

Positive pressure matters in acoustic droplet vaporization

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Acoustically vaporizable droplets are phase-change agents that can improve the effectiveness of ultrasound-based therapies. In this study, we demonstrate that the compression phase of an acoustic wave contributes to the generation of the negative pressure that initiates vaporization. This counterintuitive process is explained by separately evaluating the contribution of the compression and rarefaction phase of the incoming acoustic wave to the acoustic pressure field inside the droplet. Our analysis unifies the existing theories for acoustic droplet vaporization under a single framework and is supported by experiments and simulations. This different interpretation can be employed to identify governing parameters that allow one to vaporize droplets using predominantly compression waves, which are safer in medical use.

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I. INTRODUCTION

Micron- and submicron-sized superheated liquid perfluorocarbon droplets are a relatively new class of ultrasound-responsive agents that are typically metastable in blood circulation and can be converted into microbubbles upon acoustic excitation [1], with the possibility to target specific areas of the human body. This process, commonly known as acoustic droplet vaporization (ADV), shows promise in applications such as contrast-enhanced ultrasound imaging [2], gas embolotherapy [3], targeted drug delivery [4], and other ablation techniques [5,6]. Compared to microbubble contrast agents, droplet emulsions present greater stability against dissolution in the blood flow [7] and can be nanometric in size to leverage the enhanced permeability and retention (EPR) effect to improve drug accumulation in tumor tissue [8]. Vaporization inception is typically characterized by an acoustic threshold, which depends nontrivially on parameters such as droplet radius, frequency, and temperature [9].

Significant progress has been made in elucidating the physics of ADV [10–14], as well as in characterizing and reducing the acoustic vaporization threshold [1,15,16], which currently greatly exceeds the pressure required to excite microbubble contrast agents [17] and can question the safety of droplet-based *in vivo* treatments. Shpak *et al.* [12] suggested that the focusing of superharmonics of the driving wave, created due to nonlinear propagation in the medium surrounding the droplets, can generate localized tension (i.e., negative pressure) amplification in the liquid core that facilitates nucleation. Lajoinie *et al.* [18] described another possible mechanism for droplet vaporization based on acoustic resonance.

Most of the prior studies on ADV focus on the peak negative pressure (PNP) of the incoming ultrasound wave as the main contributor to vaporization initiation. Here, we demonstrate that the compressive phase of the driving acoustic wave can play a significant role in triggering phase change by dictating the location of the maximum tension within the droplet bulk. In some cases, we predict that the focusing incoming wave reverses its sign as it crosses the focal point. This insight advances our understanding of the physics behind ADV and the presented analysis unifies the superharmonic focusing and resonance theories under the same theoretical framework.

II. THEORY

We model the axisymmetric acoustic wave propagation within a spherical droplet of radius R , density ρ_2 , and speed of sound, c_2 , located in an infinite medium of density ρ_1 and speed of sound, c_1 , as described elsewhere [12,19,20]. The transmitted pressure within the droplet is obtained by summing the solutions for every harmonic component, n , of the incoming nonlinear ultrasound wave with fundamental angular frequency ω_1 and initial phases ϕ_n . The pressure field in the droplet core, $p_t(r, \theta, t)$, can be described as a function of the radial coordinate r , the polar angle θ [see Fig. 1(c)], and the time t as

$$p_t(r, \theta, t) = \text{Re} \left[\sum_{n=0}^{\infty} \sum_{m=0}^{\infty} a_n e^{i(n\omega_1 t + \phi_n)} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right], \quad (1)$$

where

$$\tilde{\alpha}_{m,n} = (-i)^m (2m+1) \times \frac{j_m(nk_1 R) h_m^{(2)}(nk_1 R) - h_m^{(2)}(nk_1 R) j_m'(nk_1 R)}{j_m(nk_2 R) h_m^{(2)}(nk_1 R) - \frac{\rho_1 c_1}{\rho_2 c_2} h_m^{(2)}(nk_1 R) j_m'(nk_2 R)} \quad (2)$$

is the amplification factor, with $k_1 = \omega_1/c_1$, $k_2 = \omega_1/c_2$ being the fundamental wave numbers in the surrounding and droplet

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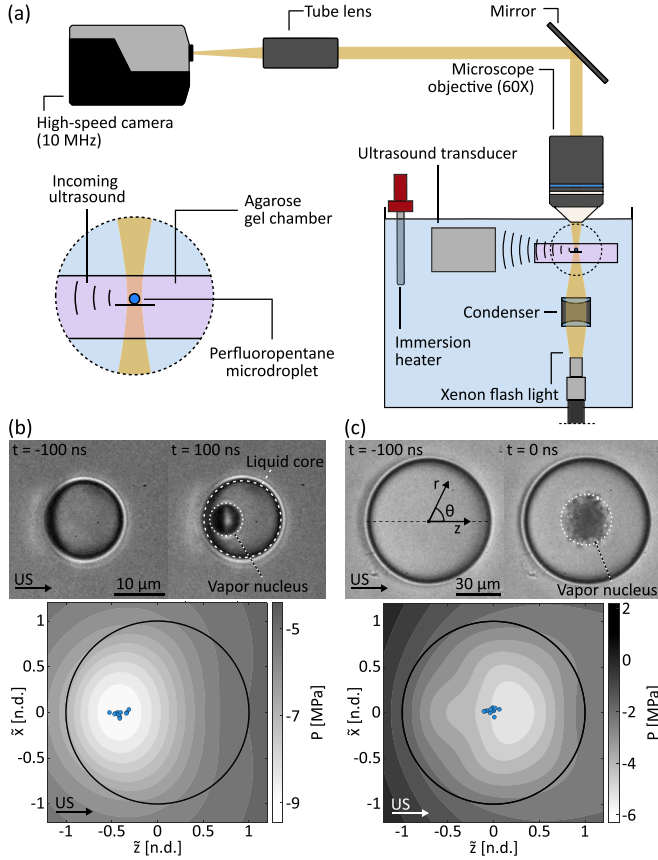


