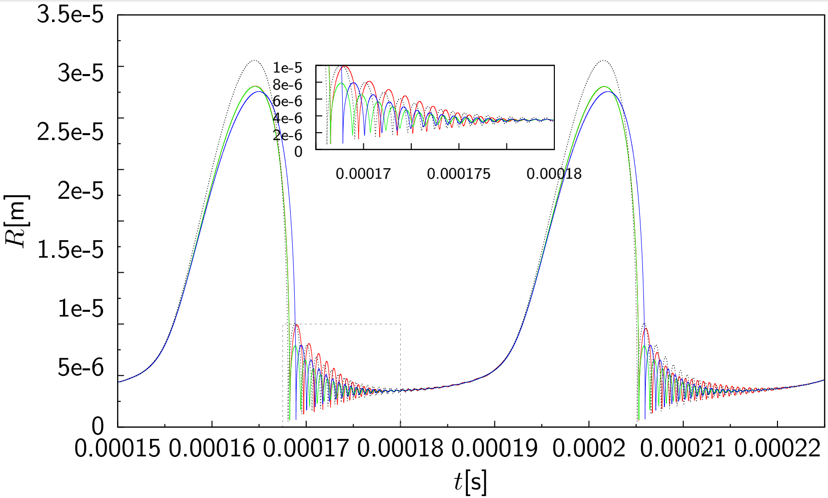


Figure: Single bubble (dotted), instant (red), constant (blue), approximation (green).

- First examine the stability of the (fully) nondimensional linearised system

$$\ddot{x}\left(t\right) + 2\zeta \dot{x}\left(t\right) + x\left(t\right) = h\ddot{x}\left(t - \tau_0\right) + p \sin \omega t$$

- For an incompressible medium the time delay is zero - system is just a scaled version of the linearised single bubble model.
- Now there are essentially two fields acting on the bubble
  - (i) The re-radiate pressure field - dependent on the bubble oscillations
  - (ii) The applied acoustic pressure

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In the absence of the applied field, the equation has a trivial steady state. The corresponding characteristic equation is

$$\lambda^2 + 2\zeta\lambda + 1 + h\lambda^2 e^{-\lambda\tau} = 0$$

which has an infinite number of solutions. Let $\lambda = \pm i\mu$, then

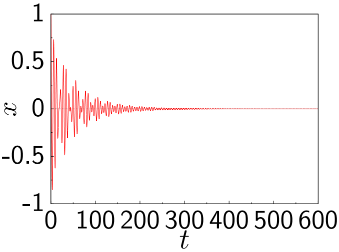
$$\mu_{\pm}^2 = \frac{1}{1-h^2}\left(\left(1-2\zeta^2\right) \pm \sqrt{\left(1-2\zeta^2\right)^2 - \left(1-h^2\right)} \right)$$

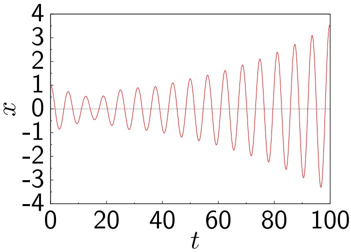
Hence there is are explicit expressions for the stability boundaries for the delay

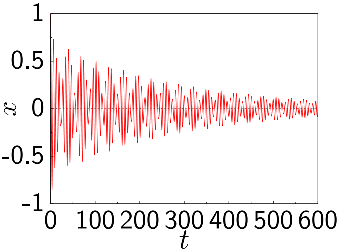
$$\tau_c = \frac{1}{\mu_{\pm}}\left(\tan^{-1}\left(\frac{2\zeta\mu_{\pm}}{\mu_{\pm}-1}\right) \pm n\pi \right)$$

This means that $\zeta = 1/\sqrt{2}$ is the critical value

- If below this value then the bubble is always stable regardless of the separation distance.
- If above this value the bubbles may grow unboundedly if the separation distances are within domains of instability.
  - If the bubbles drift apart then the delay changes, the trivial equilibrium undergoes successive switches in stability before eventually becoming unstable.
- Linearised equations of motion may yield “unphysical” results
  Currently investigating whether weakly nonlinear oscillations have this property also ...


