Characterization of cavitation-radiated acoustic power using diffraction correction

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A method is developed for compensating absolute pressure measurements made by a calibrated passive cavitation detector (PCD) to estimate the average acoustic power radiated from a region of interest (ROI) defined to encompass all cavitating bubbles. A diffraction correction factor for conversion of PCD-measured pressures to cavitation-radiated acoustic power per unit area or volume is derived as a simple analytic expression, accounting for position- and frequency-dependent PCD sensitivity. This approach can be applied to measurements made by any PCD without precise knowledge of the number, spatial, or temporal distribution of cavitating bubbles. The diffraction correction factor is validated in simulation for a wide range of ROI dimensions and frequencies. The correction factor is also applied to emission measurements obtained during *in vitro* ultrasound-enhanced sonophoresis experiments, allowing comparison of stable cavitation levels between therapeutic configurations with different source center frequencies. Results incorporating sonication at both 0.41 and 2.0 MHz indicate that increases in skin permeability correlate strongly with the acoustic power of subharmonic emissions radiated per unit skin area.

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I. INTRODUCTION

Mechanisms associated with the nucleation and acoustic excitation of gaseous bubbles, a phenomenon referred to as acoustic cavitation, have been shown to play a significant role in ultrasound-enhanced therapies such as thermal ablation,^{1–3} histotripsy,⁴ lithotripsy,⁵ thrombolysis,⁶ and drug delivery.^{7–9} Cavitation activity occurring during these applications is commonly monitored using a single-element transducer as a passive cavitation detector (PCD) to sense acoustic emissions generated by cavitating bubbles,¹⁰ which can be approximated as acoustic point sources. By conducting spectral analysis of the time-domain voltage signal acquired by the PCD, subharmonic and broadband frequency content in the voltage signal can be extracted and used to quantify the presence and relative intensity of stable and inertial cavitation, respectively.¹¹ However, voltage signals used for cavitation quantification are typically obtained as system-dependent measurements and are reported in non-physical units such as uncalibrated voltage or signal-to-noise ratio^{2,3,5,6} that are indirectly related to the observed phenomenon, making it challenging to compare results among different receiving systems or frequencies.

Recently, techniques for converting the measured voltage signal to the spatially averaged pressure at the PCD surface have been established, allowing quantitative cavitation measurements in appropriate physical units. These techniques

require characterization of the receive sensitivity of the PCD, which can be obtained from calibration measurements using self-reciprocity,^{12,13} bistatic scattering substitution,^{14,15} or pulse-echo and pitch-catch measurement configurations.¹⁶ In addition to calibration measurements, parameters employed for signal sampling and windowing are required to estimate power spectra of measured acoustic emissions quantitatively.¹⁷

For the case of a single cavitating bubble positioned at the geometric focus of a PCD, the received pressure is directly related to the radiated field by accounting for spherical spreading.¹⁴ This approach can be utilized for system-independent characterization of single-bubble cavitation, enabling the radiated acoustic power or source-strength amplitude of the cavitating bubble to be directly characterized. However, cavitation activity during most therapeutic ultrasound applications occurs as a spatiotemporal random process, consisting of an ensemble of randomly distributed cavitating bubbles at positions that are not readily predictable.¹⁸ In general, relating the received pressure to the cavitation-radiated field is complicated due to diffraction effects that vary with the frequency and positions of cavitating bubbles, as well as the geometry of the PCD used for emission measurements. Even if monitoring the same ensemble of cavitating bubbles, received pressures will vary between different PCDs due to varying diffraction effects. Hence, for the case of multiple cavitating bubbles, absolute pressure measurements alone are not a valid basis for system-independent characterization of cavitation.

Here, a method is developed for characterizing an ensemble of cavitating bubbles by estimating the time-average acoustic power radiated by cavitation per unit measure of a

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region of interest (ROI), using emission measurements made by a calibrated PCD. In this approach, an ROI is defined as a surface or volume encompassing an ensemble of cavitating bubbles. A correction factor accounting for diffraction effects is derived using the spatially averaged PCD sensitivity within the defined ROI. This diffraction correction factor converts pressure measurements made by a calibrated PCD to the average cavitation-radiated acoustic power per unit area or volume of the defined ROI. Hence, this approach enables conversion of a PCD-measured voltage signal to a system- and frequency-independent quantity that characterizes cavitating bubbles, without *a priori* knowledge of their spatiotemporal distribution or other physical properties, except for the requirement that all are encompassed within the defined ROI. Reported here are the derivation of this diffraction correction factor, numerical simulations employed for error estimation and model validation, and application to experimentally measured emissions at disparate frequencies to illustrate the utility of this approach.

II. THEORY

This section relates the signals measured by a passive cavitation detector to the acoustic power radiated, per unit source area or volume, by an ensemble of cavitating bubbles. The starting point for this analysis is PCD measurement of acoustic emissions from an ensemble of cavitating bubbles, each modeled as a radially pulsating sphere.

The radiated complex pressure P_i of a small, radially pulsating sphere centered at a position $\mathbf{r}_i$, measured at a far-field location $\mathbf{r}$, is¹⁹

$$P_i(\mathbf{r}, f) = -j\omega\rho_0 Q_i(f) \frac{e^{jk|\mathbf{r}_i - \mathbf{r}|}}{4\pi|\mathbf{r}_i - \mathbf{r}|}, \quad (1)$$

modeling a bubble pulsating with radial frequency $\omega = 2\pi f$ in an isotropic medium of density ρ_0 and sound speed c , where k is the wavenumber ω/c and the source strength $Q_i(f)$ is the volume velocity of fluid flow from the pulsating bubble.