FIG. 1. (a) Schematic of the experimental setup. (b) Top: Snapshots of the vaporization dynamics of a single 9- μm -radius droplet sonicated with a 5-MHz HIFU. Below: Nucleation positions (blue dots) overlapped with the numerically simulated differential (with respect to ambient) pressure field on the droplet center plane at the instant of global minimum pressure. (c) Similar to (b), with a 38- μm -radius droplet and a 3.5-MHz HIFU. In both cases, nucleation inception happens at the time $t = 0$ ns.

medium, respectively, j_m and y_m the spherical Bessel functions of the first and second kind of order m , $h_m = j_m - iy_m$ the spherical Hankel function of the second kind of order m , and the prime represents differentiation with respect to $k_q r$, where $q = 1, 2$. The complete derivation is provided in the Supplemental Material [21] (see, also, Refs. [22–26] therein). The expression in Eq. (2) can be rewritten in terms of the dimensionless radius $\tilde{R} = n f_1 R / c_2$,

$$\tilde{\alpha}_{m,n} = (-i)^m (2m+1) \times \frac{j_m(2\pi \frac{c_2}{c_1} \tilde{R}) h_m^{(2)}(2\pi \frac{c_2}{c_1} \tilde{R}) - h_m^{(2)}(2\pi \frac{c_2}{c_1} \tilde{R}) j_m'(2\pi \frac{c_2}{c_1} \tilde{R})}{j_m(2\pi \tilde{R}) h_m^{(2)}(2\pi \frac{c_2}{c_1} \tilde{R}) - \frac{\rho_1 c_1}{\rho_2 c_2} h_m^{(2)}(2\pi \frac{c_2}{c_1} \tilde{R}) j_m'(2\pi \tilde{R})}, \quad (3)$$

with f_1 being the fundamental angular frequency.

The pressure field inside the droplet core, $p_t(r, \theta, t)$, generated by the interaction with the pressure profile $p_f(t)$ of the incoming ultrasound wave,

$$p_f(t) = \text{Re}[\tilde{p}_f(t)] = \text{Re}\left[\sum_{n=0}^{\infty} a_n e^{i(n\omega_1 t + \phi_n)}\right], \quad (4)$$

can conveniently be expressed as the sum of two distinct pressure fields, one generated by the purely compression and one from the purely rarefaction phase of the original wave. This decomposition enables us to investigate their respective contributions to the resulting pressure field. To simplify the mathematical procedure, the Fourier expansion of the pressure profile can be expressed in a more conventional form,

$$p_f(t) = \sum_{n=-\infty}^{\infty} A_n e^{in\omega_1 t}, \quad (5)$$

where $|A_n| = a_{|n|}/2$, $\angle(A_n) = \text{sgn}(n)\phi_{|n|}$, $A_0 = a_0$ and, for $n > 0$, $a_n e^{i\phi_n} = 2A_n$. Moreover, since $p_f(t)$ is a real function of time, $A_{-n} = A_n^*$.

The decomposition operation can be seen as a multiplication of the experimentally detected pressure signal $p_f(t)$ by a square function $w^{\pm}(t)$,

$$w^+(t) = \begin{cases} 1 & lT_1 \leq t \leq lT_1 + \bar{t} \\ 0 & lT_1 + \bar{t} < t < (l+1)T_1 \end{cases}; \quad l = 0, 1, 2, \dots, \quad (6)$$

$$w^-(t) = \begin{cases} 0 & lT_1 \leq t \leq lT_1 + \bar{t} \\ 1 & lT_1 + \bar{t} < t < (l+1)T_1 \end{cases}; \quad l = 0, 1, 2, \dots, \quad (7)$$

where T_1 is the fundamental period of the driving wave $p_f(t)$ and $\bar{t}$ is the time instant at which the pressure profile crosses zero value, going from a positive to a negative value. Here, it is assumed that the compression phase of $p_f(t)$ is fully included between times lT_1 and $lT_1 + \bar{t}$, while the rest of the period is occupied by the rarefaction phase. The two windows can then be expanded in a Fourier series,

$$w^+(t) = \sum_{n=-\infty}^{\infty} C_n^+ e^{in\omega_1 t}, \quad C_0^+ = \frac{1}{T_1} \int_0^{T_1} w^+(t) dt = \frac{\bar{t}}{T_1},$$

$$C_n^+ = \frac{1}{T_1} \int_0^{T_1} w^+(t) e^{-in\omega_1 t} dt = \frac{1}{T_1} \int_0^{\bar{t}} e^{-in\omega_1 t} dt$$

$$= \frac{1 - e^{-in\omega_1 \bar{t}}}{i2\pi n}, \quad (8)$$

$$w^-(t) = \sum_{n=-\infty}^{\infty} C_n^- e^{in\omega_1 t},$$

$$C_0^- = \frac{1}{T_1} \int_0^{T_1} w^-(t) dt = \frac{T_1 - \bar{t}}{T_1},$$

$$C_n^- = \frac{1}{T_1} \int_0^{T_1} w^-(t) e^{-in\omega_1 t} dt = \frac{1}{T_1} \int_{\bar{t}}^{T_1} e^{-in\omega_1 t} dt$$

$$= -\frac{1 - e^{-in\omega_1 \bar{t}}}{i2\pi n}. \quad (9)$$

It is important to note that since $w^+(t) + w^-(t) = 1$ by definition of the two windows, we obtain $C_0^+ + C_0^- = 1$ and $C_n^+ + C_n^- = 0$. Moreover, since the function $w^{\pm}(t)$ is a real function of time, by the definition of Fourier coefficients, the property $C_{-n}^{\pm} = C_n^{\pm*}$ holds.

