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**Covert cavitation: Spectral peak suppression in the acoustic emissions from spatially
configured nucleations**

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Running title: Covert cavitation

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Abstract

Dual laser-nucleation is used to precisely configure two cavitation bubbles within a focused ultrasound field of $f_0 = 692$ kHz, in proximity to the tip of a needle hydrophone. With both bubbles responding in the $f_0/2$ sub-harmonic regime, confirmed via ultra-high speed shadowgraphic imaging, an emission spectrum with no sub-harmonic content is demonstrated, for an inter-bubble spacing $\approx \lambda_0$. A spectral model for periodic shock waves from multiple nucleations demonstrates peak suppressions at $nf_0/2$ when applied to the experiment, via a windowing effect in the frequency domain. Implications for single-element passive detection of cavitation are discussed.

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47 **1. Introduction**

48
49 The emission of sub-harmonic signals from a medium during exposure to intense ultrasound, is
50 held to be exclusive to the presence of acoustic cavitation-bubble activity within that medium.
51 Indeed, detection at the sub-harmonics, particularly $f_0/2$ and higher-harmonics at $nf_0/2$, where f_0 is
52 the frequency of the acoustic driving, is regularly used to determine the onset of cavitation-
53 mediated effects in medical^{1, 2} and industrial applications.^{3, 4} Broadband emissions, which can
54 assessed between spectral peaks,⁵ or over frequencies sufficiently greater than f_0 ,⁶ is also
55 commonly used as an indicator for inertial cavitation.

56 We recently reported optical imaging and acoustic detection of single stable-inertial
57 cavitation events at high temporal resolution,⁷ initiated via the laser-nucleation technique⁸ and
58 driven by high-intensity focused ultrasound (HIFU). Shadowgraphic imaging facilitated via
59 synchronous pulsed-laser illumination, revealed periodic shock waves (PSWs) emitted at f_0/m
60 (where m is an integer value) from the bubble activity, dependent on the pressure amplitude of the
61 driving. Detector deconvolution from the acoustic data allowed reconstruction of the PSWs, and
62 their contribution to the cavitation spectrum to be quantitatively analyzed, validating a spectral
63 model that suggested PSWs generate features at nf_0/m , for all values of n and m (where n is an
64 integer value). The results indicated that PSWs were predominantly responsible for all features of
65 the cavitation noise spectrum, other than ~ 15 dB at f_0 , attributable to linear scattering of the driving
66 field.

67 In this Letter, we describe an extension to the experimental capability such that two
68 acoustic cavitation events can be simultaneously nucleated, in predetermined spatial
69 configurations relative to each other, the tip of a needle hydrophone and HIFU focus. We present

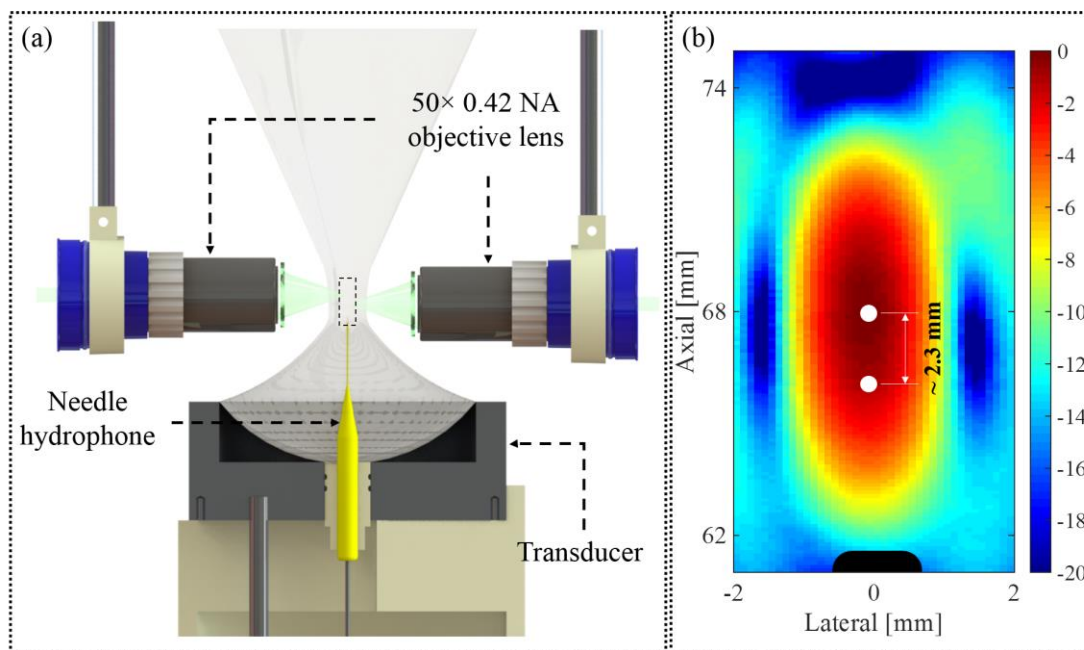
70 ultra-high speed shadowgraphic imaging to confirm that both resulting cavitation-bubbles are
 71 responding in the $f_0/2$ regime, yet the spectrum of the combined acoustic emissions reveals no
 72 perceptible sub-harmonic content, or higher harmonics of the sub-harmonic. The spectral model
 73 for PSWs is extended to account for a multi-nucleated system.