For an ensemble of N cavitating bubbles, the pressure at a far-field location $\mathbf{r}$ is calculated as a sum of complex pressures $P_i(\mathbf{r}, f)$ incident on that position. The acoustic intensity at $\mathbf{r}$ is the squared magnitude of this pressure value divided by twice the acoustic impedance.²⁰ By spatially integrating the acoustic intensity over a surface S_S enclosing the ensemble, the total radiated acoustic power is calculated as

$$\begin{aligned} \Pi_T(f) &= \frac{1}{2\rho_0 c} \int_{S_S} \left| \sum_{i=1}^N P_i(\mathbf{r}, f) \right|^2 dS_S \\ &= k^2 \frac{\rho_0 c}{32\pi^2} \int_{S_S} \left| \sum_{i=1}^N \frac{Q_i(f)}{r_{S_i}} \right|^2 dS_S, \end{aligned} \quad (2)$$

where $P_i(\mathbf{r}, f)$ is given by Eq. (1) and $r_{S_i} = |\mathbf{r} - \mathbf{r}_i|$ is the distance from the i th cavitating bubble to a field position $\mathbf{r}$ on the enclosing surface, assumed large relative to the acoustic wavelength and bubble radii.

Acoustic cavitation typically occurs as a spatiotemporally stochastic process, where the characteristics of

individual cavitating bubbles are not readily predictable. For these cases, a given ensemble can be modeled as a wide-sense stationary process, consisting of randomly cavitating bubbles that occur with stochastic independence. For an ensemble modeled as a wide-sense stationary process, means of random variables characterizing cavitating bubbles are unchanged with respect to time over a given observation period. In addition, random characteristics such as the source-strength amplitude and ensemble distribution can be assumed ergodic, so that temporal averages of these characteristics are statistically equivalent to corresponding expected values. Under these assumptions, the time-averaged total acoustic power radiated by an ensemble can be represented as the expected value of Eq. (2) and expanded as

$$\begin{aligned} \langle \Pi_T(f) \rangle &= k^2 \frac{\rho_0 c}{32\pi^2} \int_{S_S} \left(\left\langle \sum_{l=1}^N \left| \frac{Q_l(f)}{r_{S_l}} \right|^2 \right\rangle \right. \\ &\quad \left. + \left\langle \sum_{l \neq m}^N Q_l^*(f) Q_m(f) \frac{e^{jk(r_{S_l} - r_{S_m})}}{r_{S_l} r_{S_m}} \right\rangle \right) dS_S, \end{aligned} \quad (3)$$

where $*$ denotes complex conjugation and $\langle \rangle$ denotes the expected value.

For an ensemble of stochastically independent cavitating bubbles, the second summation term in Eq. (3) tends to zero. This assumption is reasonable even for an ensemble insonified by a constant-phase source, because the random spatial distribution of bubbles results in randomization of path lengths to a given field point, so that the complex pressure at any field point resembles that emanating from a random ensemble of incoherent sources. Thus, the total radiated acoustic power from the ensemble is approximated by the first term of Eq. (3). The time-average total radiated acoustic power per unit area or volume of the ROI occupied by cavitating bubbles is then

$$\frac{\langle \Pi_T(f) \rangle}{W} \approx k^2 \frac{\rho_0 c}{8\pi} \langle |Q(f)|^2 \rangle \frac{N}{W}, \quad (4)$$

where W is the dimension (area or volume) of the ROI and $|Q(f)|^2$ is the average magnitude-squared source strength.

For a phase-sensitive element, the received pressure from an acoustic source is defined as the spatial average of the complex pressure incident over its surface.²¹ For an ensemble of cavitating bubbles, the received pressure is a summation of the incident pressures received from individual bubbles, averaged over the PCD surface,

$$\begin{aligned} \bar{P}_R(f) &= \frac{1}{S_R} \int_{S_R} \sum_{i=1}^N -j\omega\rho_0 Q_i(f) \frac{e^{jk|\mathbf{r}_i - \mathbf{r}|}}{4\pi|\mathbf{r}_i - \mathbf{r}|} dS_R \\ &= \frac{\rho_0 c}{2S_R} \sum_{i=1}^N Q_i(f) \left[-\frac{jk}{2\pi} \int_{S_R} \frac{e^{jk|\mathbf{r}_i - \mathbf{r}|}}{|\mathbf{r}_i - \mathbf{r}|} dS_R \right], \end{aligned} \quad (5)$$

where $P_i(\mathbf{r}, f)$ is given by Eq. (1), $\mathbf{r}$ is a field position on the element surface S_R , and the term in square brackets is the Rayleigh integral $P_{\text{Rayl}}(\mathbf{r}_i, f)$, representing the normalized average incident pressure received from a point source at $\mathbf{r}_i$.²² The received acoustic power is defined as the magnitude-

squared received pressure multiplied by the surface area of the receiving element and divided by twice the acoustic impedance.¹⁷ Following the expansion of Eq. (3) and using the average incident pressure from Eq. (5), the time-average received acoustic power Π_R is represented by its expected value as

$$\begin{aligned}\langle \Pi_R(f) \rangle &= \left\langle \frac{S_R}{2\rho_0 c} \left| \bar{P}_R(f) \right|^2 \right\rangle \\ &= \frac{\rho_0 c}{8S_R} \left[\left\langle \sum_{l=1}^N |Q_l(f)|^2 |P_{\text{Rayl}}(\mathbf{r}_l, f)|^2 \right\rangle \right. \\ &\quad \left. + \left\langle \sum_{l \neq m}^N Q_l^*(f) Q_m(f) P_{\text{Rayl}}^*(\mathbf{r}_l, f) P_{\text{Rayl}}(\mathbf{r}_m, f) \right\rangle \right].\end{aligned}\quad (6)$$

Similar to Eq. (3), the second summation term in Eq. (6) tends to zero due to phase cancellation and the remaining term approximates the received acoustic power from a stochastically independent, wide-sense stationary random ensemble as

$$\langle \Pi_R(f) \rangle \approx \frac{\rho_0 c}{8S_R} \langle |Q(f)|^2 \rangle \frac{N}{W} \int_W |P_{\text{Rayl}}(\mathbf{r}, f)|^2 dW. \quad (7)$$