The compression phase of the driving wave can then be obtained by multiplying $p_f(t)$ by its corresponding window,

$$\begin{aligned} p_f^+(t) &= p_f(t)w^+(t) = \sum_{j=-\infty}^{\infty} A_j e^{ij\omega_1 t} \sum_{k=-\infty}^{\infty} C_k^+ e^{ik\omega_1 t} = \sum_{j=-\infty}^{\infty} \sum_{k=-\infty}^{\infty} A_j C_k^+ e^{i(j+k)\omega_1 t} \\ &= \sum_{n=-\infty}^{\infty} \left(\sum_{j=-\infty}^{\infty} A_j C_{n-j}^+ \right) e^{in\omega_1 t} = \sum_{n=-\infty}^{\infty} A_n^+ e^{in\omega_1 t}, \end{aligned} \quad (10)$$

provided the variable substitution $k = n - j$ is performed. The terms A_n^+ correspond to the Fourier coefficients of the decomposed signal. A form analogous to the one of Eq. (4) can be obtained by exploiting the property $A_{-n}^+ = A_n^{+*}$, since the signal $p_f^+(t)$ is still a real function of time. Therefore,

$$\begin{aligned} p_f^+(t) &= \sum_{n=-\infty}^{\infty} A_n^+ e^{in\omega_1 t} = \sum_{n=1}^{\infty} A_{-n}^+ e^{-in\omega_1 t} + A_0^+ + \sum_{n=1}^{\infty} A_n^+ e^{in\omega_1 t} = \sum_{n=1}^{\infty} A_n^{+*} (e^{in\omega_1 t})^* + A_0^+ + \sum_{n=1}^{\infty} A_n^+ e^{in\omega_1 t} \\ &= A_0^+ + \sum_{n=1}^{\infty} [A_n^+ e^{in\omega_1 t} + (A_n^+ e^{in\omega_1 t})^*] = A_0^+ + \sum_{n=1}^{\infty} 2\text{Re}[A_n^+ e^{in\omega_1 t}] = A_0^+ + \text{Re} \left[\sum_{n=1}^{\infty} 2A_n^+ e^{in\omega_1 t} \right] \\ &= \text{Re} \left[A_0^+ + \sum_{n=1}^{\infty} 2A_n^+ e^{in\omega_1 t} \right] = \text{Re} \left[\sum_{n=0}^{\infty} a_n^+ e^{i\phi_n^+} e^{in\omega_1 t} \right], \end{aligned} \quad (11)$$

since A_0^+ is a real number. The last expression in Eq. (11) is analogous to the one in Eq. (4).

The same procedure can be repeated again using the window $w^-(t)$, obtaining

$$p_f^-(t) = A_0^- + \text{Re} \left[\sum_{n=1}^{\infty} 2A_n^- e^{in\omega_1 t} \right] = \text{Re} \left[A_0^- + \sum_{n=1}^{\infty} 2A_n^- e^{in\omega_1 t} \right] = \text{Re} \left[\sum_{n=0}^{\infty} a_n^- e^{i\phi_n^-} e^{in\omega_1 t} \right], \quad (12)$$

where

$$A_n^- = \sum_{j=-\infty}^{\infty} A_j C_{n-j}^-$$

are the Fourier coefficients of the decomposed signal corresponding to the rarefaction phase of the driving wave.

Considering that the structure of the decomposed waves [Eqs. (11) and (12)] is the same as the one in Eq. (4), the pressure field inside the droplet can be expressed using the notation shown in Eq. (1),

$$p_t^+(r, \theta, t) = A_0^+ + \text{Re} \left[\sum_{n=1}^{\infty} \sum_{m=0}^{\infty} 2A_n^+ e^{in\omega_1 t} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right], \quad (13)$$

$$p_t^-(r, \theta, t) = A_0^- + \text{Re} \left[\sum_{n=1}^{\infty} \sum_{m=0}^{\infty} 2A_n^- e^{in\omega_1 t} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right], \quad (14)$$

where A_0^+ and A_0^- are the average values of the decomposed waves.

By summing $p_t^+(r, \theta, t)$ and $p_t^-(r, \theta, t)$, the transmitted pressure $p_t(r, \theta, t)$, given by Eq. (1), can be recovered:

$$\begin{aligned} p_t(r, \theta, t) &= p_t^+(r, \theta, t) + p_t^-(r, \theta, t) = (A_0^+ + A_0^-) + \text{Re} \left[\sum_{n=1}^{\infty} \sum_{m=0}^{\infty} 2(A_n^+ + A_n^-) e^{in\omega_1 t} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right] \\ &= \left[\sum_{j=-\infty}^{\infty} A_j (C_{-j}^+ + C_{-j}^-) \right] + \text{Re} \left\{ \sum_{n=1}^{\infty} \sum_{m=0}^{\infty} 2 \left[\sum_{j=-\infty}^{\infty} A_j (C_{n-j}^+ + C_{n-j}^-) \right] e^{in\omega_1 t} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right\} \\ &= A_0 + \text{Re} \left[\sum_{n=1}^{\infty} \sum_{m=0}^{\infty} 2A_n e^{in\omega_1 t} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right] = \text{Re} \left[a_0 + \sum_{n=1}^{\infty} \sum_{m=0}^{\infty} a_n e^{i\phi_n} e^{in\omega_1 t} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right] \\ &= \text{Re} \left[\sum_{n=0}^{\infty} \sum_{m=0}^{\infty} a_n e^{i\phi_n} e^{in\omega_1 t} \tilde{\alpha}_{m,n} j_m(nk_2 r) P_m(\cos \theta) \right], \end{aligned} \quad (15)$$

due to the relation $C_{n-j}^+ + C_{n-j}^- = 0$ for every $j \neq n$ and $C_{n-j}^+ + C_{n-j}^- = 1$ if $j = n$.

