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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 anthracycline drugs and release their contents upon application of 70 kHz ultrasound (US)¹ (Figure 1). Optimal targeting to tumors depends on focus and control of US insonation, 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 bubbles² (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 frequencies.

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

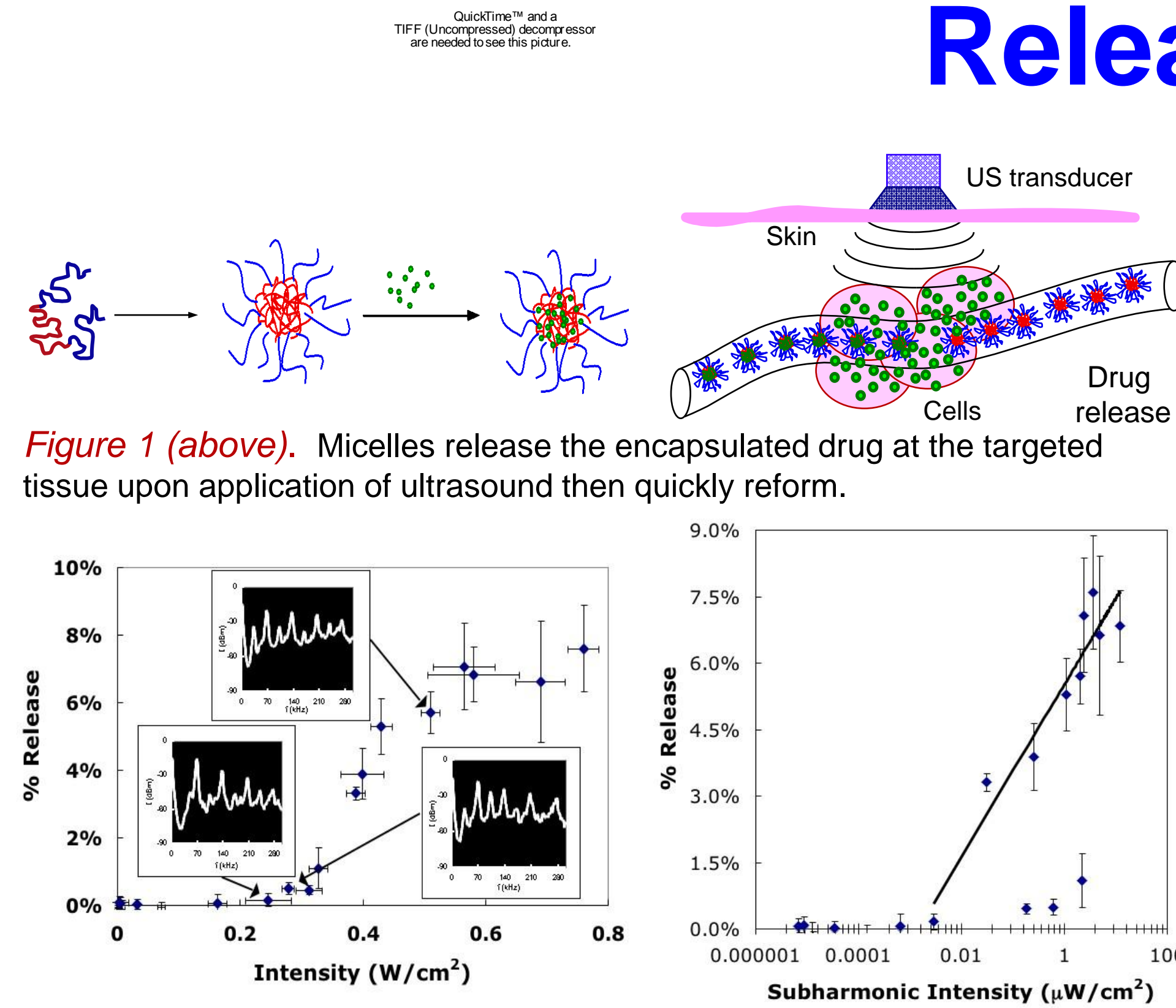


Figure 1 (above). Micelles release the encapsulated drug at the targeted tissue upon application of ultrasound then quickly reform.