In comparison to the total acoustic power radiated by cavitating bubbles, the corresponding received acoustic power is reduced by diffraction effects. In order to recover the total radiated acoustic power $\langle \Pi_T(f) \rangle$ from the received power $\langle \Pi_R(f) \rangle$, a diffraction correction factor Γ is defined as the ratio of Eqs. (4) and (7),

$$\begin{aligned}\Gamma(f) &= \frac{\langle \Pi_T(f) \rangle / W}{\langle \Pi_R(f) \rangle} \\ &= \frac{S_R}{\pi} \frac{k^2}{\int_W |P_{\text{Rayl}}(\mathbf{r}, f)|^2 dW}.\end{aligned}\quad (8)$$

Thus, the radiated power of acoustic emissions per unit area or volume $\langle \Pi_T(f) \rangle / W$ is estimated by multiplying the received power $\langle \Pi_R(f) \rangle$ by the diffraction correction factor $\Gamma(f)$. Notably, this diffraction correction requires no knowledge of characteristic quantities of the ensemble, such as the number, source-strength amplitudes, or exact positions of individual cavitating bubbles. The diffraction correction factor $\Gamma(f)$ can be readily calculated using multiple established methods for computing the Rayleigh integral.^{22–25}

Computation of this diffraction correction factor requires specification of the ROI W . If the region possibly containing cavitation bubbles is known (e.g., from the boundaries of a vessel containing bubbles or from characterization of the sonicating field), W can be set equal to that region. If the PCD is substantially sensitive only within a subset of the region to be characterized, or if the spatial location of cavitating bubbles is unknown, W can be set equal to dimensions of the entire medium characterized. The integral of Eq. (8) can then be performed over the entire medium, since only regions of substantial PCD sensitivity contribute

to the diffraction correction factor $\Gamma(f)$. In that case, diffraction correction using Eq. (8) estimates the total radiated acoustic power, per unit area or volume, from cavitating bubbles throughout the region of PCD sensitivity.

In practice, for measurements made using a system with known calibration factor M_R (units of volts per unit pressure), accounting for the receive sensitivity of the PCD system, the frequency-dependent received pressure $\bar{P}_R(f)$ can be determined from the discrete Fourier transform of the corresponding received voltage signal.^{13–17} The received acoustic power $\Pi_R[f_l]$ within the l th frequency bin can be calculated following methods described in Ref. 17, incorporating discretization factors including windowing w of the received signal, the signal duration or interval of interest T , frequency bin width Δf , and sampling frequency f_s . The time-average radiated power per unit area or volume within a frequency range of interest is estimated as

$$\begin{aligned}\frac{\langle \Pi_T[f_1; f_2] \rangle}{W} &= \sum_{l=l_1}^{l_2} \Gamma[f_l] \langle \Pi_R[f_l] \rangle \Delta f \\ &= \frac{S_R^2}{\pi \rho_0 c |w|^2 T f_s^2} \sum_{l=l_1}^{l_2} \Gamma[f_l] \left\langle \left| \frac{X_R[f_l]}{M_R[f_l]} \right|^2 \right\rangle \Delta f,\end{aligned}\quad (9)$$

where $|w|^2$ is the mean-square value of the signal window employed and X_R is the discrete Fourier transform of the corresponding received voltage signal. For cases where one or more discrete frequencies, such as harmonics, subharmonics, or ultraharmonics associated with particular cavitation mechanisms are of interest, the summation in Eq. (9) may be performed only over those discrete frequencies.

III. METHODS

A. Validation simulations

To validate the diffraction correction approach here, while also testing the assumptions made in its derivation, single-element PCD measurements of a cavitating bubble ensemble were simulated.

Simulations used a configuration from sonophoresis experiments reported previously [Fig. 1(a)].²⁶ This configuration consisted of a circular-sectioned skin sample in a diffusion cell separating two water-filled compartments, an unfocused, disk-shaped treatment transducer insonating the sample from the top compartment such that the propagating ultrasound wavefront arrived nominally parallel to the skin surface, and an unfocused, disk-shaped PCD with diameter 25 mm located 4.5 cm from the skin surface at a 45° grade in the bottom compartment.

In simulations, all cavitating sources were assumed to be located on the plane comprising the skin surface, consistent with the assumption that most cavitation occurred near the hydrophobic skin/water interface. The ROI was defined as a planar region at the skin surface with a variable circular radius, corresponding to ROI areas $W = 10\text{--}315\text{ mm}^2$. The range of normalized frequencies investigated was $ka_R = 5\text{--}450$. The relative spatial sensitivity of the PCD was determined for each

FIG. 1. (Color online) (a) Transducer configuration used during sonophoresis and replicated in simulation. The PCD is located 4.5 cm below the skin surface at a 45° grade. (b) Representative map of the PCD sensitivity at the skin surface for $ka_R = 200$. A representative circular ROI with a 5.5 mm circular radius and 95 mm^2 surface area is bounded by the solid line.

ka_R value and ROI area by calculating the associated Rayleigh integral on the simulated skin surface using an exact series expansion for an unfocused circular piston,²² implemented in MATLAB (v8.4, MathWorks, Natick, MA). The diffraction correction factor $\Gamma(f)$ for each investigated ROI area and frequency was calculated using Eq. (8), numerically integrating over the ROI with a step size less than one-fourth the shortest wavelength of interest.

This calculation is illustrated by Fig. 1(b), which shows the dB-scaled PCD sensitivity at the simulated skin surface for the normalized frequency $ka_R = 200$. A representative circular ROI of area $W = 95 \text{ mm}^2$ is indicated by a solid line.