III. EXPERIMENTAL SETUP

Monodisperse perfluoropentane (C_5F_{12} , PFP) droplets coated with fluorosurfactant and with average radii of 9 μm and 38 μm are prepared following the protocols described elsewhere [27,28]. Polydisperse droplet populations are prepared by emulsification of 1% fluorosurfactant solution and perfluoropentane. The experimental setup employed to characterize ADV is illustrated in Fig. 1(a). Vaporization dynamics are visualized using a custom-built vertical microscope [29], providing an overall magnification of $200\times$ and $66.66\times$ coupled to a high-speed camera set to record at 10 million frames per second. The droplets are placed within an agarose chamber submerged in water at a temperature of $37\text{--}40^\circ\text{C}$. The droplets are subjected to ultrasound from a 5-MHz and 3.5-MHz single-element high-intensity focused ultrasound (HIFU) transducers. A linear array probe controlled by an ultrasound open platform [30] is additionally tested. The pressure field at the optical and acoustic focus is measured using a 75- μm needle hydrophone. A detailed description of the experimental setup is provided in the Supplemental Material [21].

IV. NUMERICAL SIMULATIONS

Axisymmetric numerical simulations are performed using the k-wave toolbox in matlab [31]. The experimentally measured pressure wave at the transducer focal point is used to initialize a velocity source in the z direction [indicated in Fig. 1(c)] and to create a traveling plane wave in the domain. The droplet is modeled as a discontinuity in density and sound speed, placed in an infinite homogeneous medium (water) (see Supplemental Material for details on the material properties [21]).

V. RESULTS AND DISCUSSION

Experimental frames depicting the initial stage of ADV are presented in Fig. 1(b) for a 9- μm -radius and Fig. 1(c) for a 38- μm -radius droplet upon excitation with a 5-MHz and 3.5-MHz HIFU, respectively (full recordings are available in the Supplemental Material [21]). The initial nucleation locations, shown below, are concentrated around the two different positions of the global minimum pressure computed by the numerical simulations.

The theoretical solution perfectly agrees with the numerical simulations after the steady state is reached, as shown in Fig. 2(a), where the solid line represents the pressure field on the 9- μm -radius droplet centerline for the 5-MHz HIFU case. The experimental pressure wave, shown as a dashed line, presents a marked asymmetry between the positive and negative peaks due to the wave's distortion upon nonlinear propagation in water and the resulting presence of superharmonics. To investigate the effect of the distortion on tension generation in the droplet core, the wave is split into its compression and rarefaction parts, and the harmonic content of the resulting monopolar waves, shown in Fig. 2(b) alongside the

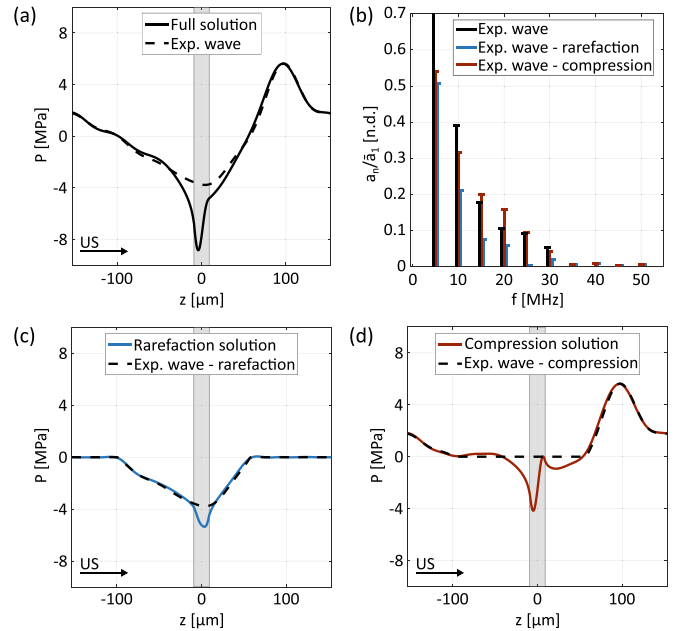


FIG. 2. (a) Theoretical differential (with respect to ambient) pressure field along the symmetry axis of a 9- μm -radius droplet, compared with a single cycle of the free-field, experimentally measured 5-MHz HIFU pressure signal. (b) Harmonic content of the compression and rarefaction phase of the experimentally measured pressure wave, normalized by the coefficient of the fundamental harmonic of the complete wave (here shown in black, with the first dimensionless coefficient equal to one). The spurious frequencies generated by the decomposition are the ones without a correspondent black line. (c) Transmission of the rarefaction and (d) compression phase of the experimental wave computed on the droplet centerline compared with the respective undisturbed reference. The shaded area represents the droplet position. All snapshots depict the time instant at which the minimum pressure of the full solution is reached.

original one, is then used to compute two separate pressure fields. Although unconventional, this decomposition allows one to perfectly recover the original pressure field within the droplet, upon summation of the two distinct contributions, as demonstrated above.

Figures 2(c) and 2(d) display two instantaneous pressure profiles corresponding to the monopolar wave solutions $p_t^+(r, \theta, t)$ and $p_t^-(r, \theta, t)$ at the instant of time in which the sum of the two has a global pressure minimum. The rarefaction-induced pressure field in Fig. 2(c) does not show a particularly localized focal region, but rather a broad amplification of the wave traveling through the droplet core. On the other hand, surprisingly, the compression-induced solution in Fig. 2(d) shows a highly localized negative pressure peak whose position matches well with the peak achieved in the combined solution. This suggests that the compression phase dictates the location of the global minimum pressure in addition to contributing to its absolute value.

