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Numerical investigation of the inertial cavitation threshold under multi-frequency ultrasound

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ABSTRACT

Through the introduction of multi-frequency sonication in High Intensity Focused Ultrasound (HIFU), enhancement of efficiency has been noted in several applications including thrombolysis, tissue ablation, sonochemistry, and sonoluminescence. One key experimental observation is that multi-frequency ultrasound can help lower the inertial cavitation threshold, thereby improving the power efficiency. However, this has not been well corroborated by the theory. In this paper, a numerical investigation on the inertial cavitation threshold of microbubbles (MBs) under multi-frequency ultrasound irradiation is conducted. The relationships between the cavitation threshold and MB size at various frequencies and in different media are investigated. The results of single-, dual and triple frequency sonication show reduced inertial cavitation thresholds by introducing additional frequencies which is consistent with previous experimental work. In addition, no significant difference is observed between dual frequency sonication with various frequency differences. This study, not only reaffirms the benefit of using multi-frequency ultrasound for various applications, but also provides a possible route for optimizing ultrasound excitations for initiating inertial cavitation.

1. Introduction

High intensity focused ultrasound (HIFU) has been used in multiple clinical trials as a promising non-invasive surgery modality [1–4]. HIFU is known to be able to elicit thermal and mechanical effects. Mechanical effects consist of cavitation, radiation force, shear stress and acoustic streaming. Cavitation is the formation and activity of a gas filled bubble under acoustic excitation in a medium [5]. The gas bubble could either oscillate stably or expand gradually and eventually collapse (stable and inertial cavitation) [5]. Cavitation could lead to thermal effects as well as chemical and optical effects [6–9]. The cavitation forces and micro-jets generated during the collapse of the bubble could break the tissue and therefore could be used in tissue ablation and thrombolysis [10–14]. The threshold upon which acoustic cavitation is initiated depends on a number of factors, including the ultrasound frequency, bubble size, and surrounding medium properties [15–17].

There are numerous models that can predict the dynamics of a single microbubble (MB) under ultrasound excitation, which produce the bubble radius response and radiated pressure. These models have been used for various studies in the field of HIFU or other areas of ultrasound. The Rayleigh-Plesset (R-P) equation [18] has been widely used as a basis for computational study of bubble dynamics by assuming an incompressible liquid. This was extended by Chen et al. who developed a method for predicting bubble growth with large density ratios and interfaces between different media [19]. Chahine and Hsiao investigated a 3-D non-spherical model for a zero-thickness shell using a non-dimensional form of the Rayleigh-Plesset differential equation [20]. Farny et al. studied the heating effect of HIFU and found a correlation between the heat generation and cavitation signal [21]. Keller and Miksis first introduced the surrounding liquid compressibility and then developed a model suitable for large amplitude oscillation [22]. Katiyar et al. modeled the subharmonics for free bubble and encapsulated bubble oscillations. They reported that the subharmonics would either monotonically increase or decrease within a particular range of ratios of the excitation frequency to the natural frequency of the bubble [23]. Yasui et al. simulated the broad band noise generated from bubble cavitation under experimental conditions using the Keller-Miksis model [24]. Wang and Yuan utilized the R-P equation to describe a radially symmetric free bubble in the acoustic field and found a correlation between acoustic cavitation and microalga cells disruption [25]. Mancia et al. inspected the bubble responses by changing the surrounding medium properties and waveform parameters using the Keller-Miksis model. They analyzed the surrounding medium stress and strain and found that stiffer tissues were less likely to be damaged by acoustic irradiation [26]. Yang and Church investigated the gas bubble cavitation threshold in soft tissue by extending the Keller-Miksis model

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Abbreviations and nomenclature

HIFU	High Intensity Focused Ultrasound
MB	microbubble
ρ	density of the medium
ρ_0	density at equilibrium
r	dimension along the radial axis
τ_r	stress in the radial direction
τ_θ	stress in the polar direction
σ	surface tension
p_g	gas pressure
p	pressure in the medium
p_∞	pressure in the medium at infinite radial distance
$p_{internal}$, $p_{external}$	pressure in the near-field and far-field
p_s	pressure at the bubble surface
P_A	driving acoustic pressure amplitude
$g(t)$	arbitrary transient driving pressure input function
R_0	initial bubble radius
R	transient bubble radius
$\dot{R}$	bubble wall velocity
$\ddot{R}$	bubble wall acceleration
φ	the velocity potential
φ_1,φ_2	outgoing and incoming acoustic wave velocity potentials
c	speed of sound
μ	dynamic viscosity
G	shear modulus
γ_r	radial strain
$\dot{\gamma}_r$	radial strain rate
λ	polytropic index
v_r	radial component of the velocity
f_1,f_2,f_3	fundamental frequencies of individual wave components

to take the shear modulus of the media into account [27,28]. Bader and Holland further employed the Yang and Church model to predict the expansion of nuclei under histotripsy pulses [29].

