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Simulated destructive release from antibubble microcapsules

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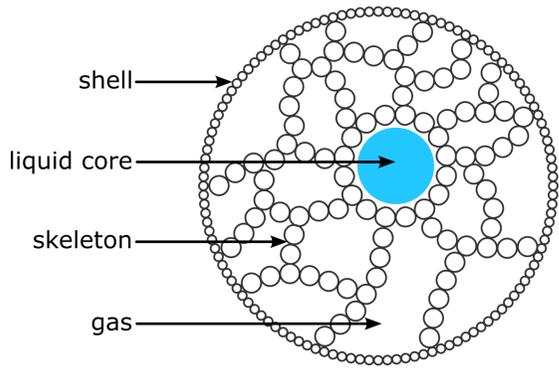
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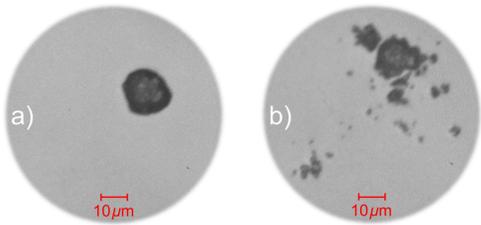
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Antibubbles are small gas bubbles comprising one or multiple liquid or solid cores, typically surrounded by stabilising shells. Acoustically active microscopic antibubbles have been proposed for use as theranostic agents. For clinical applications such as ultrasound-guided drug delivery and flash-echo, it is relevant to know the fragmentation threshold of antibubbles and the influence of the stabilising shells thereon. For antibubbles with an infinitesimal frictionless elastic shell of constant surface tension, we simulated ultrasound-assisted fragmentation by computing radial pulsation as a function of time using an adapted Rayleigh-Plesset equation, and converting the solutions to time-variant kinetic energy of the shell and time-variant surface energy deficit. By repetition over a range of pressure amplitudes, fragmentation thresholds were found for antibubbles of varying size, core volume, shell stiffness, and driving frequency. As backscattering increases with scatterer size, and as drug delivery would require vehicles just small enough to pass through capillaries with a relatively large payload, we chose to present typical results for antibubbles of resting diameter 6 μm with a 90% incompressible core. At a driving frequency of 13 MHz, the fragmentation threshold was found to correspond to mechanical indices less than 0.4, irrespective of shell stiffness. This mechanical index is not considered unsafe in diagnosis. That means that antibubbles acting as drug-carrying vehicles could release their payload under diagnostic conditions.



Schematic representation of an endoskeletal antibubble.



Antibubble before (a) and after (b) sonication and resulting fragmentation.

Methods

Fundamental pulsation

$$R\ddot{R} + \frac{3}{2}\dot{R}^2 = \frac{1}{\rho} \left[\left(p_0 - p_v + \frac{2\sigma R_0}{R_0^2 - R_c^2} \right) \left(\frac{R_0^3 - R_c^3}{R^3 - R_c^3} \right)^\gamma + p_v - \frac{2\sigma R}{R^2 - R_c^2} - 2\chi \left(\frac{1}{R_0} - \frac{1}{R} \right) - \frac{4\eta\dot{R}}{R} - \delta\omega\rho R\dot{R} - p_0 - p(t) \right],$$

where

$p(t)$	– time-dependent acoustic driving function	
p_0	– ambient pressure	1.00 atm
p_v	– vapour pressure	2.33 kPa
R	– instantaneous radius	
R_0	– initial radius	variable
R_c	– equivalent core radius	variable
γ	– ratio of specific heats	1.4
δ	– damping coefficient	
η	– liquid viscosity	1.00 mPas
ρ	– liquid density	998 kg m ⁻³
σ	– surface tension	
χ	– shell stiffness	variable
ω	– angular driving frequency	variable