Since the acoustic impedance, $Z_2 = \rho_2 c_2$, of liquid PFP is lower than the one of water, $Z_1 = \rho_1 c_1$, tension generation cannot be attributed to the reflection of the monopolar compression wave at the internal boundary of the droplet. Instead, it can be seen from the provided animations of the

5-MHz HIFU wave (see Supplemental Material [21]) that the monopolar compression wave, once transmitted into the droplet core, converges and, at its focus, develops a negative tail that is then reflected at the rear boundary and refocused at the second focal position in the proximal side of the droplet. Here, the negative pressure generated by the compression peak, combined with the amplified negative pressure obtained from the transmission of the rarefaction phase, generates a global minimum throughout the whole excitation period. A plausible explanation could lie in the occurrence of a *Gouy phase shift* happening while the compression wave crosses both focal points. Gouy first reported this effect in 1890 [32] for electromagnetic waves, but this principle can be applied to any wave subjected to transverse spatial confinement [33] and has recently been experimentally verified for focusing acoustic waves [34]. For a three-dimensional focusing beam, the Gouy phase shift consists of an additional variation in phase of $-\pi$ with respect to a plane wave traveling in the same medium, gradually acquired as the wave crosses the focal point [35] and corresponding to a sign inversion. However, classical modeling of the Gouy phase shift, which relies on the fact that the wave travels in an infinite medium [33,35–37], cannot be directly applied due to the high longitudinal spatial confinement within the droplet, and a direct proof of this effect is beyond the scope of the present study.

When a continuous sinusoidal excitation meets a spherical discontinuity (as in the case of a droplet), the subsequent focusing and reflection of the wavefronts generate standing wave patterns in the liquid core, which can be described by the superimposition of the acoustic modes, as presented in Eq. (1). Every n th harmonic component of the driving wave excites an infinite number of modes, represented by Bessel functions of the first kind or order m multiplied by Legendre polynomials. Every acoustic mode is multiplied by a gain factor $\tilde{\alpha}_m$ that depends on the ratio between density ρ_1/ρ_2 and speed of sound, c_1/c_2 , of the droplet and surrounding medium, the order of the considered mode m , and the dimensionless droplet radius $\tilde{R} = fR/c_2$, where the dependency on the harmonic index n is incorporated in the generic frequency, f . Assuming fixed material properties (water and PFP in this case), the whole range of possible amplification factors can be compactly described as a function of $\tilde{R}$ only. The modulus of the amplification factors, $|\tilde{\alpha}_m| = \alpha_m$, is depicted in Fig. 4(a).

Every mode presents multiple frequencies in which the amplification has a local maximum, as shown in Fig. 4(a) for the mode $m = 0$. For a monochromatic wave, the full set of amplification factors required to calculate the theoretical solution can be obtained by intersecting a vertical line $\tilde{R} = \tilde{f}R/c_2$ for appropriate values of R and f , with the curves of the different α_m . Modes with $m \geq 1$ share the property of being equal to zero at the droplet center, while the mode $m = 0$ presents a global maximum due to the shape of the spherical Bessel functions. Therefore, if the zeroth mode is the most excited, focusing of the wave in the classical sense, i.e., at the focal point predicted by geometrical acoustics, is not clearly visible and the droplet will be in an “acoustic resonance” regime, as described by Lajoinie *et al.* [18]. However, if higher modes are excited, two main focal points will be visible, one on the distal and one on the proximal side of the droplet due to successive

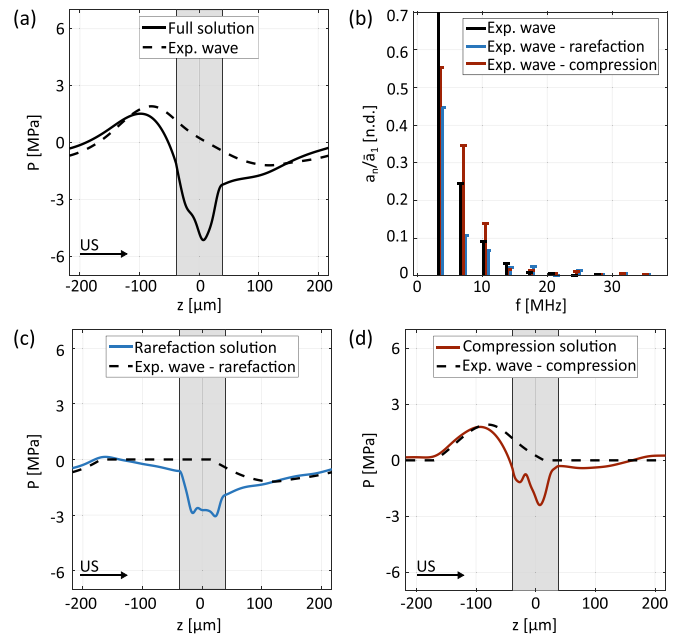


FIG. 3. (a) Theoretical differential (with respect to ambient) pressure field along the symmetry axis of a 38- μ m-radius droplet, compared with a single cycle of the free-field, experimentally measured 3.5-MHz HIFU pressure signal. (b) Harmonic content of the compression and rarefaction phase of the experimentally measured pressure wave, normalized by the coefficient of the fundamental harmonic of the complete wave (here shown in black, with the first dimensionless coefficient equal to one). The spurious frequencies generated by the decomposition are the ones without a correspondent black line. (c) Transmission of the rarefaction and (d) compression phase of the experimental wave computed on the droplet centerline compared with the respective undisturbed reference. The shaded area represents the droplet position. All snapshots depict the time instant at which the minimum pressure of the full solution is reached.

