Non-linear cavitation cloud oscillations in High-Intensity Focused Ultrasound

A mechanistic source of the subharmonic signal

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Abstract* — Cavitation driven by high-intensity focused ultrasound is being investigated as a potential mechanism for therapeutic ultrasound. In this role, the mechanical bubble activity could be used for localised tissue disruption, facilitating targeted drug delivery. The cavitation sub-harmonic signal, which is emitted at sub-multiple values of the driving frequency, is often used to discern the onset of cavitation at a level sufficient to elicit a required bio-effect. Despite this, a convincing mechanistic source for the signal has been elusive. In this paper, we report on high-speed observations of non-linear cloud oscillatory response to propagating HIFU insonations, at two intensities typical of those used for therapeutic applications. Single cavitation clouds are reproducibly introduced to the focus of a 254 kHz HIFU field at peak-to-peak pressure amplitudes of 0.48 and 0.62 MPa, and the subsequent activity is resolved via high-speed shadowgraphic imaging at 1×10^6 frames per second. Cavitation clouds develop rapidly from nucleation, via component bubble fragmentation, and undergo repetitive oscillations from $t \approx 30$ μs following nucleation, periodically emitting shock-waves at moments of concerted cloud collapse. The frequency of cloud collapse, and coincident shock-emission, occurs at one-half (~127.0 kHz) of the driving frequency at 0.48 MPa, and one-third (~84.7 kHz) of the driving at 0.62 MPa. By way of analysis, cloud oscillations are compared to a single bubble Rayleigh-Plesset model, subject to equivalent acoustic conditions. The comparison is favourable for selected values of model quiescent radius, in terms of the period of oscillation - and therefore shock-wave emission frequency - at each of the pressure amplitudes. We conclude that periodic shock emission from acoustically driven cavitation clouds provides a previously unidentified source of the sub-harmonic signal.

***Keywords* — cloud dynamics; shock-wave; Rayleigh-Plesset model, sub-harmonic signal**

I. INTRODUCTION

Acoustic cavitation refers to the formation and excitation of bubbles within a host medium exposed to the pressure fluctuations of an acoustic wave. The occurrence of cavitation in the application of high-intensity focused ultrasound (HIFU) to tissue, is receiving renewed attention as a possible alternative to the thermal mechanism that currently mediates Focused Ultrasound Surgery [1]. To monitor cavitation occurrence, and level of activity, acoustic detection at frequency values sub-harmonic to the fundamental driving of the applied HIFU, f_0, is often employed. Cavitation is known to generate signal at a range of frequency values, including higher harmonics and broadband emissions under higher intensity insonations, but sub-multiple to the fundamental ($f_0/2$, $f_0/3$, $f_0/4$ …) are considered to be exclusive to bubble formation [2]. Higher harmonics are also known to be generated during the non-linear propagation of ultrasound, for instance. Accordingly, a number of bio-effects have been correlated to the onset of sub-harmonic emission, including, for example, cell membrane disruption in the presence of contrast agent microbubbles [3, 4]. Remarkably, however, a convincing mechanistic source for the generation of the sub-harmonic in cavitating fluids has not been identified. A number have been proposed [2, 5], but none satisfactorily explain the signal generation in the variety of experimental configurations where it has been detected.

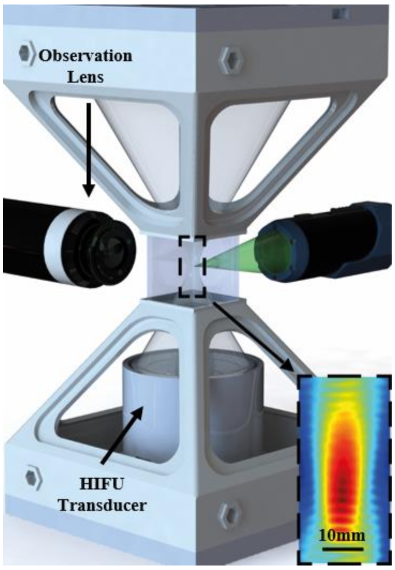

Fig. 1. The Sonoptic chamber was designed to house a 254 kHz HIFU transducer, the focus of which (at 64mm from the front face) is centrally located within a central glass section. Cavitation activity is nucleated via a 6-8 ns laser pulse (green). *Inset bottom right* is a normalized axial scan of the acoustic focus, generated in-situ by fibre optic hydrophone, confirming the HIFU field is not affected by the chamber housing.