Cavitating bubbles were simulated as an ensemble of 25 monopole sources with identical complex source-strength amplitude $Q(f)$ in room-temperature water ($\rho_0 c = 1.49 \text{ MPa s/m}$ at 25°), randomly distributed and confined within the boundaries of a given ROI on the simulated skin surface. By using a constant number of sources and varying the ROI dimensions, the number density of radiators was varied over the range 0.08–2.5 per square millimeter.

Using repeated random sampling, 40 independent realizations were simulated for each investigated frequency and ROI area, randomizing source positions within the ROI for each cycle. The simulated pressure field radiated by the ensemble for each realization was used to calculate the received acoustic power using Eq. (7) and the theoretical total radiated acoustic power was found using Eq. (4). Values of the received acoustic power were ensemble-averaged over the 40 realizations simulated for each configuration.

To test the diffraction correction method proposed here, ensemble-averaged simulated values of the received acoustic power were compensated by the diffraction correction factor $\Gamma(f)$ computed for the simulated frequency and ROI. The resulting estimates of total radiated power per unit area of the source region were compared with the corresponding theoretical acoustic powers per unit area. The relationship between estimated and theoretical values was tested using linear regression in the R statistical software package.²⁷ Linear hypothesis testing on regression estimates was

conducted to determine the significance of one-to-one correspondence (i.e., regression slope statistically equivalent to unity) between the estimated and theoretical power values. The root-mean-squared error between these values was determined to assess the accuracy of the derived diffraction correction method.

B. Experimental measurements

To demonstrate application of the proposed diffraction correction method to acoustic emission measurements, including quantitative comparisons between ultrasound therapy performed at different source frequencies, PCD measurements from previously reported experiments were analyzed. All emission measurements investigated here were made during previous sonophoresis experiments²⁶ using the configuration employed in the simulations described above [Fig. 1(a)].

Briefly, sonophoresis experiments were conducted by exposing *in vitro* porcine skin samples (circular exposed region 31 mm diameter) to intermediate-frequency sonophoresis (IFS) or high-frequency sonophoresis (HFS), employing 0.41 or 2 MHz ultrasound, respectively. For either treatment frequency, skin was treated using ultrasound that was generated in a pulsed continuous-wave mode with a 20% duty cycle (1 s on, 4 s off) and using two different acoustic power levels, as measured by a radiation force balance (UPM-DT-10, Ohmic Instruments). For IFS, the acoustic power output levels employed were 0.79 and 1.68 W. Linear simulation of the transmitted pressure field using an exact series expansion,²² scaled to match these acoustic powers, indicated pressure amplitudes (peak compressional or rarefactional pressures) P_0 of 0.28 and 0.40 MPa at the center of the skin surface, respectively. For HFS, acoustic power output levels of 8.44 and 21.7 W were employed, corresponding to P_0 values 0.53 and 0.77 MPa, respectively. For each investigated treatment frequency and acoustic pressure, three degassing schemes were employed to control the location of cavitation during treatment. Specifically, cavitation was suppressed within skin by degassing tissue samples prior to treatment (skin-degassed), suppressed outside the skin by

degassing the phosphate buffered saline (PBS) buffer surrounding samples (PBS-degassed), or suppressed within and outside the skin (control trials).

During each sonophoresis treatment, an unfocused, broadband disk transducer with 25 mm diameter and 1 MHz nominal center frequency (C302, Olympus, Waltham, MA) was used as a PCD to monitor acoustic emissions from cavitation. Emission measurements were acquired as a series of 1800 voltage traces, each of 0.2 s duration, measured throughout each 30-min sonophoresis treatment. Each trace was divided into 500 non-overlapping 0.4 ms segments, the squared magnitude of the discrete Fourier transform for each segment was computed, and the average over these segments was taken as the estimated voltage power spectra for each trace. Discretization and other parameters used for unit conversion included the element surface area $S_R = 505.7 \text{ mm}^2$, sampling frequency $f_s = 10 \text{ MHz}$, windowing $|\overline{w}| = 1$, segment duration $T = 0.2 \text{ s}$, and acoustic impedance $\rho_0 c = 1.49 \text{ MRayl}$ for room-temperature water. The electrical conductance of skin was concurrently measured throughout each treatment as a surrogate for the time-dependent skin permeability.^{28,29}

The sensitivity of the PCD as a receiver was characterized using a pulse-echo calibration approach.^{16,30} Briefly, pulse-echo measurements were made using the PCD with a flat, 51 mm thick by 51 mm circular-diameter aluminum reflector at the distance 32.5 mm. Reference pressure measurements were made over a planar region matching the surface of the PCD at the range 65 mm using two hydrophones; one to measure frequencies less than 1 MHz (TC4038, Reson, Slangerup, Denmark) and another to measure frequencies greater than 1 MHz (0.5 mm diameter; 1239, Precision Acoustics, Dorchester, Dorset, UK). The ratio of the spatially averaged pressure amplitude over the circular region to the voltage amplitude for pulse-echo measurements comprised the sensitivity, $M_R(f)$ in units of volts per unit pressure, of the PCD.

C. Diffraction correction of experimental emission measurements

Because the ROI is the region containing all cavitating bubbles of interest, its extent can be defined to incorporate physical barriers, transmit beam parameters including experimentally determined or estimated cavitation threshold values,^{31,32} or by a combination of these factors. Here, cavitation was assumed to occur primarily at or near the skin surface; this assumption is considered reasonable because observed acoustic emission levels were comparable between the skin-degassed case, in which cavitation was isolated to the PBS above the skin surface, and the PBS-degassed case, in which cavitation was confined to occur within the skin.³⁰ ROI dimensions were determined based on the transmit beam shapes, determined from field simulations²² matched to acoustic power measurements, and calculated thresholds for generation of subharmonic emissions.³¹ Thus, the ROI was defined to match the region of the skin surface in which cavitation activity causing subharmonic emissions was most likely to occur.

