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Bubble Dynamics of Ultrasonic Drug Release from Polymeric Micelles

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**Introduction**

We have reported the ability of Pluronic P-105 micelles to sequester antiangiogenic drugs and release their contents upon application of 70 kHz ultrasound (US) (Figure 1). Optimal targeting to tumors depends on focus and control of US ablation, which is better achieved at higher frequencies. While no evidence of in vitro drug release was found at 500 kHz, drug release at 70 kHz correlates with the intensity of the subharmonic signal in the acoustic spectrum generated by the insonated bubbles (Figure 2). Having established that bubble oscillations (cavitation) are directly related to drug release at 70 kHz, we now investigate the differences in the dynamics of oscillating bubbles at both 70 and 500 kHz.

**Methods:**

For this study we followed the bubble dynamics treatment of Parlitz et al. by using a modification to the Keller-Miksis model:

\[ P(R, t) = \frac{1}{2 \rho_0 c} \frac{d^2 R}{dt^2} + \frac{1}{\rho_0} \frac{d P_{\text{stat}}}{dt} + \frac{1}{\rho_0} \frac{d^2 P_{\text{V}}}{dt^2} + \frac{1}{\rho_0} \frac{d^2 P_c}{dt^2} \]

where \( R \) is the bubble radius, \( c \) is the speed of sound in water, \( \rho_0 \) is the density of the liquid, \( \rho_{\text{stat}} \) is the static pressure, \( P_{\text{V}}(T) \) is the vapor pressure far from the bubble, \( S \) is the surface tension, \( R_0 \) is the equilibrium radius, \( k \) is the polytropic constant, \( \rho_0 \) is the viscosity of the liquid, and \( t \) is time. The last term represents a sinusoidal driving pressure of frequency \( f \) and amplitude \( \frac{2 \pi f_0}{c} \), where \( p_{\text{stat}} \) is the static pressure, \( P_{\text{V}}(T) \) is the vapor pressure far from the bubble, \( S \) is the surface tension, \( R_0 \) is the equilibrium radius, \( k \) is the polytropic constant, \( \rho_0 \) is the viscosity of the liquid, and \( t \) is time. The last term represents a sinusoidal driving pressure of frequency \( f \) and amplitude \( \frac{2 \pi f_0}{c} \).

**Conclusions**

**Results:** Figure 3 shows that the bubble undergoes the classic period-doubling route to chaos at 500 kHz, shown by the appearance of all periods after MI=0.4. This is peculiar since no subharmonics were seen during experiments for this frequency. It also shows that at 70 kHz the bubble instead first period-doubles near MI=0.32, in agreement with the experimental subharmonic (and drug release) threshold of 0.35, and then goes back to a single period oscillation, only to suddenly burst into chaos (intermittent route to chaos). In general, bubble behavior at 70 kHz is more erratic and violent than at 500 kHz (expected due to resonance) and is reflected in the “quasi-stable” subharmonic oscillations that accompany the intermittent route to chaos as opposed to the more deliberate and repeating subharmonics expected of the latter. If drug release is to be seen at 500 kHz, the same geometry seen at 70 kHz must first be identified in parameter space and then reproduced experimentally. These results also suggest the need to update the current categorization of cavitation phenomena (Figure 4).

**References:**


**Figure 1** (above). Micelles release the encapsulated drug at the targeted tissue upon application of ultrasound then quickly reform.

**Figure 2** (right). Drug release correlates with subharmonic intensity at 70 kHz.

**Figure 3**. Trajectories in state space projection (R and u, Figs 3a, c,f,h) frequency spectra (Fourier transform of radial oscillations, Figs 3b, d, g, j) and bifurcation diagrams (for radial displacement, Figs 3c, e, i, j) for 500 kHz (top, Figs 3a-f) and 70 kHz (Figs 3g-j). The plots correspond to mechanical index (MI) values of 0.275 (top, Figs 3a,b) and 0.3875 (bottom, Figs 3c,d) for 500 kHz and 0.32 (top, Figs 3g,h) and 0.35 (bottom, Figs 3i,j) for 70 kHz.

**Figure 4**. The classic view of cavitation classification and their corresponding acoustic attributes.