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In this paper, we briefly describe a novel experimental arrangement (Section II), for the observation of cavitation activity at unprecedented spatial and temporal resolution, in a well characterized HIFU field, typical of those used for therapeutic ultrasound [6]. Cavitation dynamics are imaged with ultra-high speed shadowgraphic photography, which facilitates the observation of the repetitive emission of shock-waves from the clouds. We report on the effect of increasing the intensity of the HIFU exposure on the period of shock-wave emission (Section III). By way of analysis, we compare cloud oscillatory dynamics to those of the well-known Rayleigh-Plesset model for a single bubble [2], under equivalent acoustic conditions, and at a selected quiescent radius (under hydrostatic pressure, Section IV).

II. Experimental Arrangement

A. *The sonoptic chamber*

A sonoptic chamber [6] was custom designed and rapid-prototyped to accommodate the field of a 254 kHz HIFU transducer, fabricated in-house. This experimental configuration is specifically designed to permit cavitation observations to be undertaken in a burst of propagating focused ultrasound, without reflection or scatter i.e. no part of the chamber housing perturbs the field, fig. 1. Comprehensive fiber-optic hydrophone (Precision Acoustics, UK) scans of the acoustic field, at the pressure amplitudes of interest, generated both within the chamber and a 1 × 1 × 1 m^3 scanning tank, confirmed this to be the case. Acoustic absorber material (Precision Acoustics, UK) located at the top of the chamber, minimizes reflection of the primary field, incident from below. For an experiment, the chamber was filled with de-ionised and degassed water (to an O_2 content of below 4 mgL^{-1}), via sustained boiling. For the results presented, 54 cycles of sinusoid at 254 kHz, and the voltage required to generate the peak-to-peak pressure amplitude (PA_{pp}) as quoted (pre-calibrated via the radiation force balance approach), was used to drive cavitation activity.

B. *Laser-nucleation of cavitation clouds*

Cavitation was controllably and reproducibly nucleated in a pre-established HIFU field via a 6-8 ns 532 nm laser-pulse (Litron Lasers, UK), focused by a 50× long working distance objective lens (Mitutoyo, Japan). The pulse energy, measured at the back aperture of the objective lens, was set to 0.9 mJ, which is below the optical breakdown threshold for the host medium. This avoids the large vapor bubbles generally associated with pulsed-laser cavitation studies [7]. The laser-pulse is electronically triggered to arrive at the sonoptic chamber ~70µs following focused ultrasound generation. This ensures ultrasound has both propagated to the central region of the chamber and that the transducer has 'rung-up' to the required PA_{pp} value.

C. *High-speed imaging*

All imaging data was collected with a Kirana 05-M high-speed camera (Specialised Imaging, UK), operating at 1 × 10^6 frames per second (fps). This is a single CCD camera capable of recording 180 frames at 924 × 768 pixels. The camera is electronically triggered to capture several frames before the nucleating laser-pulse arrives, to ensure cavitation dynamics are imaged from the outset, and that no pre-existing activity has occurred in the preceding HIFU exposure. Illumination was achieved via a synchronous pulsed laser system (Specialised Imaging, UK) coupled to a liquid light guide, through a condenser lens. The laser delivered 20 ns pulses at 640 nm, dictating the exposure time per frame. The short illumination duration, over a narrow wavelength bandwidth, permits the visualization of acoustic transients within the field of view, via the refractive index dependence on local pressure. Imaging was undertaken through a Monozoom7 lens system (Bausch & Lomb, USA) set to a magnification of 3.5×. The spatial scale of the imaging was determined via the in-situ imaging of 400 µm polymer spheres (Duke Standards, UK).