Because sonophoresis trials utilized relatively long-duration pulses of 1 s, resonant-sized bubbles were assumed to have formed via coalescence.³³ Based on simulation results used to derive the Cavitation Index,³¹ the peak negative pressure, P_{SHRES} required to initiate subharmonic emissions from resonant sized bubbles in water at ambient pressure was calculated as

$$P_{\text{SHRES}} = (0.01f_0)^{1/2.65}, \quad (10)$$

where the fundamental frequency f_0 is measured in MHz and the rarefactional pressure amplitude P_{SHRES} is measured in MPa. The ROI was defined as the region on the skin surface where the transmit beam pressure amplitude exceeded P_{SHRES} for each set of treatment parameters. Transmit beam profiles at the skin surface are shown in Figs. 2(a) and 2(b) for both acoustic powers employed for IFS and HFS, respectively, with dashed horizontal lines representing the associated thresholds P_{SHRES} .

The diffraction correction factor $\Gamma(f)$ for each sonophoresis configuration was calculated from Eq. (8), using the approach employed in the simulations described above, for each ROI and the corresponding subharmonic frequencies $f_0/2 = 0.205 \text{ MHz}$ for IFS and 1.0 MHz for HFS. Shown in Figs. 2(c) and 2(d) are maps of the dB-scaled PCD sensitivity P_{Rayl} on the skin surface for $k_{\text{SH}}a_R = 10.8$ and 50.3 , corresponding to subharmonic emissions for IFS and HFS, respectively, with solid lines bounding the ROIs determined from subharmonic emission thresholds. For comparison, diffraction correction factors were also calculated using an ROI comprising the entire exposed skin surface; boundaries of this ROI are shown in Figs. 2(c) and 2(d) as dashed lines. These diffraction correction factors and associated parameters are summarized in Table I.

Using the measured calibration factors M_R , calculated diffraction correction factors Γ , and compensation for discretization effects, the subharmonic component of the emission power spectrum from each sonophoresis trial was converted to the radiated subharmonic acoustic power per unit skin surface area using Eq. (9).

Because all system- and frequency-dependent components were removed from the emission measurements by the diffraction correction, radiated acoustic powers per unit skin area from IFS and HFS trials could be quantitatively compared despite being obtained at different frequencies. Linear regression was employed to model the relationship between skin resistance reductions and corresponding subharmonic acoustic powers per unit area. Correlation coefficients between these measured values were determined for IFS and HFS trials alone, as well as for all sonophoresis trials combined. Correlation coefficients among these groups were compared using a Williams' test or a Fisher's z-transformation for independent and dependent groups, respectively. Skin resistance decreases and estimates of radiated acoustic power were grouped by treatment regime and compared using a Kruskal–Wallis rank sum test, with corresponding *post hoc* pairwise comparisons conducted simultaneously by adjusting the p value to account for multiple comparisons using a Holm–Bonferroni method.

FIG. 2. (Color online) (a) Radial profile of acoustic pressure at the skin surface from the transmit transducer used for IFS. The solid lines correspond to the two acoustic power levels used for treatment, while the dashed lines indicate the threshold P_{SHRES} for subharmonic emissions. (b) Corresponding radial profile for HFS. (c) Decibel-scaled PCD sensitivity at the skin surface for the subharmonic frequency of IFS ($k_{SHaR} = 10.8$). Solid lines bound ROIs based on the subharmonic emission threshold for each acoustic power level, while the dashed line bounds the entire exposed skin surface. (d) Corresponding PCD sensitivity map for HFS ($k_{SHaR} = 50.3$).

The assumption of wide-sense stationarity of the monitored cavitation ensemble was tested by conducting change-point analysis on PCD voltage signals acquired during sonophoresis.³⁰ Specifically, 2808 measured voltage time traces of 0.2 s duration were randomly selected, divided into 500 non-overlapping 0.4 ms segments, and the power spectrum of each was calculated as described above. The subharmonic component was extracted from each power spectrum, resulting in a 500-point time series, which was normalized to its maximum value for each investigated trace. Changes in the mean of each subharmonic time series were identified

using a pruned exact linear time (PELT)³⁴ algorithm. Algorithm penalty parameters were selected in order to avoid spurious change point detection by first conducting analysis on time series signals simulated as normalized Gaussian noise with changes in signal mean at known time points. Penalty parameter values that properly identified changes in mean of simulated signals were employed for change point analysis on measured signals.

IV. RESULTS

A. Calculated diffraction correction factor

The correction factor $\Gamma(f)$, calculated for a simulated sonophoresis configuration, is shown in Fig. 3(a) for the investigated range of frequencies and ROI areas. For this configuration, the correction factor is shown to increase smoothly with increasing frequency and PCD size, approximately as the square of ka_R , for any given ROI area. For any given frequency, the correction factor decreases with increasing ROI area. These diffraction correction values were used to correct simulated PCD measurements.

Shown in Fig. 3(b) are diffraction correction factor values as a function of ROI skin surface area calculated for ka_R values of 10.8 and 50.3, the normalized subharmonic frequencies for IFS and HFS, respectively. The correction factor and skin surface area corresponding to ROI boundaries defined using the subharmonic emission threshold [Eq. (10)] are marked by a square and triangle for the lower and higher

TABLE I. Summary of parameters for IFS and HFS subharmonic ($k_{SHaR} = 10.8$ and 50.3, respectively) correction factor calculation over ROIs based on the subharmonic emission threshold (listed by acoustic power output or APO) and for the ROI comprising the exposed skin surface area (no APO listed). Also listed are the axial pressure amplitude P_0 at the skin surface, the calculated threshold pressure P_{SHRES} to initiate subharmonic emissions from resonant sized bubbles, the ROI area W , and the calculated diffraction correction factor Γ .

