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Numerical investigation of the inertial cavitation threshold by dual-frequency excitation in the fluid and tissue

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ABSTRACT

Inertial cavitation thresholds, which are defined as bubble growth by 2-fold from the equilibrium radius, by two types of ultrasonic excitation (at the classical single-frequency mode and dual-frequency mode) were calculated. The effect of the dual-frequency excitation on the inertial cavitation threshold in the different surrounding media (fluid and tissue) was studied, and the paramount parameters (driving frequency, amplitude ratio, phase difference, and frequency ratio) were also optimized to maximize the inertial cavitation. The numerical prediction confirms the previous experimental results that the dual-frequency excitation is capable of reducing the inertial cavitation threshold in comparison to the single-frequency one at the same output power. The dual-frequency excitation at the high frequency (i.e., 3.1 + 3.5 MHz vs. 1.1 + 1.3 MHz) is preferred in this study. The simulation results suggest that the same amplitudes of individual components, zero phase difference, and large frequency difference are beneficial for enhancing the bubble cavitation. Overall, this work may provide a theoretical model for further investigation of dual-frequency excitation and guidance of its applications for a better outcome.

1. Introduction

Acoustic cavitation induced by ultrasonic irritation, stable and inertial cavitation, is known to play a key role in a wide range of therapeutic ultrasound applications [1,2]. Bubble oscillation about its equilibrium radius at the low acoustic pressure is termed as stable cavitation whereas inertial cavitation releases high energy, increases the temperature of the vapor to several thousand kelvins, and generates high pressure and/or high-speed jets at the bubble collapse, which may produce mechanical damages to the nearby media [3,4]. Increasing the driving acoustic pressure could result in the transition from stable cavitation to inertial cavitation. Examples of successful ultrasound therapies utilizing acoustic cavitation include the tissue heating in which stable cavitation causes high shear stress between the bubble and surrounding medium and inertial cavitation produces the broadband noise emission for the substantially promoted and enhanced thermal deposition [5,6]; histotripsy in which inertial cavitation releases shockwaves capable of destroying cell membranes, mechanically fractionating the soft tissues, and in many cases even completely liquefying them into subcellular components [7,8]; thrombolysis in which stable cavitation in the vicinity of blood clots promotes the uptake of lytic agent and inertial cavitation produces micro-jet and pitting to directly and mechanically damage the clot's surface [9,10]; blood-brain barrier (BBB) opening in which stable cavitation temporarily affects the integration of the tight junction and reduces the blood flow. It could be seen that stable cavitation and inertial cavitation function distinctively different in the aforementioned cavitation facilitated therapeutic processes. Therefore, it is of a great concern to determine the threshold pressure for the transition from stable cavitation to inertial cavitation in order to assess the likelihood of different ultrasound-induced bio-effects.

In contrast to the conventional single-frequency acoustic excitation, the dual- or multiple-frequency excitation shows some remarkable merits in sonoluminescence and sonochemistry, such as low cavitation threshold, more chemical activities, and high reaction efficiency, effective elimination of standing wave, and better control over the cavitational activity in the acoustic field in terms of bubble oscillation mode and the spatial distribution [11]. The maximum photocurrent could be boosted up to 300% using double harmonic driving compared with single harmonic driving [12]. In the context of biomedicine, some initial investigations of enhancing the inertial cavitation by the dual-frequency have also been carried out. Dual-frequency excitation in both kHz (525 + 565 kHz) and MHz (~1.5 MHz) improved the *in vitro* thrombolysis efficiency [13,14]. Guo et al. [15] showed ~5% to 10% improvement in the temperature elevation in the chicken breast by the dual-frequency excitation. Kuang et al. [16] and He et Al. [17] have

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demonstrated that using two confocal transducers driven at two neighboring frequencies (1.495 + 1.505 MHz and 1.563 + 1.573 MHz) a large lesion could be achieved. Liu et al. [18] and Chen et al. [19] showed that lesions created by the dual-frequency excitation were more uniform and closer to the desired target region. Dual-frequency (500 kHz + 3 MHz) excitation in histotripsy has been shown to precisely tailor the bubble expansion [20,21]. Sokka et al. [22] have successfully manipulated the cavitation distribution and preferentially lowered the cavitation threshold at the focus by the means of dual-frequency phased array. The first *in vivo* dual-frequency sonodynamic therapy performed on mice showed more effective in terms of suppressing tumor growth and reducing the tumor volumes [23].

The mechanism for the enhancement of bubble cavitation by dual- or multiple-frequency excitation has not been fully understood although some unique characteristics were found in some preliminary investigations. The modeling developed by Zhang et al. [24] shows that bubble cavitation induced by the dual-frequency excitation has a reduced critical radius for the generation of inertial cavitation comparing with that by the single-frequency one. Acoustical scattering cross section by the dual-frequency excitation displayed more resonances for a much broader range of bubbles [25]. In addition, dual-frequency excitation can lead to a more rapid growth of a wide range of bubbles through the rectified mass diffusion as long as the acoustic pressure is above a certain threshold [26].

So far, plenty of experimental work has confirmed that the dual-frequency excitation could significantly reduce the inertial cavitation threshold [27,28], but few theoretical studies have been devoted to this subject. Numerical modeling shows promise towards understanding the mechanisms due to its universe applications under various conditions. A theoretical prediction of the inertial cavitation threshold by dual-frequency excitation in the various media, such as fluid (i.e., water and blood) and viscoelastic tissue (i.e., kidney and liver), was studied here, and the paramount parameters that influence the inertial cavitation threshold (i.e., amplitude ratio, phase difference, frequency ratio) were thoroughly investigated in order to optimize the bubble dynamics.