Multi-frequency sonication [30–37] has recently been reported as a promising method to enhance cavitation activities and reduce the cavitation threshold. Avvaru and Pandit found that the measured cavitation signal from the hydrophone can be increased by introducing a second and third frequencies, indicating an enhanced cavitation activity [38]. Guedra et al. found that the cavitation signal power generated from a dual frequency excitation was twice as high as that generated from a single frequency excitation [39]. Guo et al. reported a faster temperature rise in *ex vivo* chicken tissue when treated with multi-frequency ultrasound compared with single-frequency excitation [32]. Previous research from our and other groups also showed better thrombolysis efficiencies and stronger inertial cavitation signals when using multi-frequency HIFU excitation as opposed to the conventional single frequency excitation [34–36].

The mechanism of multi-frequency excitation for enhancing the inertial cavitation is still poorly understood, though experimental and numerical studies have been actively pursed to shed light on why multi-frequency is advantageous. Saletes et al. showed that dual-frequency could enhance the cavitation activity while reducing the heating in their HIFU cavitation experiments [40] and later on in their dual-frequency thrombolysis experiments [34]. Zhang et al. [41] reported on the critical bubble radii dividing stable and unstable regions of bubbles under dual-frequency acoustic excitation. The critical bubble radii are strongly affected by the amplitudes of dual-frequency acoustic excitation rather than the frequencies of the excitation. Zhang and Li numerically calculated the scattering cross section for single bubbles under dual frequency excitations [42]. They found that dual-frequency could increase the acoustic scattering cross section over a broad range of bubble size because of more resonances. To enhance the effect, the energy allocated to the two frequency components should be almost identical and the ratio of the two frequencies should be relatively large [42]. They further investigated the mass transfer and mass diffusion of gas bubble under dual frequency excitation [43,44].

In contrast to what [41–44] have studied, this paper aims to estimate the inertial cavitation threshold under multi-frequency sonication by solving bubble dynamics equations, which provides a more direct evidence as to why the additional frequencies can facilitate the enhancement of inertial cavitation. While our primary interests are multi-frequency based thrombolysis and thermal ablation, the results from this study may also have implications for sonoluminescence and drug delivery.

2. Numerical model

The methodology employed in the numerical prediction of transient bubble radial response is based on the Yang and Church model [27]. This model considers the effects of medium elasticity on a single microbubble's oscillation and will be briefly revisited here. In this investigation, the spherical bubble behaves as if it was in an unbounded viscoelastic medium. In the spherical co-ordinate system, the equation of continuity takes the following form

$$\frac{\partial \rho}{\partial t} + \frac{\partial (\rho v_r)}{\partial t} + \frac{2\rho v_r}{r} = 0, \tag{1}$$

where ρ is the density of the medium, v_r is the radial velocity, and r is the dimension along the radial axis. Conservation of radial momentum in a spherically symmetric radial direction yields

$$\rho\left(\frac{\partial v_r}{\partial t} + v_r\frac{\partial v_r}{\partial r}\right) = -\frac{\partial p}{\partial r} + \frac{\partial \tau_r}{\partial r} + \frac{2}{r}[\tau_r - \tau_\theta]. \tag{2}$$

here p is the pressure, τ_r is the stress in the radial direction, and τ_θ is the stress in the polar direction. In terms of surface tension σ and gas pressure P_g, the pressure in the medium can be expressed as $p = p_g - \frac{2\sigma}{R} + \tau_r$for a transient bubble radius R. Furthermore, at the initial time, at the interface of the bubble and surrounding medium, i.e. at a radial position R_0, the derivative $\left|\frac{dR}{dt}\right|$ would be zero. Also, at $R = \infty$, the pressure would equal that of the free fluid.

Yang and Church suggested that in the near field of the bubble, it is safe to approximate that only effects of compression and expansion are perceptible while the surrounding medium remains incompressible [27]. The Bernoulli momentum equation would then account for the radial pressure inside the bubble as

$$v_r = -\frac{R\dot{R}}{r^2} \tag{3}$$

and

$$p_{internal} = p_s - \rho_0\left(R\ddot{R} + \frac{3}{2}\dot{R}^2\right) + \frac{\rho_0}{r}(R^2\dot{R})' - \frac{\rho_0}{2}\frac{R^4\dot{R}^2}{r^4} + \tau_r|_R^r + 3\int_R^r \frac{\tau_r}{r}dr, \tag{4}$$

where p_s is the pressure at the bubble surface and $\ddot{R}$ is the acceleration of the bubble wall. The linear acoustic field equation is used in the far field. This assumption is strengthened by the expectation that density variation, stress and nonlinear convection terms bear little effect in the far-field. Therefore, as a linear superposition of incoming and outgoing waves, the velocity potential can be expressed as

$$\varphi_{external} = \frac{1}{r}\left[\varphi_1\left(t - \frac{r}{c}\right) + \varphi_2\left(t + \frac{r}{c}\right)\right], \tag{5}$$