Treatment regime	APO (W)	P_0 (MPa)	P_{SHRES} (MPa)	W (mm ²)	Γ (mm ⁻²)
IFS	0.79	0.28	0.13	30.3	2.2
	1.68	0.40	0.13	100.3	0.70
	—	—	—	754.8	0.28
HFS	8.44 W	0.53	0.23	167	13.3
	21.7 W	0.77	0.23	189	11.6
	—	—	—	754.8	5.69

FIG. 3. (Color online) (a) Diffraction correction factor $\Gamma(f)$ for various circular ROI dimensions on the skin surface as a function of normalized frequency ka_R . (b) Diffraction correction factors $\Gamma(f)$ for $ka_R = 10.8$ (solid line) and 50.3 (dashed line) as a function of circular ROI area. Values corresponding to ROIs defined by the subharmonic emission threshold are indicated by Δ and $\square$, while values calculated for the entire exposed skin surface are indicated by $\circ$ for each frequency.

acoustic power output levels, respectively, employed for IFS and HFS. For comparison, the circle for each line indicates the correction factor value calculated over the entire exposed skin surface area for each frequency. When defining ROIs based on the subharmonic emission threshold, the higher acoustic output employed at either frequency resulted in an increase of the characterized ROI surface area and a corresponding decrease in the calculated diffraction correction factor. ROI areas for IFS were 30.3 and 100.3 mm² for insolation acoustic power levels of 0.79 and 1.68 W, respectively. For HFS-treated skin, ROI areas were 167 and 189 mm² for acoustic power levels of 8.44 and 21.7 W, respectively. These diffraction correction values were used to correct emissions measured in sonophoresis experiments.

B. Validation simulations

The theoretical radiated acoustic power and ensemble-averaged simulated PCD-received acoustic power, before diffraction correction, are shown in Fig. 4(a) as a function of normalized frequency, ka_R . Each plotted point, corresponding to a distinct ROI area and frequency, is normalized to the respective theoretical or simulated maximum power. The theoretical acoustic power increases as $(ka_R)^2$ for any given ROI and is constant for each ROI area, due to the constant

number of cavitating bubbles simulated for each condition. However, the average received acoustic power varies significantly and unpredictably with ka_R and the ROI area, due to diffraction and phase cancellation effects from the spatially random ensemble of cavitating bubbles. This figure illustrates the lack of clear one-to-one correspondence between simulated PCD measurements and corresponding calculated total radiated powers.

In Fig. 4(b), the theoretical radiated power per unit skin surface area is plotted against corresponding estimates of the radiated power per unit area, obtained using diffraction correction of the simulated PCD-received power. Each value, corresponding to the same cases as Fig. 4(a), is normalized by the maximum simulated acoustic power value. Agreement between corresponding calculated and estimated power values is typically within ± 1 dB, indicated by the shaded region extending above and below the one-to-one line, for all investigated frequencies and ROI areas. Linear regression between theoretical and estimated power values indicated nearly one-to-one correspondence ($r^2 = 0.986$, root-mean-squared error 1.6×10^{-2}). Deviations from one-to-one correspondence are likely due to imposed simulation limitations, including the identical amplitude and phase of all sources and the sparse source density within each ROI (25 sources per realization).

FIG. 4. (Color online) (a) Uncorrected, average simulated received power, with each point representing an ensemble-averaged value for a distinct ROI and ka_R value (dots), and theoretical total radiated power (triangles) as a function of normalized frequency ka_R . (b) Diffraction-corrected received acoustic power versus corresponding theoretical total radiated power, each defined per unit ROI area. The shaded gray region indicates ± 1 dB deviation from one-to-one correspondence.

C. Analysis of acoustic emissions during sonophoresis

Shown in Fig. 5 are representative spectra of the system-measured voltage (a), (d), received acoustic power (b), (e), and estimated cavitation-radiated acoustic power per unit area of the skin surface (c), (f) during IFS and HFS, respectively. For representative purposes, the diffraction correction factor used for compensation of these spectra was for an ROI comprising the entire exposed skin surface. For each plot, black lines indicate a control trial in which little or no cavitation was detected. Red and blue lines are representative trials with significant levels of measured emissions, associated with acoustic cavitation. Half-harmonic subharmonic components, corresponding to 0.205 MHz for IFS and 1.0 MHz for HFS, are highlighted in each respective figure. Relatively frequency-independent increases of emission spectra levels above the electronic noise floor (red and blue lines) indicate broadband emissions from inertial cavitation. Broadband emissions were observed at all frequencies within the sensitive range of the measurement system, for both IFS and HFS trials. Due to the PCD frequency response as well as bandpass filtering applied to measured signals, these broadband emissions are seen most prominently between the one-third and one-half harmonics of the respective insonation frequencies.

In change point analysis conducted on subharmonic time series measurements for IFS and HFS, approximately 97% of the randomly selected voltage traces were found to

provide no change in the mean-squared voltage associated with subharmonic emissions with respect to time. These results indicate that the subharmonic emission levels over the duration of each measurement used to estimate average power spectra were typically constant in mean, consistent with the wide-sense stationary assumption employed for the derivation of the diffraction correction factor.