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75 2. Experimental arrangement

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80 Fig. 1. (Color online) Illustration of experimental setup: (a) cross-sectional view of HIFU
 81 transducer-NH configuration, and two long-working distance objective lenses facilitating dual-
 82 laser nucleation of cavitation bubbles. (b) An axial scan of the HIFU focal region, including the
 83 targeted laser-nucleation zones, to which the nucleating laser foci were aligned.

84 The experimental arrangement is broadly similar to that described in detail in our previous
85 report,⁷ with two modifications distinguishing the current work. Briefly, a single element
86 piezoceramic transducer (H-149, Sonic Concepts, Bothell, WA), generates a 90-cycle burst of
87 HIFU at $f_0 = 692$ kHz and peak-positive pressure amplitude, $PPPA_{HIFU} \cong 1.63 \pm 0.12$ MPa, which
88 drives cavitation at the focus in the $f_0/2$ regime.⁷ A needle hydrophone (NH, 1.0 mm diameter,
89 PVdF, Precision Acoustics, Dorchester, UK), calibrated for magnitude and phase over a bandwidth
90 of 125 kHz to 20 MHz, in 25 kHz increments⁹ (National Physical Laboratory, Teddington, UK,
91 2016), is mounted within a central hole through the body of the HIFU transducer, such that it aligns
92 to the propagation axis of the field generated, Fig. 1 (a) and (b). Steps taken to measure the HIFU
93 amplitude with the NH in the inverted position, Fig. 1 (a), which may be expected to perturb the
94 field are described in detail.⁷

95 Cavitation is introduced to the focus of the HIFU field via the laser-nucleation technique.⁸
96 To generate the results presented below, however, a 50:50 beam splitter (BS010, Thorlabs, Ely,
97 UK) is introduced to the nucleating laser-pulse beam path. The component beams from a 2.4 ± 0.2
98 mJ (instrument error according to manufacturer), 6–8 ns laser pulse (Nano S 130-10 frequency
99 doubled Q-switched Nd:YAG, Litron Lasers, Rugby, UK), are steered to the back apertures of two
100 long-working distance microscope objective lenses ($50\times$ 0.42 NA Mitutoyo, Kawasaki, Japan),
101 Fig. 1 (a), sealed in water-tight units and mounted on xyz manipulators. This configuration permits
102 simultaneous dual laser-nucleation of two, independently positioned, cavitation-bubbles, Fig. 2.