III. High speed camera observations

Fig 2 (a) and (b) are representative frames extracted from high-speed sequences capturing the evolution of two clouds under HIFU bursts of PA_{pp} = 0.48 and 0.62 MPa, respectively, some 40 µs following nucleation. Time t = 0 µs is taken as the moment the nucleating laser-pulse is incident to HIFU focal region. By this stage, the first single nucleation bubble has responded to ~10 acoustic cycles, fragmenting within each to form a cloud of closely interacting, multiple component bubbles. The larger cloud of fig. 2 (b) has occurred due to more energetically driven fragmentation events, at the higher $PA_{pp.}$ Notably, the bubble ensemble responds as a single entity to the ensuing

(a)

(b)

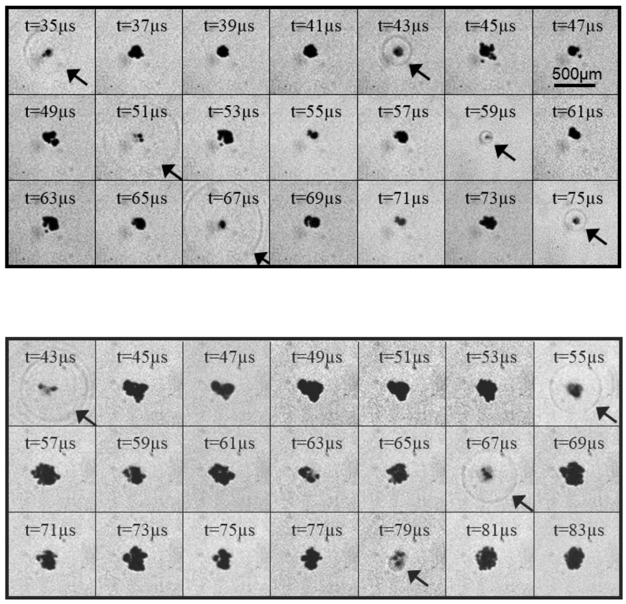

Fig. 2 Two image sequences illustrating cloud dynamics at HIFU PA_{pp} = (a) 0.48 and (b) 0.62MPa. (a) represents five growth, oscillation and collapse (GOC) cycles, with shock-waves (arrowed) emitted periodically every ~ 8µs. (b) demonstrate three GOC cycles over an equivalent time, with shock-waves periodically every ~12µs.

HIFU exposure, and enters complex non-linear oscillatory behavior as soon as the cloud becomes sufficiently established. Furthermore, the repeated instances of concerted cloud collapse coincide to the emission of a shock-wave (arrowed throughout), indicating that all component bubbles have collapsed in unison. Inspection of fig. 2 (a), and back projection of the shock-fronts (assuming a shock-propagation speed of ~1500 ms^{-1}) to determine the instant of emission, reveals a shock-wave emission period, T_{sw} ≈ 7.9 µs. This equates to an emission frequency of approximately 127.0 kHz, which corresponds to the half-harmonic, $f_0/2$. Equivalently, the shock-emission frequency of the cloud in fig. 2 (b) is approximately 84.7 kHz (T_{sw} = 11.8 µs), or $f_0/3$, the 'first higher-order sub-harmonic' to the driving. Comparison of fig. 2 (a) and (b) would therefore suggest that on increasing the HIFU PA_{pp} from 0.48 to 0.62 MPa, the cloud system transitions to a regime of more pronounced non-linearity. This is perhaps most obvious from the longer T_{sw} from the larger cloud at the higher PA_{pp}, and the transition from $f_0/2$ to $f_0/3$ emission frequencies. At intermediate HIFU PA_{pp}'s to those reported above, cloud response tends to be a combination of the $f_0/2$ and $f_0/3$ regimes, with clouds emitting shock-waves at a T_{sw} ≈ 7.9 µs, then switching to T_{sw} ≈ 11.8 µs within the same insonation burst (and vice versa).