Shown in Fig. 6(a) are mean values of the decibel-scaled (dB) subharmonic acoustic power per unit area, using a diffraction correction factor from a surface ROI defined by the subharmonic emission threshold [Eq. (10)], plotted against corresponding mean values of the normalized decrease in skin resistance for each sonophoresis treatment group. Vertical and horizontal lines indicate one standard deviation for either measurement. The treatment groups split approximately into two clusters, with respect to both acoustic emissions and skin resistance decrease. First, among IFS-treated PBS-degassed, HFS-treated control, and IFS-treated control trials, incurring minimal cavitation, no significant difference ($p > 0.1$) was found in the measured radiated power or the decrease in skin resistance. Similarly, among HFS-treated PBS-degassed, IFS-treated skin-degassed, and HFS-treated skin-degassed trials, incurring substantial cavitation, no significant difference ($p > 0.05$) in either measurement was found. The second cluster had significantly greater ($p < 0.05$) subharmonic acoustic power per unit area and significantly greater ($p < 0.03$) skin resistance reductions than the first cluster. This result further indicates the significant

FIG. 5. (Color online) (a) Representative power spectra of PCD-measured voltage signals vs frequency for IFS. (b) Representative spectral density of the received acoustic power for IFS. (c) Representative spectral density of the acoustic power radiated per unit source area, estimated using diffraction correction, during IFS. (d)–(f) Corresponding spectra for HFS. In each plot, the black dashed line represents a trial where minimal acoustic emissions were measured, and thus approximates the electronic noise floor. Subharmonic components are highlighted for IFS ($f_0/2 = 0.205$ MHz) and HFS ($f_0/2 = 1.0$ MHz) trials.

FIG. 6. (Color online) Normalized skin resistance decreases and dB-scaled subharmonic acoustic power per unit area, estimated using diffraction correction factors for surface ROIs defined by the subharmonic emission threshold. (a) Mean and standard deviation of the normalized skin resistance decrease vs dB-scaled subharmonic power per unit area for each treatment group. (b) Skin resistance decrease vs corresponding decibel-scaled subharmonic acoustic power per unit area for each individual IFS (red) and HFS (blue) trial. The dashed line indicates the line of best fit, based on least-squares regression applied to all points.

correspondence of subharmonic-producing cavitation to changes in skin resistance during IFS and HFS.

Shown in Fig. 6(b) are dB-scaled subharmonic acoustic powers per unit area, using diffraction correction factors for surface ROIs defined by subharmonic emission threshold, against corresponding decreases in normalized skin resistance measured for each individual IFS and HFS trial. Significant ($p < 10^{-10}$) log-linear correlations were found among IFS ($r = 0.925$) and HFS ($r = 0.858$) subharmonic acoustic powers per unit area and corresponding skin resistance reductions. Correlation coefficients for IFS trials were not significantly different from those for HFS trials ($p = 0.21$). Combining values for all IFS and HFS trials resulted in a significant correlation ($r = 0.823$, $p < 10^{-10}$) between subharmonic acoustic powers per unit area and corresponding skin resistance reductions. This correlation coefficient was not significantly different from those for IFS or HFS results alone ($p > 0.07$). The linear least-squares regression line associated with this relationship is shown in Fig. 6(b) as a dashed line. These results indicate that comparable subharmonic power per unit area radiated by cavitation corresponds to comparable reductions in skin resistance, both for IFS and HFS treatments.

V. DISCUSSION

In past studies, the voltage signal generated by a PCD while monitoring acoustic cavitation has often been used to predict bioeffects including thermal ablation,¹⁻³ thrombolysis,^{6,33} cellular damage,^{35,36} and vessel rupture.³⁷ Although providing useful information, a common limitation of these studies is that their results are specific to the employed receiving system, experimental configuration, and frequencies of interest, preventing comparison among measurements made using different components. Here, a method was derived for characterizing the average acoustic power radiated by an ensemble of cavitating bubbles per unit measure of a defined ROI by correcting emission measurements made by a calibrated PCD for diffraction effects. The result

is a fully system- and frequency-independent method for quantitatively characterizing cavitation activity.

The method derived enables cavitation activity to be directly characterized from PCD-measured emissions as the frequency-dependent radiated acoustic power per unit area or volume of the source ROI. When employing this approach, appropriate definition of the ROI for the application of interest is important. When feasible, the ROI can be defined to coincide as precisely as possible with the region of cavitating bubbles. For this reason, an ROI surface was defined here using measurements of the sonicating beam and estimated thresholds for stable cavitation. In other applications, characterization of volumetric ROIs are of interest. For example, the primary ROI approximates a cylindrical volume for experiments conducted on blood vessels⁶ or vessel-mimicking tubing.⁴³ For these applications, the diffraction correction calculation and application are identical to that employed here, except that the correction factor is calculated in units of inverse volume. Validation simulations performed for cylindrical regions of interest, employing both focused and unfocused PCDs, indicate that radiated acoustic power per unit volume can be quantified with comparable accuracy to that of the surface characterization shown here.³⁰

If the sonicating beam, cavitation thresholds, or spatial limits of the region containing cavitating bubbles are not well characterized for the problem of interest, the average radiated power per unit area or volume may be overestimated if significant cavitation activity occurs outside the defined ROI at locations of high spatial sensitivity of the PCD. To avoid this problem, the ROI can be specified as the entire medium of interest. The diffraction correction factor of Eq. (8) can then be computed based on an integral over the entire medium of interest, e.g., over a planar region for characterization of cavitating bubbles on a surface or over an extended volumetric region for characterization of cavitating bubbles distributed in three dimensions (3D). The result is an estimate of radiated acoustic power, per unit source area

or volume, within the entire region where the PCD is sensitive. For example, analysis of the same experimental data described here, with diffraction correction factors defined by integration over a larger planar surface (dashed lines in Fig. 2) is reported in Ref. 30. Correlations between skin resistance decrease and radiated acoustic power are statistically equivalent to those reported here, suggesting that in practical applications, correlations between quantified acoustic emissions and bioeffects may not be highly sensitive to ROI choice. In general, for a conservatively defined ROI with boundaries exceeding the extent of a given bubble ensemble, the estimated acoustic power per unit area or volume will be smaller with increasing ROI size, consistent with the physical decrease in source density.