103 Ultra-high speed imaging is undertaken at 5×10^6 frames per second (fps) with a Shimadzu
104 HPV-X2 camera (Shimadzu, Kyoto, Japan), with 256 frames per sequence. Synchronous 10 ns
105 laser pulses (CAVILUX Smart, Cavitar, Tampere, Finland) provide the illumination and effective
106 temporal resolution, per frame. A macro-objective lens (Zeiss 100mm f2 Makro-Planar Milvus

107 ZF.2, Oberkochen, Germany) facilitates a larger field of view than that reported previously,⁷ such
108 that HIFU propagation as well as shock wave emission from cavitating bubbles, can be
109 visualized.¹⁰

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111 3. Results

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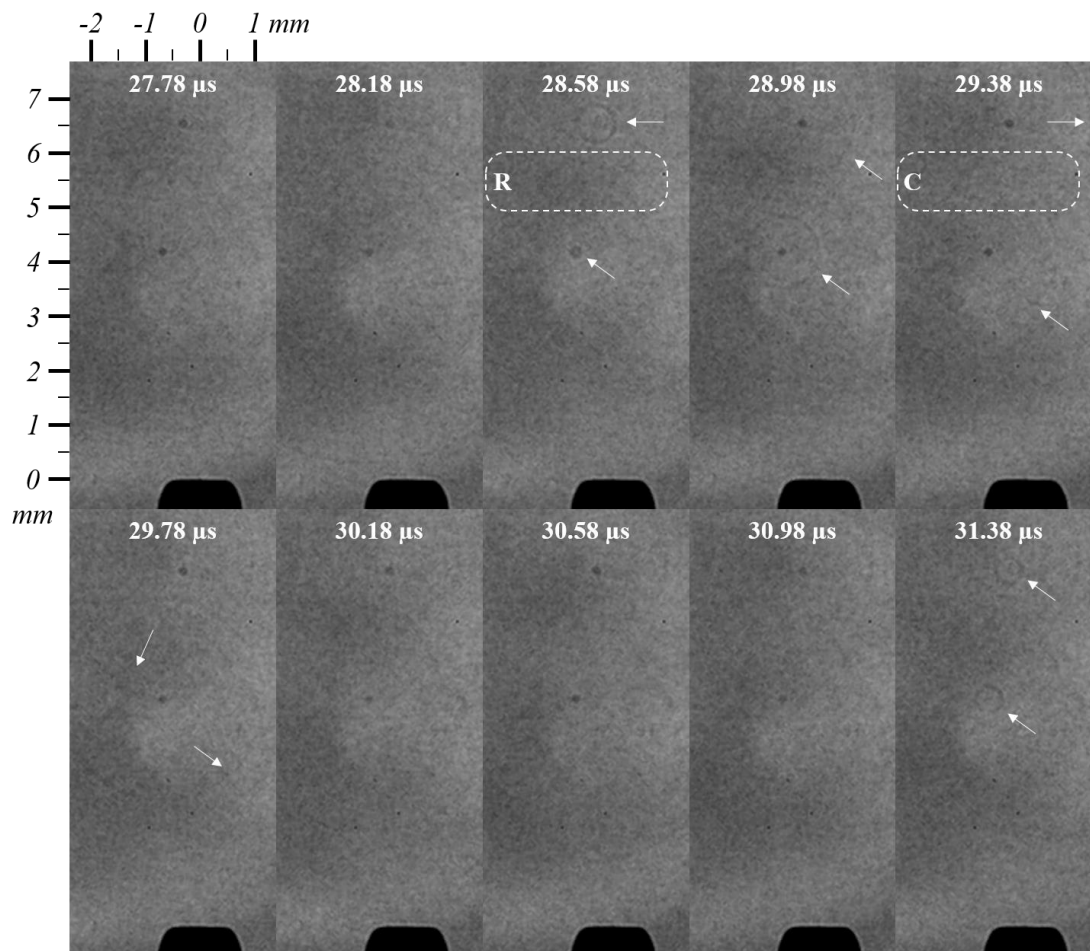
113 3.1 High-speed imaging

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115 Figure 2 depicts representative images extracted from a high-speed sequence of dual-nucleated
116 acoustic cavitation activity, each comparable to the single bubble $f_0/2$ regime activity reported
117 previously,⁷ characterized by stable $f_0/2$ PSW emission. At the field of view delivered by the
118 macro-objective, the bubble activity is barely resolved. However, the compressional and
119 rarefactional phases of the propagating HIFU can be appreciated,¹⁰ as fringes slightly brighter and
120 darker than the ambient background (labelled C and R, Figure 2), respectively. The effect is better
121 perceived from the movie version of the data, Mm.1, where it can also be seen that the bubbles
122 collapse and emit shockwaves in response to every other compressional phase, confirming the $f_0/2$
123 response regime. The salient features of this data are two cavitating bubbles (hereafter referred to
124 as top^t and bottom^b bubbles), separated by 2.3 ± 0.1 mm, which compares to the HIFU wavelength,
125 $\lambda_0 = 2.14$ mm, emitting $f_0/2$ PSWs approximately in-phase. Intuitively, this leads to a combined
126 effective shock wave detection frequency of f_0 , at the NH tip, visible to the bottom of each image,
127 Fig. 2.