1
0.5
0
-0.5
-1
x
0 100 200 300 400 500 600
t
(a)


4
3
2
1
0
-1
-2
-3
-4
x
0 20 40 60 80 100
t
(b)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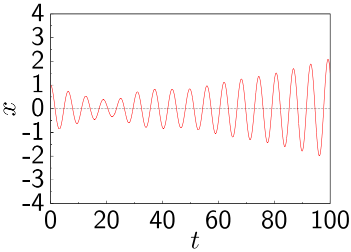
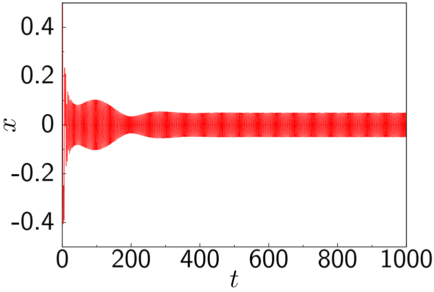
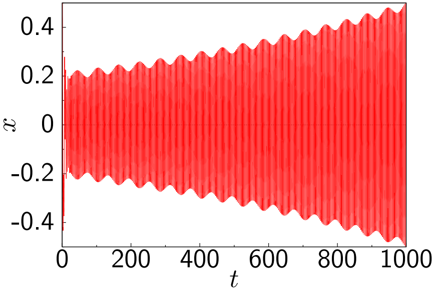
t
(c)


4
3
2
1
0
-1
-2
-3
-4
x
0 20 40 60 80 100
t
(d)

With the applied field the system may undergo a subcritical Hopf bifurcation into a limit cycle.



(e) $\tau = 0$



(f) $\tau = 0$

Idea

is to decompose the radius-time profile into three distinct regions determined by the dominant forces on the bubble and solve the corresponding *approximated* governing equation within each regime *exactly*.

The expansion regime can be written in terms of the kinetic energy of the bubble, the driving pressure and the ‘effective surface tension’

$$R\ddot{R} + \frac{3}{2}\dot{R}^2 = \frac{1}{3}\frac{\omega_0}{\omega}\left(p\cos\left(\omega t + \phi\right) - A\right)$$

where $A = \left(1 + \dfrac{2\sigma}{p_0}\dfrac{1}{K\left(p\right)}\right)$ is the ‘effective surface tension’. Note

$$R\ddot{R} + 2\dot{R}^2 = \frac{1}{2}\frac{\mathrm{d}^2}{\mathrm{d}t^2}R^2 \quad \text{and} \quad \frac{R}{D}\left(R\ddot{R} + 2\dot{R}^2\right) = \frac{1}{3}\frac{1}{D}\frac{\mathrm{d}^2}{\mathrm{d}t^2}R^3$$

and

$$R\ddot{R} + \frac{3}{2}\dot{R}^2 = \frac{1}{2}\frac{\mathrm{d}^2}{\mathrm{d}t^2}R^2 + \frac{1}{2}\dot{R}^2 = \frac{3}{4}\frac{\mathrm{d}^2}{\mathrm{d}t^2}R^2 - \frac{1}{2}R\ddot{R}$$

$$\frac{\mathrm{d}^2}{\mathrm{d}t^2} R^2 \left(1 + 2R/3D\right) = \begin{cases} \dfrac{4}{9}\alpha^2 \left(p \cos\left(\omega t + \phi\right) - A\right) & \text{on} \quad \left[-t_+, t_+\right] \\ & \text{as} \quad \dot{R}^2 \ll R\ddot{R}, \\ \dfrac{2}{3}\alpha^2 \left(p \cos\left(\omega t + \phi\right) - A\right) & \text{on} \quad \left[t_+, t_{\min}\right] \\ & \text{as} \quad \dot{R}^2 \gg R\ddot{R}. \end{cases}$$

Integrating twice and enforcing continuity between regions yields an analytic closed form solution for the expansion phase of the bubble oscillations.

Summary & Conclusions

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Transcostal High-Intensity Focussed Ultrasound for the Treatment of Cancer

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Any questions?

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