IV. ANALYSIS

A. *Dark pixel counting algorithm*

To quantify the cloud dynamics, a dark-pixel counting algorithm [8], written in MATLAB, was implemented to each of the 180 frames within a high-speed sequence. A threshold grey-scale value was selected for the pixels within the image that represent the cavitation cloud, given that the bubbles deflect the laser illumination, and therefore appear dark on a bright background. The algorithm simply processes each frame sequentially, and outputs a 'dark-pixel variation with time curve', which can be taken to be representative of the cloud oscillations for the duration of the imaging. The curves thereby generated for the images of fig. 2 (a) and (b) are depicted by the blue traces of fig. 3 (a) and (b) respectively, from t ≈ 30 – 90 µs. The cloud minima within the oscillations that were observed to result in shock-wave generation in fig. 2, are similarly arrowed in black (six at 0.48, and four at 0.62 MPa). The switching to the longer T_{sw} at the higher PA_{pp}, throughout the duration of cloud observation, is also evident in this depiction.

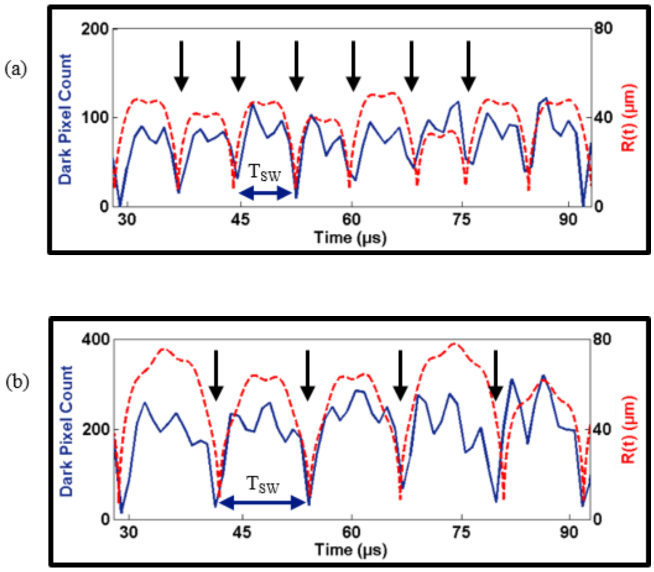

Fig. 3(a, b). Dark pixel counting algorithm (blue) used to analyze high speed camera data and quantify clouds dynamics at HIFU PA_{pp} = 0.48 and 0.62 MPa. Rayleigh-Plesset model results for a single bubble (red dash), under equivalent acoustic driving and of selected quiescent radius, R_0.

B. *Single bubbe Rayleigh-Plesset model*

By way of preliminary analysis of the observational data, we compare the temporal cloud oscillation behavior to that of an acoustically driven, single bubble Rayleigh-Plesset (RP) model [2, 9], known to include non-linear bubble oscillation properties, and represented by eq. 1.

$$R\ddot{R} + \frac{3\dot{R}^2}{2} = \frac{1}{\rho}\left\{\left(p_0 + \frac{2\sigma}{R_0} - p_v\right)\left(\frac{R_0}{R}\right)^{3\kappa} + p_v - \frac{2\sigma}{R} - \frac{4\eta\dot{R}}{R} - p_0 - P(t)\right\} \qquad (1)$$

where R is the time-varying radius of the model single bubble, and R_0 the quiescent radius under a hydrostatic pressure of p_0 = 100 kPa. p_v = 2.33 kPa and κ = 5/3 are the vapor pressure and polytropic exponent, respectively, of the gas phase within the bubble. ρ = 10^3 kgm^{-3}, σ = 72 × 10^{-3} Nm^{-1} and η = 0.894 × 10^{-3} Pas are the density, surface tension and liquid viscosity of the host medium (water), respectively. $P(t)$ represents the acoustic driving and is given the form, eq. 2,

$$P(t) = 0.5\, PA_{pp} \sin(2\pi f_0 t) \qquad (2)$$

to model the HIFU, at each of the PA_{pp}'s, used to generate the experimental observations.