reflections at the droplet wall. Since modes with $m \geq 1$ have a global maximum away from the origin, they are able to describe the focusing of a wave in both the proximal and distal side of the droplet, as well as the consequent sign inversion process. In this case, the droplet will be in a “focusing” regime, with wave sign inversion occurring as it crosses the focal points. This corresponds to the “superharmonic focusing” effect reported by Shpak *et al.* [12]. The high amplification factor α_m of these modes makes them particularly efficient in generating negative pressure, even when the excitation wave is purely compressive. The transition between the two regimes is gradual, but a conventional limit can be fixed at the $\tilde{R}$ value where the gain for the mode $m = 1$ overcomes the one for $m = 0$, corresponding to $\tilde{R} \simeq 0.4$ and represented in Fig. 4(a) as a vertical line.

Considering now the harmonic content of the 5-MHz wave, Fig. 2(b) shows a negligible rarefaction component above 20 MHz, corresponding to a dimensionless radius of $\tilde{R}_{\text{rar}} \sim 0.44$ for a 9- μ m-radius droplet. The energy content of the rarefaction phase will then mostly excite the mode $m = 0$. The compression phase instead presents energy in the fifth harmonic (25 MHz), corresponding to a value $\tilde{R}_{\text{comp}} \sim 0.55$ very close to the $m = 1$ resonance peak, thus explaining

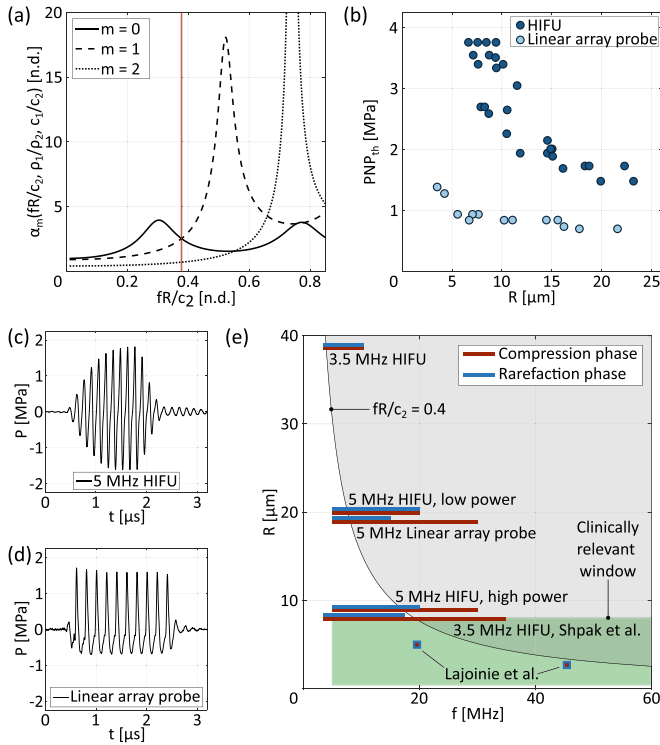


FIG. 4. (a) Amplification factor for the acoustic modes of the order of m of a PFP droplet surrounded by water. The red line represents the point at which the amplification of the mode $m = 1$ is higher than the amplification for the zeroth-order mode. (b) Experimental vaporization threshold of PFP droplets for two different ultrasound transducers as a function of droplet radius. The pressure measurements have an accuracy of $\pm 10\%$, while the error on the radius measurements is estimated to be $\pm 0.32 \mu\text{m}$. (c), (d) Waveforms of the 5-MHz HIFU and the linear array probe driven at 5-MHz, respectively. (e) Harmonic content of the rarefaction and compression phase of the waves employed in this study and some selected works from the literature on the (f, R) space. The spurious frequencies generated by the decomposition and the ones with a dimensionless value less than 0.04 are not shown in the graph. The gray area represents the (f, R) value-pairs in the “focusing” regime. The green area represents the clinically relevant operating window, considering the maximum size allowed for intravenous agents and the minimum frequency typically employed for ultrasound diagnostics [38].

the localization of the nucleation spots. Similarly, the 3.5-MHz wave employed for sonicating the 38- μm -radius droplets contains significant energy in the $n = 1$ harmonic (both for the compression and rarefaction phase), corresponding to $\bar{R}_{\text{comp}} \sim 0.33$, for which the amplification of the $m = 0$ has a maximum. As shown in Figs. 3 and 1(c), this configuration presents a pressure minimum and nucleation location much closer to the droplet center. Due to the presence of a non-negligible energy content in the harmonics above the fundamental and the excitation of the correspondent acoustic modes, the position of the global minimum is slightly moved to the distal part of the droplet.

A direct implication of the wave’s positive pressure contribution to enhance tension generation is a significant reduction of the vaporization threshold, PNP_{th} , as shown in Fig. 4(b), which combines the data obtained from a 5-MHz HIFU

and a linear array probe driven with the same fundamental frequency. The vaporization threshold is a parameter defined by extracting the PNP of the driving wave for which single droplet vaporization is first optically observed, obtained by gradually increasing the energy supplied to the transducer. The apparent distinction between the HIFU and the linear array probe in the vaporization threshold could possibly be attributed to the different harmonic content of the two excitation waves, with the HIFU wave in Fig. 4(c) being much less distorted than the one driven by the linear array probe in Fig. 4(d) (see, also, the Supplemental Material [21]). Wave distortion enables significant tension generation with relatively low PNP, facilitated by the focusing of the compression phase of the driving wave.