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132 Fig. 2. Selected high-speed shadowgraphic images from Mm. 1, recorded at 5×10^6 fps, of two

133 cavitation-bubbles with an inter-bubble spacing $\approx \lambda_0$. Transitory brighter and darker regions,

134 imposed over an already inhomogeneous background illumination, such as indicated by dash box

135 C and R, represent compressional and rarefactional phases of the HIFU driving. The propagating

136 HIFU can be better perceived in the movie version of the data Mm. 1. PSW emission, arrowed at

137 28.58 μ s and 31.38 μ s (but not 30.18 μ s, when an intervening compressive phase is incident)

138 verifies that both bubbles are in the $f_0/2$ sub-harmonic regime.

139

140 Mm. 1. Movie of the entire image sequence represented in Fig. 2, at full field of
141 view, showing in phase $f_0/2$ PSW emission from both bubbles. Video duration is
142 20s, file type “avi” (1.74 MB).

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144 *3.2 Hydrophone data*

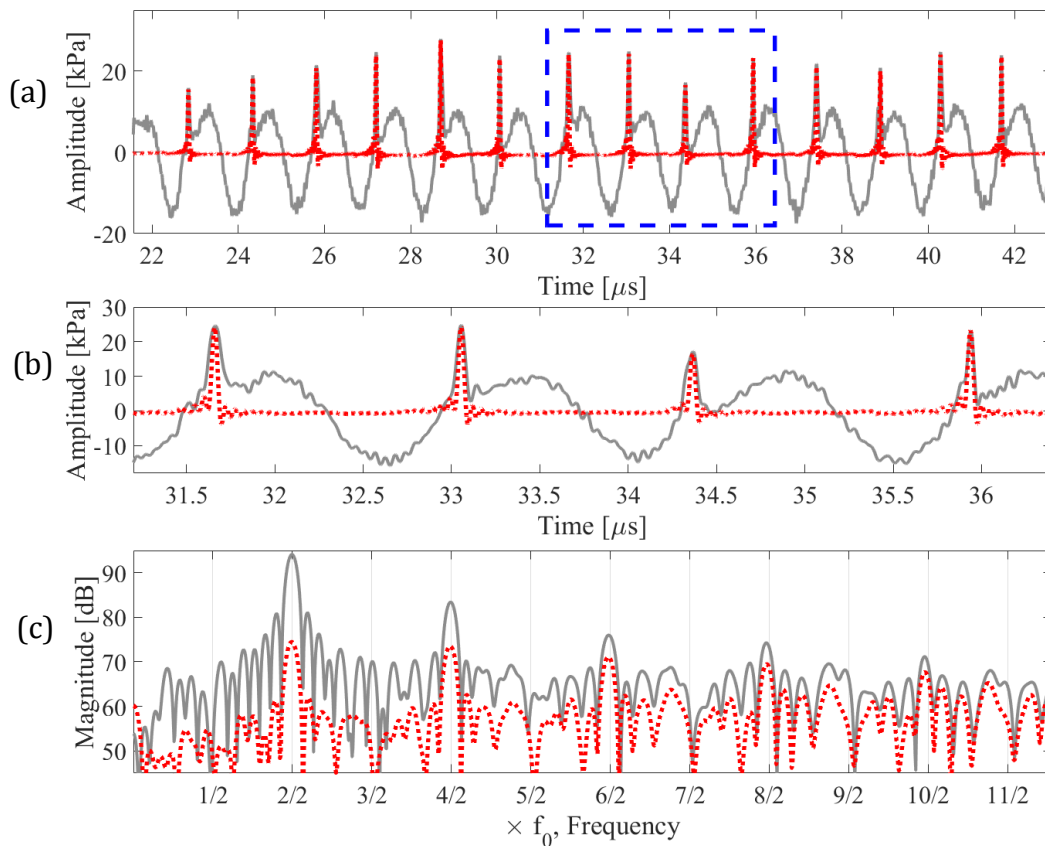
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146 Figures 3 (a) and (b) (solid grey) represent the needle hydrophone data collected during the
147 cavitation activity represented in Fig. 2, deconvolved from the impulse response of the hydrophone
148 with magnitude and phase calibration. A HIFU control exposure, for which a burst of identical
149 parameters was generated, but no cavitation nucleated, has also been subtracted.