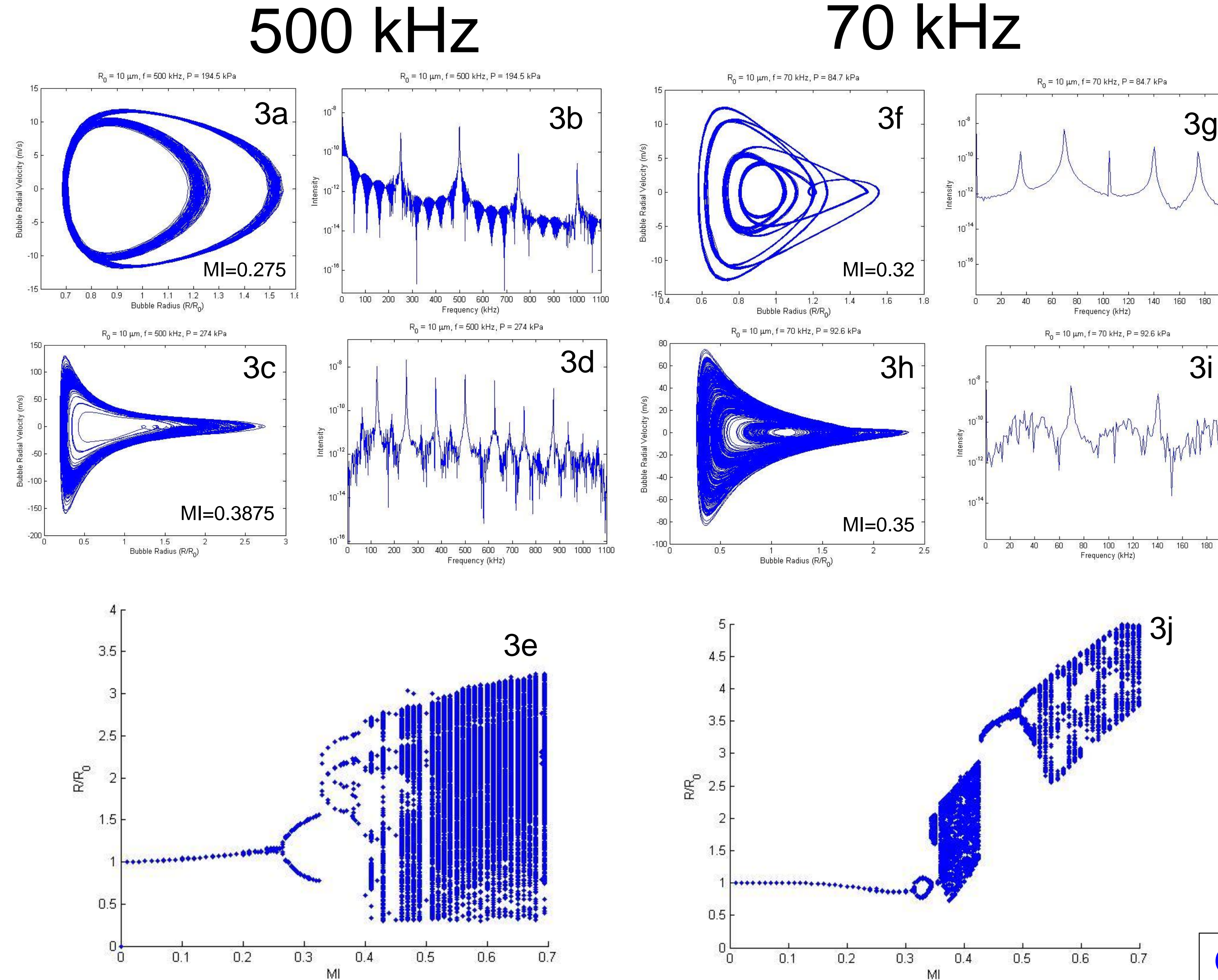


Figure 3. Trajectories in state space projection (R and u, Figs 3a, c,f,h), frequency spectra (Fourier transform of radial oscillations, Figs 3b, d, g, i), and bifurcation diagrams (for relative radial displacement, Figs 3e, j) for insonated 10 μm bubbles at 500 (Figs 3a-e) and 70 kHz (Figs 3f-j). The 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 3f,g) and 0.35 (bottom, Figs 3h,i) for 70 kHz.

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 about 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 experimental² 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).

Methods:

For this study we followed the bubble dynamics treatment of Parlitz *et al.* by using a modification to the Keller-Miksis model³:

$$\left(1 - \frac{\dot{R}}{c}\right) R \ddot{R} + \frac{3}{2} \dot{R}^2 \left(1 - \frac{\dot{R}}{3c}\right) = \left(1 - \frac{\dot{R}}{c}\right) \frac{P}{\rho_L} + \frac{R}{\rho_L c} \dot{P}$$

where R is the bubble radius, c is the speed of sound in water, ρ_L is the density of the liquid, the dot denotes differentiation with respect to time, and P is given by

$$P = \left(p_{stat} - p_v(T_\infty) + \frac{2S}{R_0}\right) \left(\frac{R_0}{R}\right)^{3k} - \frac{2S}{R} - \frac{4\mu_L \dot{R}}{R} - p_{stat} + p_v(T_\infty) - A \sin(2\pi f t)$$