Once the critical value of the dimensionless radius has been set, the function, $\tilde{R} = 0.4$, can be plotted on the frequency-radius, (f, R) , space as an hyperbole delimiting the “resonance” and the “focusing” regime. The resulting graph is presented in Fig. 4(e), where the gray-shaded area represents the necessary conditions for focusing occurrence within the droplet core. The harmonic content of the compression (red) and rarefaction (blue) phases of the ultrasound signals tested in our experiments and in selected past studies [12, 18] are reported against the correspondent droplet radius. In general, the presence of harmonics in the “focusing” regime indicates the opportunity to achieve elevated tension, either due to the focusing of the rarefaction part of the wave or the sign inversion of the compression one. A broad range of harmonics in the compression phase gives then the opportunity to generate low pressure in the droplet bulk without increasing the PNP of the driving wave.

VI. CONCLUSIONS

The results presented here demonstrate the significance of the compression phase of a distorted ultrasound wave in promoting ADV. The main outcome lies in the finding that for a given radius, harmonics with a frequency $f > 0.4c_2/R$ present pronounced focusing in the PFP droplet, as well as a sign reversal of the waveform. The distortion of a wave due to nonlinear propagation in the surrounding medium causes the high-frequency harmonic content to concentrate in the compression phase of the ultrasound, promoting the occurrence of sign inversion at the droplet focus and the generation of a localized tension region. The proposed scaling using the dimensionless radius allows extending the range of droplet sizes while maintaining a similar pressure field with the practically relevant solutions [i.e., green area in Fig. 4(e)], potentially solving the inherent technological limitation of optical observation of submicron droplet dynamics.

Our results suggest that describing the acoustic vaporization threshold of a droplet solely by the applied PNP of the incoming wave is insufficient. The full extent of the wave spectrum is rarely taken into account despite its importance in determining the maximum tension generated in the droplet core, and this could be a reason behind the discrepancies between vaporization thresholds measured in prior ADV studies, as discussed in Aliabouzar *et al.* [15] and Wu *et al.* [17].

The occurrence of compression-tension conversion offers the opportunity to optimize the acoustic driving for micro-

and nanodroplets by designing the shape of the driving wave. Distorted waves with a weak rarefaction phase and a strong peak positive pressure can generate the required tension in the droplet core without affecting the surrounding medium, improving the safety of ADV while still achieving the desired therapeutic effects.