The simulations performed confirm that the present diffraction correction approach, although derived under somewhat idealized assumptions, should accurately characterize practical cavitation measurements. First, spatial averaging of the PCD sensitivity pattern assumes that the bubble distribution is statistically homogeneous throughout the ROI. In simulations, the number density of cavitating bubbles was relatively low, corresponding to number densities 0.08–2.5 per mm², so that local bubble distributions varied substantially within a given ROI. Second, although the diffraction correction factor was derived assuming incoherent interaction between all sources, the simulations employed sources with equal amplitude and phase, consistent with uniform excitation by a plane incident wave. Thus, contributions from different sources combined incoherently only because of spatial variations in the complex sensitivity pattern of the PCD. Nonetheless, the disagreement between simulated estimates and theoretical cavitation-radiated powers was low, typically not exceeding ± 1 dB for any given set of parameters. This error is modest relative to typical uncertainties of PCD calibration, which may exceed ± 2 dB depending on the instruments and methods used.^{15,16,30} The low error between simulated estimates and theoretical cavitation-radiated powers confirms that the proposed diffraction correction method does not depend on strict assumptions of statistical homogeneity or source incoherence. Thus, this method can accurately quantify the radiated power of acoustic emissions from cavitating bubble fields encountered in therapeutic ultrasound applications, including those such as histotripsy^{4,38} where strong coupling between bubbles is observed.

The diffraction correction method presented here did not consider electronic noise effects on acoustic emission measurements. Measured emission energy associated with the noise floor of the PCD and receiving electronics can potentially affect quantification of radiated power from acoustic emissions. To avoid this issue, the noise floor can be measured in the absence of sonication; the frequency-dependent energy of the measured noise floor, e.g., quantified as watts of acoustic power per unit frequency based on acoustic calibration of the receiving system,¹⁷ can then be subtracted from subsequent PCD measurements.

For sonophoresis, previous studies suggest that cavitation permeabilizes skin by multiple frequency-dependent mechanisms.³⁹ For example, the role of inertial cavitation has been established for low-frequency applications (LFS, $f < 100$ kHz),^{40,41} and stable cavitation has been shown to

induce changes in skin permeability for IFS and HFS.^{26,42} However, relationships between cavitation-radiated acoustic power and resultant changes in skin permeability have previously not been elucidated. Here, by employing a diffraction correction method, acoustic emission measurements made during IFS and HFS were effectively normalized such that they could be quantitatively compared, although made at different source frequencies. The relationship between subharmonic acoustic power radiated and skin permeability change was statistically equivalent for IFS and HFS. Using this knowledge, sonophoresis treatments could be further optimized to use insonation pressures eliciting subharmonic emission levels corresponding to the desired skin permeability change, potentially reducing the total acoustic energy delivered to skin in a given treatment. Such optimization approaches could also reduce the incidence of undesired cavitation outside the treatment ROI, as well as bioeffects associated with heating and radiation force.

In the analysis reported here, only single-frequency emissions were characterized. This characterization approach was conducted for sonophoresis experiments because subharmonic emissions were previously found to correlate strongly with decreases in skin permeability.²⁶ For characterization of broadband emissions generated by inertial cavitation, the power spectral density can be integrated over a specified bandwidth. For example, in Figs. 5(c) and 5(d), an appropriate frequency band would include portions of the emission spectrum exceeding the electronic noise floor but falling between subharmonic, harmonic, or ultraharmonic peaks.²⁶ The result would be a measurement of acoustic power radiated per unit source area or volume, within the given frequency band.

The diffraction correction method presented here has implications for design of passive cavitation detection systems. First, the source transducer and exposure conditions may be planned to provide a relatively uniform pressure profile, exceeding an estimated threshold for acoustic cavitation, throughout the targeted volume or surface. The PCD may then be designed either for a sensitivity pattern encompassing the entire targeted ROI (e.g., using a non-directive receiving transducer), or for a sensitivity pattern entirely contained within the ROI (e.g., a highly focused receiver). The PCD may also be oriented in a manner convenient for interpretation of measured acoustic radiation, e.g., perpendicular or coaxial to the source transducer. In some cases where only one frequency is of interest (e.g., the subharmonic of a known fundamental sonication frequency), a coaxial source and receiver may be designed to have approximately coincident beam patterns, thus further simplifying interpretation of measured acoustic radiation.¹⁷ In any of these cases, the ROI for computation of the diffraction correction factor should include all locations where cavitating bubbles are possible. The present methods should then provide a valid estimate of the acoustic power radiated from cavitating bubbles, per unit area or volume, within the ROI.

Array-based passive cavitation imaging (PCI) techniques been recently developed^{44,45} that, in comparison to passive monitoring of emissions using single-element receivers, are capable of providing information about the spatiotemporal distribution of cavitation^{46,47} as well as quantitative

estimates of the acoustic power⁴⁸ and energy⁴⁹ radiated by isolated cavitating bubbles. Diffraction correction using measured or simulated sensitivity patterns of array elements has been applied to passive cavitation imaging, resulting in improved accuracy.⁵⁰ However, due to the finite spatial resolution of these methods, non-zero energy is mapped to locations where no cavitating bubbles exist, so that this approach only provides correct radiated power estimates at known locations of individually resolved bubbles.⁴³ In addition, when large numbers of cavitating bubbles are present, the magnitude of a reconstructed passive cavitation image cannot be directly related to radiated acoustic energy or power, due to interference between the fields radiated from each bubble, as well as diffraction effects. Alternatively, following the approach developed here for single-element PCDs, the average sensitivity of a beamformed array can be determined throughout a given ROI. The position-dependent sensitivity of the beamformed array aperture can be used for diffraction correction of time-averaged, passively measured image frames in order to estimate the acoustic power from cavitation within the defined ROI.

VI. CONCLUSION

A method for quantitative measurement of acoustic radiation, based on emissions measured by passive cavitation detectors, has been derived, validated, and applied to experimental measurements. This approach corrects for frequency- and transducer-dependent diffraction effects, enabling quantitative characterization of cavitation independent of experimental configurations. Use of this approach should enable quantitative comparison of the dependence of bioeffects on acoustic cavitation across many different measurement configurations.

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