where p_{stat} is the static pressure, p_v(T_∞) is the vapor pressure far from the bubble, S is the surface tension, R₀ is the equilibrium radius, k is the polytropic constant, μ_L is the viscosity of the liquid, and t is time. The last term represents a sinusoidal driving pressure of frequency f and amplitude A. The equation was solved numerically in MATLAB by introducing the variables u = dR/dt and Q = ft mod 1. The solutions for a 10 μm bubble at both 70 and 500 kHz of applied US were used to generate trajectories in state space and Fourier transformed to create analogs to experimental acoustic spectra (Figure 3). Poincaré plots (maps of first return on a surface of section) were also constructed and the results used to create bifurcation diagrams that give the entire dynamic history of the bubble (in R/R₀) as a function of mechanical index (MI=P⁺/f^{0.5}).

REFERENCES: 1. Hussein, G.A. *et al.* (2000) *J Cont Rel* **69:43-52** 2. Hussein, G.A. *et al.* (2005) *J Cont Rel* **107:253-26** 3. Parlitz *et al.* (1990) *J Acoust Soc of Am* **88:1061-1077**.

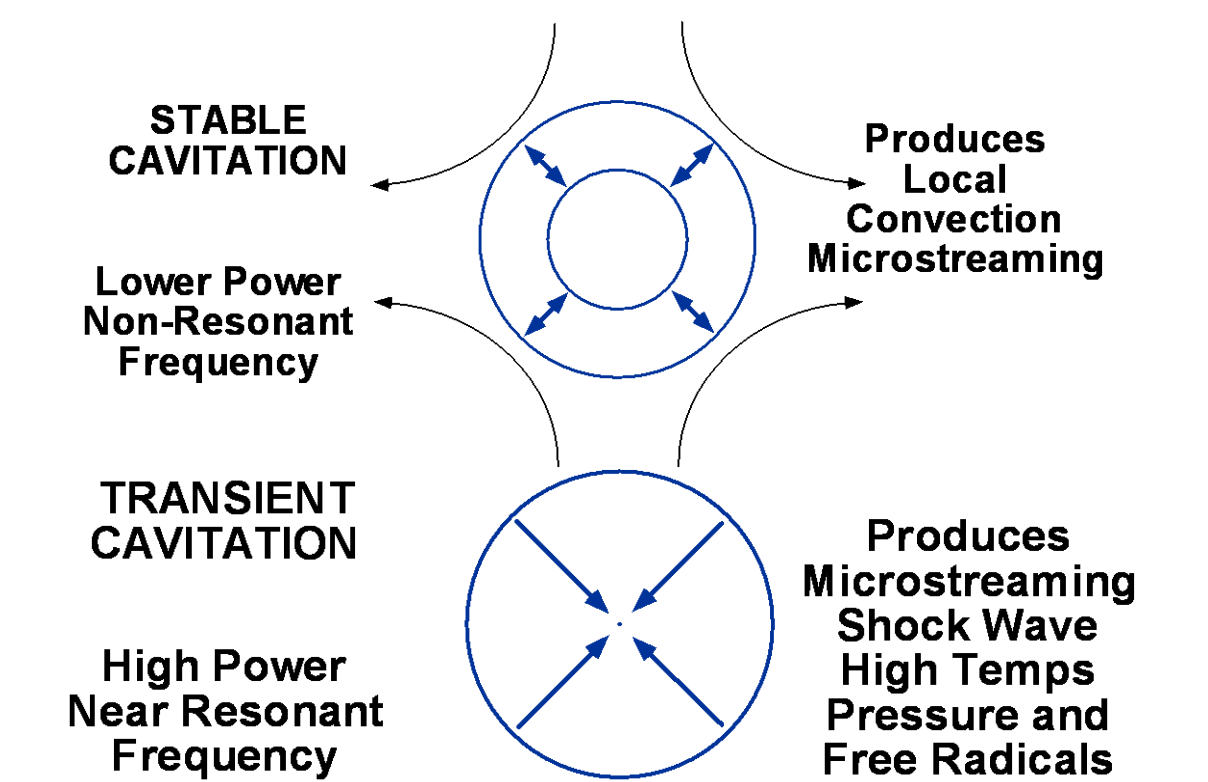


Figure 4. The classic view of cavitation classification and their surrounding effects does not account for the behavior observed.

Conclusions Bubble oscillations under US at 70 kHz and 500 kHz are fundamentally different as the bubble exhibits an intermittent route to chaos in the former and a period-doubling one in the latter. Drug release from Pluronic micelles at high frequencies is expected to occur under parameter values that reproduce the intermittent type of cavitation seen at 70 kHz.