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- [1] O. D. Kripfgans, J. Fowlkes, D. L. Miller, O. Eldevik, and P. L. Carson, Acoustic droplet vaporization for therapeutic and diagnostic applications, *Ultrasound Med. Biol.* **26**, 1177 (2000).
- [2] C. M. Sehgal, P. H. Arger, and C. R. Pugh, Sonographic enhancement of renal cortex by contrast media, *J. Ultrasound Med.* **14**, 741 (1995).
- [3] J. N. Harmon, F. Kabinejadian, R. Seda, M. L. Fabiilli, S. Kuruvilla, C. C. Kuo, J. M. Greve, J. B. Fowlkes, and J. L. Bull, Minimally invasive gas embolization using acoustic droplet vaporization in a rodent model of hepatocellular carcinoma, *Sci. Rep.* **9**, 11040 (2019).
- [4] C. C. Chen, P. S. Sheeran, S.-Y. Wu, O. O. Olumolade, P. A. Dayton, and E. E. Konofagou, Targeted drug delivery with focused ultrasound-induced blood-brain barrier opening using acoustically-activated nanodroplets, *J. Control. Release* **172**, 795 (2013).
- [5] E. Vlaisavljevich, O. Aydin, Y. Y. Durmaz, K.-W. Lin, B. Fowlkes, M. ElSayed, and Z. Xu, Effects of ultrasound frequency on nanodroplet-mediated histotripsy, *Ultrasound Med. Biol.* **41**, 2135 (2015).
- [6] M. Zhang, M. L. Fabiilli, K. J. Haworth, F. Padilla, S. D. Swanson, O. D. Kripfgans, P. L. Carson, and J. B. Fowlkes, Acoustic droplet vaporization for enhancement of thermal ablation by high intensity focused ultrasound, *Acad. Rad.* **18**, 1123 (2011).
- [7] M. A. Borden, G. Shakya, A. Upadhyay, and K.-H. Song, Acoustic nanodrops for biomedical applications, *Curr. Opin. Colloid Interface Sci.* **50**, 101383 (2020).
- [8] H. Maeda, H. Nakamura, and J. Fang, The EPR effect for macromolecular drug delivery to solid tumors: Improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging in vivo, *Adv. Drug Delivery Rev.* **65**, 71 (2013).
- [9] G. Shakya, M. Cattaneo, G. Guerriero, A. Prasanna, S. Fiorini, and O. Supponen, Ultrasound-responsive microbubbles and nanodroplets: A pathway to targeted drug delivery, *Adv. Drug Delivery Rev.* **206**, 115178 (2024).
- [10] O. Shpak, T. J. A. Kokhuis, Y. Luan, D. Lohse, N. De Jong, B. Fowlkes, M. Fabiilli, and M. Versluis, Ultrafast dynamics of the acoustic vaporization of phase-change microdroplets, *J. Acoust. Soc. Am.* **134**, 1610 (2013).
- [11] N. Reznik, O. Shpak, E. C. Gelderblom, R. Williams, N. De Jong, M. Versluis, and P. N. Burns, The efficiency and stability of bubble formation by acoustic vaporization of submicron perfluorocarbon droplets, *Ultrasonics* **53**, 1368 (2013).
- [12] O. Shpak, M. Verweij, H. J. Vos, N. De Jong, D. Lohse, and M. Versluis, Acoustic droplet vaporization is initiated by superharmonic focusing, *Proc. Natl. Acad. Sci.* **111**, 1697 (2014).
- [13] D. S. Li, O. D. Kripfgans, M. L. Fabiilli, J. B. Fowlkes, and J. L. Bull, Initial nucleation site formation due to acoustic droplet vaporization, *Appl. Phys. Lett.* **104**, 063703 (2014).
- [14] D. Qin, Q. Zou, S. Lei, W. Wang, and Z. Li, Predicting initial nucleation events occurred in a metastable nanodroplet during acoustic droplet vaporization, *Ultrasonics Sonochem.* **75**, 105608 (2021).
- [15] M. Aliabouzar, K. N. Kumar, and K. Sarkar, Acoustic vaporization threshold of lipid-coated perfluoropentane droplets, *J. Acoust. Soc. Am.* **143**, 2001 (2018).
- [16] M. Aliabouzar, K. N. Kumar, and K. Sarkar, Effects of droplet size and perfluorocarbon boiling point on the frequency dependence of acoustic vaporization threshold, *J. Acoust. Soc. Am.* **145**, 1105 (2019).
- [17] Q. Wu, C. Mannaris, J. P. May, L. Bau, A. Polydorou, S. Ferri, D. Carugo, N. D. Evans, and E. Stride, Investigation of the acoustic vaporization threshold of lipid-coated perfluorobutane nanodroplets using both high-speed optical imaging and acoustic methods, *Ultrasound Med. Biol.* **47**, 1826 (2021).
- [18] G. Lajoinie, T. Segers, and M. Versluis, High-frequency acoustic droplet vaporization is initiated by resonance, *Phys. Rev. Lett.* **126**, 034501 (2021).
- [19] V. C. Anderson, Sound scattering from a fluid sphere, *J. Acoust. Soc. Am.* **22**, 426 (1950).
- [20] C. Feuillade and C. S. Clay, Anderson (1950) revisited, *J. Acoust. Soc. Am.* **106**, 553 (1999).
- [21] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/rj55-6bs1> for (I) full theoretical derivation, (II) simulation parameters, (III) additional information on the experimental setup, and (IV) harmonic content of a 5-MHz HIFU (low power) and a 5-MHz linear array probe pressure wave.
- [22] *Fundamentals of Acoustics*, 4th ed., edited by L. E. Kinsler (Wiley, New York, 2000).
- [23] J. W. Strutt, *The Theory of Sound*, 1st ed. (Cambridge University Press, Cambridge, 2011).
- [24] *Handbook of Mathematical Functions: With Formulas, Graphs and Mathematical Tables (Conference under the auspices of the National Science Foundation and the Massachusetts Institute of Technology)*, unabridged, unaltered and corr. republ. of the 1964 ed., Dover Books on Advanced Mathematics, edited by M. Abramowitz and I. A. Stegun (Dover, New York, 1972).
- [25] G. Hallewell, V. Vacek, and V. Vinš, Properties of saturated fluorocarbons: Experimental data and modeling using perturbed-chain-SAFT, *Fluid Phase Equilib.* **292**, 64 (2010).
- [26] W. Wagner and A. Pruß, The IAPWS formulation 1995 for the thermodynamic properties of ordinary water substance for general and scientific Use, *J. Phys. Chem. Ref. Data* **31**, 387 (2002).
- [27] D. Bardin, T. D. Martz, P. S. Sheeran, R. Shih, P. A. Dayton, and A. P. Lee, High-speed, clinical-scale microfluidic generation of stable phase-change droplets for gas embolotherapy, *Lab Chip* **11**, 3990 (2011).
- [28] Z. Liu, J. Zhao, Y. Pang, and X. Wang, Generation of droplets

- in the T-junction with a constriction microchannel, [Microfluid. Nanofluid.](#) **22**, 124 (2018).
- [29] M. Cattaneo and O. Supponen, Shell viscosity estimation of lipid-coated microbubbles, [Soft Matter](#) **19**, 5925 (2023).
- [30] P. Tortoli, L. Bassi, E. Boni, A. Dallai, F. Guidi, and S. Ricci, ULA-OP: An advanced open platform for ultrasound research, [IEEE Trans. Ultrason. Ferroelectr. Freq. Control](#) **56**, 2207 (2009).
- [31] B. E. Treeby and B. T. Cox, k-Wave: MATLAB toolbox for the simulation and reconstruction of photoacoustic wave fields, [J Biomed. Opt.](#) **15**, 021314 (2010).
- [32] L. Gouy, *On a new property of light waves*, Mélanges scientifiques (Gauthier-Villars, Paris, 1890).
- [33] K. J. Kaltenecker, J. C. König-Otto, M. Mittendorff, S. Winnerl, H. Schneider, M. Helm, H. Helm, M. Walther, and B. M. Fischer, Gouy phase shift of a tightly focused, radially polarized beam, [Optica](#) **3**, 35 (2016).
- [34] T. Lee, Y. Cheong, H. W. Baac, and L. J. Guo, Origin of gouy phase shift identified by laser-generated focused ultrasound, [ACS Photon.](#) **7**, 3236 (2020).
- [35] T. Tyc, Gouy phase for full-aperture spherical and cylindrical waves, [Opt. Lett.](#) **37**, 924 (2012).
- [36] S. Feng and H. G. Winful, Physical origin of the Gouy phase shift, [Opt. Lett.](#) **26**, 485 (2001).
- [37] W. Zhu, A. Agrawal, and A. Nahata, Direct measurement of the Gouy phase shift for surface plasmon-polaritons, [Opt. Express](#) **15**, 9995 (2007).
- [38] M. A. Borden and K.-H. Song, Reverse engineering the ultrasound contrast agent, [Adv. Colloid Interface Sci.](#) **262**, 39 (2018).