2. Methods

For the single-frequency excitation, the driving signal is described as:

$$P_a = P_A \sin(2\pi f t) \tag{1}$$

where f is the driving frequency and P_A is the acoustic pressure. For the dual-frequency excitation, the driving signal is described as:

$$P_a = P_1 \sin(2\pi f_1 t) + P_2 \sin(2\pi f_2 t + \varphi) \tag{2}$$

where $f_1$and f_2 (usually $f_1 < f_2$) and P_1 and P_2 are the driving frequencies and acoustic pressures of two harmonics, respectively, and φ is the phase difference between them. The common setting is $P_1 = P_2 = P_A/\sqrt{2}$, where the coefficient $1/\sqrt{2}$ is to ensure the same acoustic output power delivered as that of the single-frequency excitation.

Since the bubble behaves differently in various media, two theoretical models are employed to calculate its dynamics in the fluid and tissue. For simplicity, several important assumptions are made [6,29,30]. 1) The medium is homogeneous and isotropic; 2) The air bubble is always spherical and initially at rest ($\dot{R} = 0$) so that bubble dynamics can be calculated in one-dimensional space; 3) The gas inside the bubble is ideally adiabatic ($\gamma = 1.4$); 4) There is no gas or vapor exchange between the gas and the surrounding medium; 5) The pressure inside the bubble is spatially uniform, and the vapor pressure is constant throughout the bubble oscillation.

For the fluid (i.e., water and blood), the Gilmore-Akuliches equation was utilized [31].

$$R\left(1-\frac{U}{C}\right)\frac{dU}{dt} + \frac{3}{2}\left(1-\frac{U}{3C}\right)U^2 = \left(1+\frac{U}{C}\right)H + \frac{1}{C}\left(1-\frac{U}{C}\right)R\frac{dH}{dt} \tag{3}$$

where R is the bubble radius, U ($=dR/dt$) is the velocity at the bubble wall, and C and H are the speed of sound in the liquid at the bubble wall and enthalpy difference between the pressure at the bubble wall $P(R)$ and the pressure at infinity P_∞, respectively, which are given by

$$H = \int_{P_\infty}^{P(R)} \frac{dP}{\rho} \tag{4}$$

$$C = [C_l^2 + (m-1)H]^{1/2} \tag{5}$$

where P is the time-varying pressure, ρ is the medium density, C_l is the infinitesimal speed of sound in the liquid, and m is a constant normally set to 7. The state equation of a compressible fluid and $P(R)$ in relation to the gas pressure inside the bubble of P_g, medium viscosity of μ, and surface tension of σ in the liquid are given by

$$P = A(\rho/\rho_0)^m - B \tag{6}$$

$$P(R) = P_g - \frac{2\sigma}{R} - \frac{4\mu}{R}U \tag{7}$$

where ρ_0 is the equilibrium liquid density, $A = C_l^2\rho/P_0$ and $B = A-1$ are two constants.

Whereas in the tissue, the bubble dynamics was modeled by the modified Keller-Miksis equation that includes the compressibility and viscoelasticity of the surrounding medium [29].

$$\left(1-\frac{\dot{R}}{c}\right)R\ddot{R} + \frac{3}{2}\left(1-\frac{\dot{R}}{3c}\right)\dot{R}^2 = \left(1+\frac{\dot{R}}{c}\right)\left[\frac{p_B - p_\infty(t)}{\rho} - \frac{4\mu\dot{R}}{R} - \frac{2S}{\rho R} - E_{NT}\right] + \frac{R}{\rho c}\frac{d}{dt}(p_a - p_\infty) \tag{8}$$

where c is the constant speed of sound in the medium, and S is the surface tension coefficient. Kelvin–Voigt approach was used to model the viscoelasticity of tissue. Considering the large deformations during the bubble growth, a hyperelastic (Neo-Hookean) constitutive relation was utilized to yield the elastic term [32].

$$E_{NT} = \frac{G}{2}\left[5 - 4\left(\frac{R_0}{R}\right) - \left(\frac{R_0}{R}\right)^4\right] \tag{9}$$

where R_0 is the initial bubble radius, and G is the linear shear modulus.

There are many definitions of the inertial cavitation threshold [30,33–35]. The maximum bubble expansion to twice of the initial bubble radius is commonly used in the investigation of cavitation and chosen as the onset of inertial cavitation in this paper. The Gilmore and Keller-Miksis equations were numerically solved using the fifth-order Runge-Kutta-Fehlberg method with a step-size control algorithm in MATLAB (MathWorks, Naticks, MA, USA) with an absolute and relative tolerance of 1e-12 and 1e-7, respectively, to obtain the radius-time profiles with satisfactory precision. The sonication period is 60 μs, which is sufficiently long for bubble dynamics. Throughout this study, the threshold value was determined by varying the acoustic pressure in a step size of 2 kPa for a bubble radius ranging from 0.1 μm to 10 μm. The driving frequencies (f_1 and f_2) were set to 1.1 MHz and 1.3 MHz, 3.1 MHz, and 3.5 MHz, which are within the -6 dB bandwidth of a commercial HIFU transducer (H102, Sonic Concepts, Woodinville, WA, USA) at its fundamental and third harmonic. Water, blood, kidney, and liver are commonly used for the study of sonochemistry reaction, thrombolysis, blood-brain barrier opening, and ultrasound-induced biological effects, respectively, and their physical parameters are listed in Table 1 [30,36]. Vapor pressure in the tissue and ambient pressure were assumed to be 6 kPa and 101.3 kPa, respectively.