150 A synthetic PSW signal (red dot, Figs. 3 (a) and (b)), is constructed from simulated shock
151 wave profiles, derived from solving the Gilmore equation for a freely collapsing resonant bubble,
152 and fitted to the experimental data.⁷ Synthetic acoustic f_0 and $2f_0$ components from both bubbles
153 in combination, of amplitudes and phases 10.68 ± 0.62 kPa, $121.75^\circ \pm 5.31^\circ$ and 1.88 ± 0.52 kPa
154 and $52.59^\circ \pm 21.96^\circ$, respectively, can be added for consistency with the full synthetic spectrum
155 construction procedure described previously.⁷ This yields a cross correlation coefficient of 0.96
156 between the full synthetic and experimental spectra (solid grey, Fig. 3 (c)), indicating the signal is
157 well represented. However, for the purpose of developing the model below to derive a window
158 function in the frequency domain, we consider only the PSW spectra (red dot, Fig 3. (c)) of the
159 synthetic PSW signal, which presents peaks at all relevant frequency values.

160 Inspection of the PSW profiles of Fig. 3 (b), demonstrates that the shock waves from the
161 top and bottom bubbles can be distinguished by their full-width at half maximum (FWHM), with
162 the wider shocks from the lower bubble, detected at 31.66 and 34.37 μ s, due to the more oblique

163 incidence to the NH tip. Bandpass filtering of the experimental deconvolved and control-subtracted
 164 NH signal, Fig. 3 (a), from 1.5 to 20 MHz to remove f_0 and $2f_0$ components within the NH
 165 calibration range, reveals detected shock widths of $FWHM_{PSW}^t = 40.57 \pm 3.97$ and $FWHM_{PSW}^b =$
 166 65.00 ± 7.62 ns from the top and bottom bubbles, respectively.
 167



168
 169 Fig. 3. (Color online) (a) Pressure-time waveforms of control-subtracted and deconvolved NH
 170 data (solid grey) and synthetic PSW signal (red dot), with the blue-dash box reproduced in (b)
 171 corresponding directly to the selected images of Fig. 2. (c) The experimental NH (solid grey) and
 172 PSW synthetic (red dot) spectra for the combination system, revealing no sub-harmonic content
 173 including at odd-numbered higher harmonics.
 174

175 Analysis of Fig. 3 (a) also reveals that the period of shock wave emission, $T_{PSW}^t = 2.893 \pm$
 176 $0.068 \mu\text{s}$ and $T_{PSW}^b = 2.905 \pm 0.116 \mu\text{s}$, compared to $2T_0 = 2.890 \mu\text{s}$, for the HIFU field.

177

178 4. Spectral analysis model for dual bubbles

179

180 To analyze the effect on the spectrum of the combined emissions from the dual cavitation-bubble
 181 system represented in Fig. 2, we consider the synthetic PSW signal that would be detected by the
 182 NH from both bubbles, $x_{PSW}^{NH}(t)$, as the sum of the synthetic PSW signals from the top bubble,
 183 $x_{PSW}^t(t)$, and bottom bubble, $x_{PSW}^b(t)$, emitted in isolation from the other. The effects of bubble-
 184 bubble interactions, which will be particularly prevalent at smaller inter-bubble distances, are
 185 discussed below. $x_{PSW}^t(t)$ and $x_{PSW}^b(t)$ are deduced from the distinct shock wave profile FWHMs
 186 apparent from Fig. 3 (b), in combination with the high speed image sequence of the activity, such
 187 that each shock wave and its source bubble is individually identified. As both bubbles are
 188 responding to the HIFU in the same $f_0/2$ sub-harmonic regime, $x_{PSW}^t(t)$ can be approximated in
 189 terms of $x_{PSW}^b(t)$, as