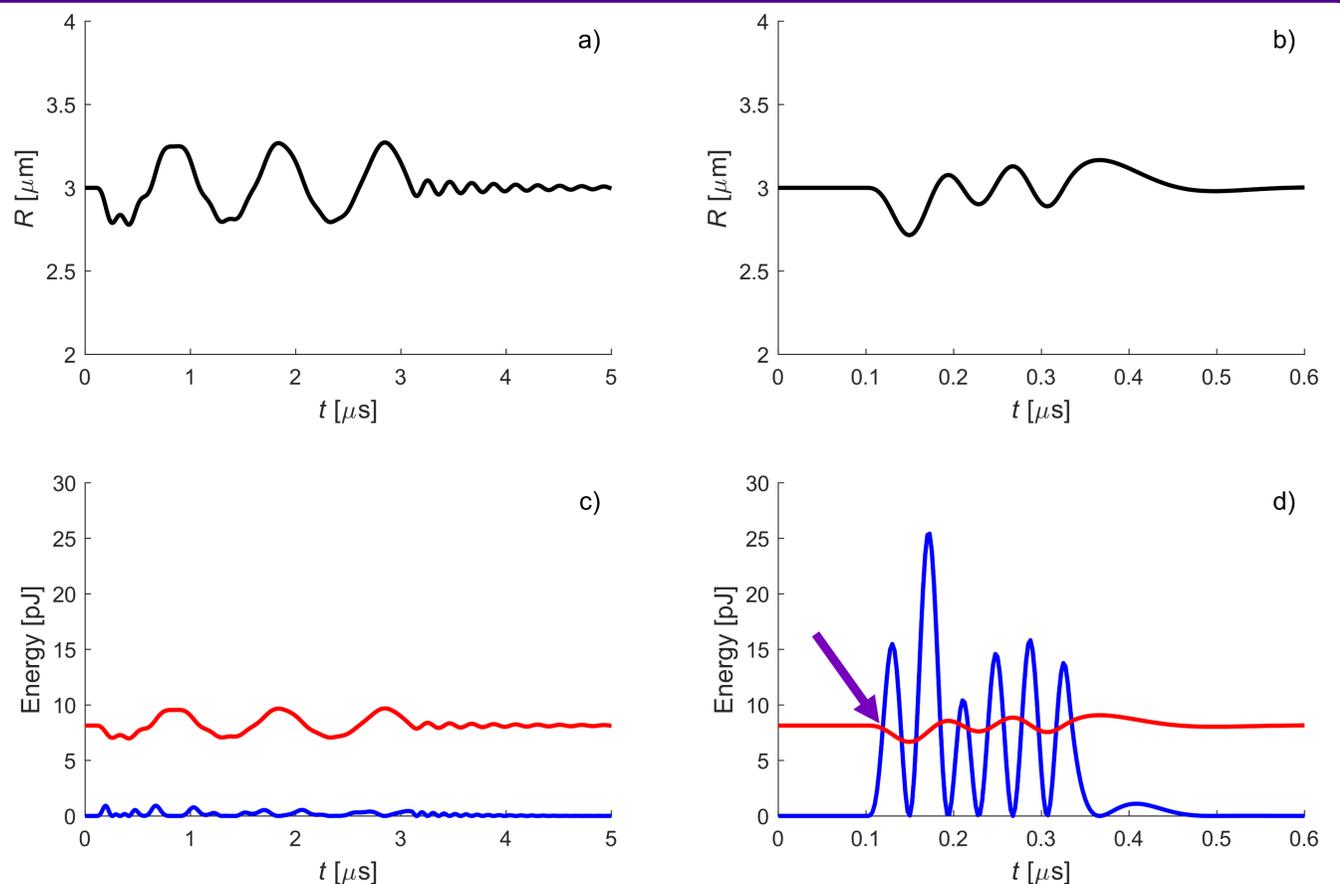
Instantaneous kinetic energy

$$E_k \approx 2\pi\rho R^3 \dot{R}^2$$

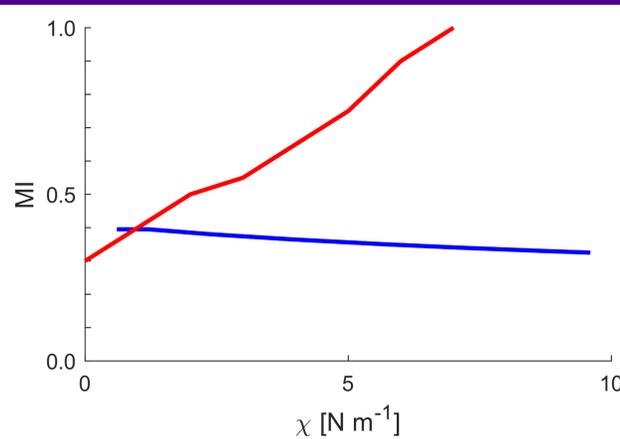
Surface energy deficit

$$\Delta E_s \approx 4\pi R^2 \sigma$$

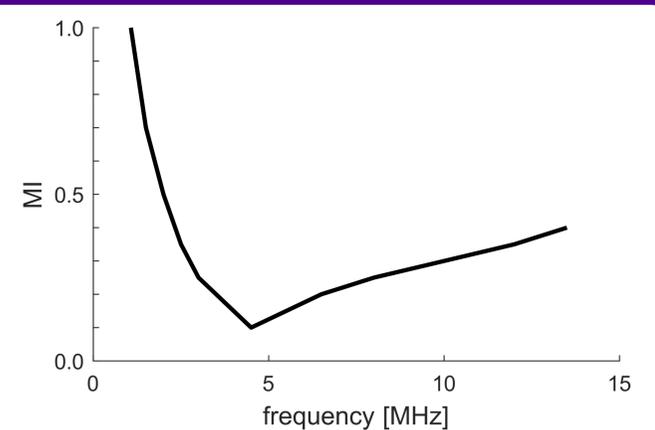
Results



Radius and instantaneous energies as a function of time simulated for an antibubble of initial radius $R_0=3\mu\text{m}$ with a 90% core radius and shell stiffness $\chi=7.6\text{Nm}^{-1}$ driven with a 0.6-MI pulse of centre frequency 1 MHz (a, c) and 13 MHz (b, d). Instantaneous kinetic energies are indicated by blue lines and surface energy deficits by red lines. The purple arrow indicates the point of fragmentation.



Fragmentation threshold in MI as a function of shell stiffness χ , simulated for a 3- μm radius antibubble with a 90% core radius, subjected to a pulse of centre frequency 1 MHz (red) and 13 MHz (blue).



Fragmentation threshold in MI as a function of driving frequency, simulated for a 3- μm radius antibubble with a 90% core radius and a 7.6-Nm⁻¹ shell stiffness.

Conclusions

Shell stiffness only influences antibubble fragmentation at lower driving frequencies.

At 13-MHz, stiff-shell-encapsulated antibubbles fragment at amplitudes not considered diagnostically unsafe.

Shell-stabilised, drug-loaded antibubbles could be forced to release their contents using diagnostic ultrasound.

Author statement

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