C. *Comparison of cloud data and single bubble model*

Analysis of cavitation cloud dynamics through the RP single bubble model has been undertaken previously [9]. In this study a cavitation cluster was observed at 0.1 × 10^6 fps, within a cylindrical transducer, operating at ~13 kHz, and a pressure amplitude of ~33 kPa. A remarkably good fit between the RP single model oscillations and bubble cloud observations was reported, with the results indicating a linear bubble system was studied. The strong attractive forces between component bubbles within the cloud, and the resulting tendency for the cloud to respond as a single entity, justifies the comparison. Here, we adapt the approach for the non-linear cloud responses at the two HIFU PA_{pp}'s as described in Section III, for the purpose of modelling the periodic cloud collapses (and coincident shock-wave emission), in terms of compressible object of a given scattering cross section. Accordingly, the experimental results of fig. 3 (blue), are presented in parallel with equivalent RP model predictions (*R(t)*, in red dash), for an R_0 selected such that moments of single bubble collapse match those observed for the cloud. The terms of eq. 1 and 2 are otherwise set to those used experimentally, for each HIFU PA_{pp}, and a representative duration of HIFU exposure is depicted. The values of R_0 required to deliver the RP single bubble model oscillations presented are 21.50 µm (fig. 3 (a)) and 27.56 µm (fig. 3 (b)), at PA_{pp}'s of 0.49 and 0.62 MPa, respectively. It is not possible to explicitly deduce an equivalent value of R_0 for the clouds, from the high-speed observations. However, averaged values of minimum and maximum cloud radius may be estimated as $R_{min} \approx 10$ µm and $R_{max} \approx 75$ µm at $PA_{pp} = 0.48$ MPa, and $R_{min} \approx 20$ µm and $R_{max} \approx 110$ µm, from the image sequences. These estimates are based on an assumption that the void fraction within the cloud ~1 (i.e. the interior of the cloud is predominantly gas), which would seem reasonable for the inflation phases at R_{max}, but may not hold for deflations and collapses. Nonetheless, the cloud oscillations, and particularly the instances of collapse, and therefore periodic shock-emission are indeed predicted by the RP model, for selected R_0's that are at least comparable to the observations. Notably, the amplitude of oscillation is not so well predicted, with the single bubble model typically undergoing larger displacements. This may be explained as due to losses within the cavitation cloud, via bubble-bubble interactions (including coalescence events), and could perhaps be corrected for with the implementation a damping coefficient to the model oscillations.

V. CONCLUSION

We present high-speed observations of single cavitation clouds at an early stage of development, under HIFU insonations at intensities relevant to therapeutic ultrasound. Shadowgraphic imaging, facilitated by pulsed laser illumination, allowed the observation of periodic shock-wave emission, coincident to moments of concerted collapse within the cloud oscillatory response. The most significant finding is that shock-waves occur at frequencies sub-harmonic to the driving, and the period of emission depends primarily on the intensity. As such, we conclude that periodic shock-emission provides a previously unidentified source of the acoustic cavitation sub-harmonic signal [5]. As stated, the observations reported here were undertaken in water, within a well characterized propagating burst of HIFU. The role of periodic shock-emission for the generation of the sub-harmonic in tissue (and other viscous media), for cavitation-enhanced therapeutic ultrasound applications, remains an open topic of ongoing investigation. We recommend that future studies correlating the onset of bio-effect to detection of sub-harmonic signals, analyze the acoustic data for evidence of periodic shock-wave profiles.

The observation that the cavitation clouds oscillate as a single entity prompted the implementation of a simple single-bubble model in an attempt to predict the moments of cloud collapse, which correspond to the incidence of shock-wave generation. The approach predicts the transition from an emission frequency of $f_0/2$ to $f_0/3$, under increasing the PA_{pp} of the HIFU driving reasonably well, although comparison of the oscillation amplitude was not so favorable. The component bubble-bubble interactions within a cloud are evidently key to the cloud behaving, and collapsing, as a single entity. A greater understanding of these interactions, particularly from a modelling perspective, is critical to elucidating the physics of the intra-cloud dynamics that produce the oscillatory dynamics, and ultimately periodic shock-wave emission.

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