$$190 \quad x_{PSW}^t(t) \approx r \cdot x_{PSW}^b(t - \tau) \quad (1)$$

191

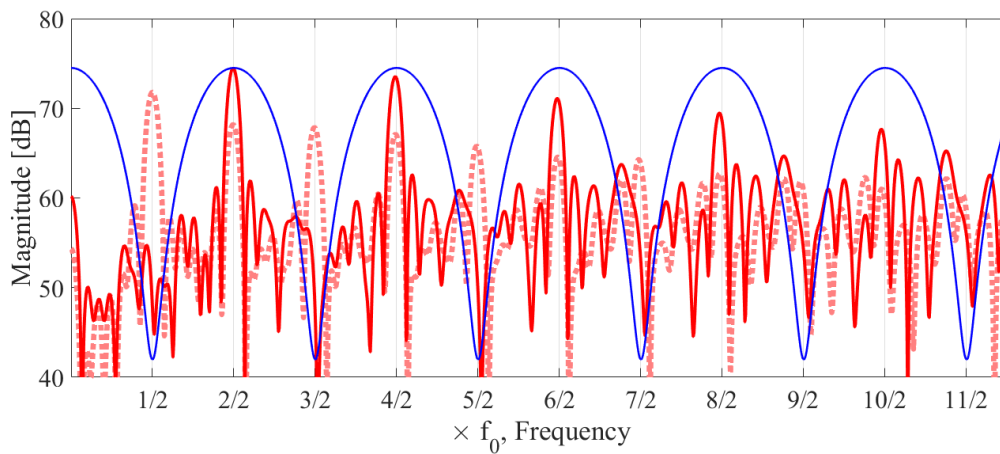
192 where r is the ratio of peak-positive pressure amplitudes $PPPA_{SW}^t:PPPA_{SW}^b$, of the PSWs from
 193 the top and bottom bubbles, respectively, and τ is the difference in propagation time from each
 194 bubble, to the NH tip. The frequency spectrum of the combined PSW signal detected by the NH,
 195 $X_{PSW}^{NH}(f) = \mathcal{FT}\{x_{PSW}^{NH}(t)\}$, where $\mathcal{FT}\{\cdot\}$ is the Fourier transform, can therefore be expressed in
 196 terms of the magnitude of the PSW spectrum from the bottom bubble, as

$$|X_{PSW}^{NH}(f)| \approx |1 + r \cdot \cos(2\pi f\tau)| \cdot |X_{PSW}^b(f)| \quad (2)$$

198

199 The $[1 + r \cdot \cos(2\pi f\tau)]$ term of Eq. (2) acts as a “periodic windowing” function to the
 200 magnitude response of the PSW spectrum of the bottom cloud, to obtain magnitude of the NH
 201 spectrum, $|X_{PSW}^{NH}(f)|$. τ thus determines the spacing of the window suppressions in the frequency
 202 domain, with r determining the degree of suppression. To apply the model to the dual-bubble
 203 cavitation system of Fig. 2, values are ascertained for the windowing parameters as $\tau = 1.444 \pm$
 204 $0.074 \mu\text{s}$, and $r = 1.07 \pm 0.18$ (with $PPPA_{SW}^t = 22.92 \pm 2.20 \text{ kPa}$ and $PPPA_{SW}^b = 21.91 \pm 4.29 \text{ kPa}$).
 205 The resulting window function (solid blue, Fig. 4) imposed to the synthetic PSW spectrum,
 206 $X_{PSW}^b(f)$ (red dot), of the bottom bubble, generates the PSW spectrum as detected by the NH from
 207 the dual-bubble system, $X_{PSW}^{NH}(f)$ (solid red).

208



209

210 Fig. 4. (Color online) The magnitude of the synthetic $f_0/2$ PSW spectrum, $|X_{PSW}^b(f)|$, expected
 211 from the bottom bubble only (red dot), the windowing function (solid blue) with r and τ deduced
 212 from the experimental NH data, and the resulting NH PSW spectrum, $|X_{PSW}^{NH}(f)|$ (solid red), on
 213 application of the window.

214 Figure 4 confirms that $X_{PSW}^b(f)$, in isolation, generates peaks at all values of $nf_0/2$,
 215 including the sub-harmonic and its higher harmonics, and f_0 and its higher harmonics, consistent
 216 with our previous report.⁷ In applying the window function of Eq. (2), to deduce the PSW spectrum
 217 from the dual-bubble system, however, all spectral content at $nf_0/2$ for odd-values of n , are
 218 suppressed, in line with the experimental spectrum of the dual-bubble emissions, collected by the
 219 NH, (solid grey, Fig. 3 (c)).

220

221 5. Discussion

222

223 With this experiment, we have definitively demonstrated that a medium can host cavitation activity,
 224 of a particular regime, and yet appear not to generate the acoustic signals specifically associated
 225 with that regime. In the particular example presented, the cavitation sub-harmonic at $f_0/2$, and its
 226 higher harmonics, which are signals widely used to infer the very existence of acoustic cavitation,¹⁻
 227 ⁴ are significantly suppressed for any detector aligned to the HIFU axis. A windowing function is
 228 analytically expressed to predict the frequency values at which peak suppressions will occur for
 229 the spectrum of the dual-bubble cavitation activity, in terms of the PSW spectrum from one of the
 230 component bubbles. This confirms suppression at $nf_0/2$, for odd values of n , as seen in the
 231 experimental results. Moreover, the resulting signal enhancement, at even values of n (harmonics
 232 of f_0), could easily be misinterpreted as due to nonlinear HIFU propagation, rather than cavitation
 233 activity.

234 From Fig. 2, the distance between the hydrophone tip and the top and bottom bubbles is
 235 6.6 and 4.3 ± 0.1 mm, respectively. Fig. 3 (b) indicates that the maximum instantaneous amplitude
 236 of the emissions from each bubble ≈ 30 kPa. Assuming the pressure amplitude decays in inverse

237 proportion to the propagation distance, the highest instantaneous pressure within the emissions
238 from the source bubble, at the location of the second bubble, is ~ 100 kPa. The analysis therefore
239 assumes that the emissions from either bubble are dominated by the HIFU driving, and not
240 significantly influenced by the other bubble, for the short duration of ~ 20 μ s over which they are
241 sampled. For extended driving durations, and smaller inter-bubble distances, bubble-bubble
242 interactions will become significant. For example, secondary radiation force-induced translation,
243 which is not perceptible within the high speed imaging of Fig. 2 and Mm. 1, would lead to
244 windowing parameters that are also a function of time.

245 The model easily allows other configurations of two $f_0/2$ bubbles to be considered, under
246 the assumption that they can be considered as two independent sources. If the bubbles, emitting
247 PSWs in phase, were configured orthogonally to the HIFU propagation axis, at an inter-bubble
248 spacing of λ_0 , the shock waves from each bubble would arrive at the hydrophone tip, at the same
249 time. The magnitude of the $f_0/2$ peak would therefore be double that from either bubble, emitting
250 individually. Alternatively, an inter-bubble spacing of $\lambda_0/2$, along the HIFU propagation axis, will
251 result in an effective shock wave detection frequency of $2f_0$ at the hydrophone. This would halve
252 the value of τ used above, doubling the frequency values at which suppression occurs, such that
253 odd-order f_0 harmonics ($f_0, 3f_0, 5f_0, 7f_0\dots$) are suppressed.

254 More than two bubbles responding in the same regime would result in additional r and τ
255 values, and more complex periodic windowing functions, of variable frequency spacing and
256 degrees of suppression. For multiple cavitation-bubbles responding to an insonation in different
257 sub-harmonic regimes, such as for a HIFU field with bubbles simultaneously within the focus and
258 also outside of it, the windowing function cannot be analytically derived. However, the presented
259 model may be applicable for combinations of f_0/n and f_0/m (where $n \neq m$) bubbles within limited

260 frequencies, if they have common spectral peaks at $k \cdot L f_0$ where $k \in \mathbb{N}$, and L is the least common
261 multiple of $1/m$ and $1/n$. By taking the approximation that $X_{PSW}^b(f) \approx r' \cdot X_{PSW}^t(f)$ where $r' =$
262 $r \cdot m/n$ and $f = k \cdot L f_0$, constructive and destructive interference at specific spectral peaks may be
263 anticipated.

264 Evidently, the precision of laser-nucleation has allowed us to spatially configure bubble
265 activity for maximum effect, to demonstrate spectral windowing and peak suppression. The near-
266 complete suppression, demonstrated here for $f_0/2$ because the shock wave amplitude ratio, $r \approx 1$,
267 of any peak would not be expected for experiments involving spontaneous and stochastically
268 distributed cavitation. We also note that the experimental results presented above have been
269 selected from a longer data set, as an ideal case in terms of shock wave amplitude and periodicity,
270 to demonstrate the effect. Generally, however, care should be taken with gauging the level of
271 cavitation activity from the magnitude of any single spectral peak.

272 A second detector, aligned orthogonally to the one in the configuration described here,
273 would certainly be expected to detect sub-harmonic signal. This would indicate that multiple,
274 spatially configured cavitation detectors would yield reliable, and reproducible measurements for
275 correlation of cavitation-mediated effects, particularly for systems where a low number of
276 nucleations may be anticipated. Parallel assessment of cavitation emissions over a sufficiently
277 large bandwidth will also minimize the effects of spectral windowing.

278

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280

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285

286 **References**

287

288 ¹C. M. Schoellhammer, A. Schroeder, R. Maa, G. Y. Lauwers, A. Swiston, M. Zervas, R.

289 Barman, A. M. DiCiccio, W. R. Brugge, D. G. Anderson, D. Blankschtein, R. Langer, and G.

290 Traverso, “Ultrasound-mediated gastrointestinal drug delivery,” *Sci. Transl. Med.* **7**, 310ra168

291 (2015).

292 ²M. A. O’Reilly and K. Hynynen, “Blood-Brain Barrier: Real-time feedback-controlled focused

293 ultrasound disruption by using an acoustic emission-based controller,” *Radiology* **263**, 96-106

294 (2012).

295 ³K. Kawabata and S. Umemura, “Use of second-harmonic superimposition to induce chemical

296 effects of ultrasound,” *J. Phys. Chem.*, **100**, 18784-18789 (1996).

297 ⁴H. Hasanzadeh, M. Mokhtari-Dizaji, S. Z. Bathaie, and Z. M. Hassan, “Evaluation of

298 correlation between chemical dosimetry and subharmonic spectrum analysis to examine the

299 acoustic cavitation,” *Ultrason. Sonochem.*, **17**, 863-869 (2010).

300 ⁵W. S. Chen, A. A. Brayman, T. J. Matula, and L. A. Crum, “Inertial cavitation dose and

301 hemolysis produced *in vitro* with or without Optison,” *Ultrasound Med. Biol.*, **29**, 725-737

302 (2003).

303 ⁶C. C. Coussios, C. H. Farny, G. ter Haar, and R. A. Roy, “Role of acoustic cavitation in the

304 delivery and monitoring of cancer treatment by high-intensity focused ultrasound (HIFU),” *Int. J.*

305 *Hyperthermia*, **23**, 105-120 (2007).

- 306 ⁷J. H. Song, K. Johansen, and P. Prentice, “An analysis of the acoustic cavitation noise spectrum:
307 The role of periodic shock waves,” *J. Acoust. Soc. Am.*, **140**, 2494-2505 (2016).
- 308 ⁸B. Gerold, S. Kotopoulos, C. McDougall, D. McGloin, M. Postema, and P. Prentice, “Laser-
309 nucleated acoustic cavitation in focused ultrasound,” *Rev. Sci. Inst.* **82**, 044902 (2011).
- 310 ⁹K. Johansen, J. H. Song, K. Johnston, and P. Prentice, “Deconvolution of acoustically detected
311 bubble-collapse shock waves,” *Ultrasonics*, **73**, 144-153 (2017).
- 312 ¹⁰K. Johansen, J. H. Song, and P. Prentice, “Characterising focused ultrasound via high speed
313 shadowgraphic imaging at 10 million frames per second” *IEEE Ultrasonics Symposium, Tours*
314 (2016), pp. 1-4.
- 315
- 316
- 317