Spectral Profiles of Sonothrombolysis Bubble Radiation

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Abstract

Sonothrombolysis is an emerging application of ultrasound-induced cavitation to the treatment of conditions such as acute myocardial infarction. A system for acoustic detection of the cavitation activity effectively being induced in a patient in real time could help keep the procedure in an optimal operating area. As a preparatory step for the development of such a system, we decided to investigate spectral characteristics of the sound radiated by cavitation bubbles under a host of conditions compatible with those to be found in a sonothrombolysis procedure.

Using the Gilmore model to simulate the dynamics of individual bubbles, as well as models of acoustic attenuation and nonlinear propagation in biological tissue, we found that as the ultrasound pressure incident on the bubble increased, integer and then noninteger harmonics developed in the radiated sound, and its broadband noise component increased in power—but not with respect to the most energetic component of each spectrum, once a threshold amplitude for the onset of noninteger harmonics was crossed. Our results are expected to help distinguish between high-energy cavitation at remote positions and low-energy cavitation near the ultrasound transducer used in a sonothrombolysis procedure.

1. Introduction

Acute myocardial infarction is one of the leading causes of death in the world. A new technique that has been emerging for the treatment of this and other conditions, with added benefits over conventional approaches, is *sonothrombolysis*: the application of ultrasound with the intent of eroding thrombi, by means of acoustically induced cavitation of microbubbles.[1] During a sonothrombolysis procedure, information regarding the type and intensity of cavitation activity taking place in the patient would be desirable for real-time control of the efficacy and safety of the procedure. In order to assess the feasibility of a cavitation reporting system based on the acoustic detection of cavitating bubbles, we sought to identify characteristic profiles of the sound reradiated by bubbles driven by various acoustic fields.

2. Methods

The Gilmore model[2] (more specifically its equations for bubble wall motion, natural oscillation frequency and sound reradiation) was implemented in MATLAB® and used to simulate the response of variously sized bubbles, one at a time, in a medium with blood-like properties, as they were driven by an external ultrasound source. The center frequency of the driving ultrasound was fixed at 250 kHz, a choice that significantly minimizes tissue attenuation and heating effects and is currently under investigation in our laboratory, and the bubble radii to be probed were kept in the low micrometer range, in order to mimic the use of widely available commercial ultrasound enhancing agents (UEAs) as a reproducible, consistent source of cavitation bubbles.

We performed an initial batch of simulations by slowly ramping up the instantaneous amplitude of the sinusoidal driving ultrasound from 0 Pa to 4 MPa (measured at the position of the bubble), and attempting to detect emanations of the bubble at different distances as they traversed a medium fitted with similar acoustic attenuation to that of human myocardium.

Partly guided by the results of the first batch, we moved on to more thorough simulations, including models of more complicated physical phenomena, such as nonlinear effects during wave propagation, which may not be negligible in the propagation of megapascal quantities. The k-Wave® toolbox[3] for MATLAB® was used to that end. A phased array with 25 independent 4-by-4-mm transducing elements, devised as an approximation of a planar transducer that might be used in practice, was aimed at the known position of the bubble for transmission of a relatively short ultrasound pulse, in the low tens of fundamental periods, so as to preserve the spatial focusing ability of the array. The sound that arrived near the bubble was then extracted from the k-Wave simulation and used as the forcing function of the Gilmore equation. The sound reradiated by the now cavitating bubble was calculated at the voxel centers closest to the bubble and injected back into the k-Wave grid for a new sound propagation simulation. The phased array, which had remained focused at the position of the bubble, received and beamformed (through simple delaying-and-summing)

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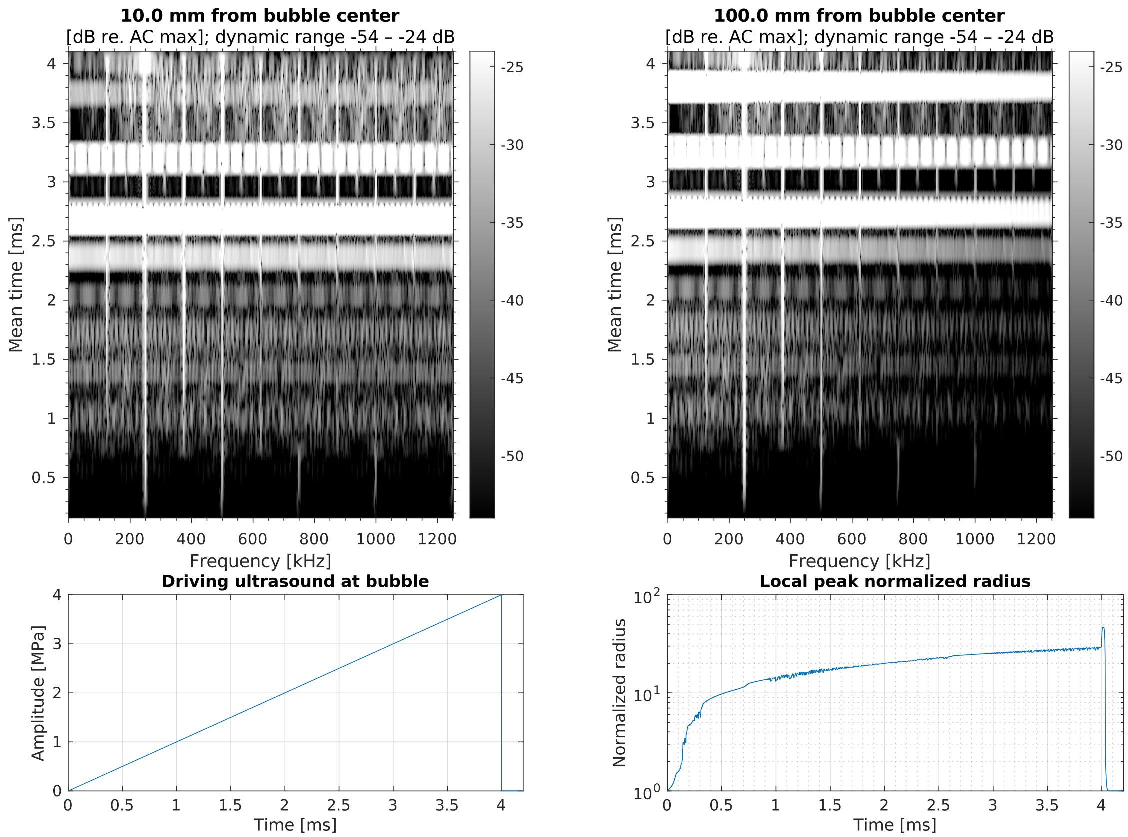


Figure 1: Response of a Gilmore bubble (3.5-μm equilibrium radius) driven with a gently increasing ultrasound amplitude (4 kPa per fundamental period of 4 μs) in a blood-like liquid. Top row: spectrogram of sound radiated by bubble, as detected 1 cm (left) or 10 cm (right) away from bubble center; bottom left: instantaneous amplitude of driving ultrasound at the bubble; bottom right: moving maximum (sliding window twice as long as the fundamental period) of the instantaneous bubble radius normalized by its equilibrium value.

the sound radiated by the bubble, which we then proceeded to analyze.

This second batch of simulations was overall aimed more at mimicking actual sonothrombolysis conditions than at probing vast amounts of bubble configurations in depth.

3. Results

The first batch of experiments led to the finding that bubbles quite often tended not to radiate sound with a complicated subharmonic and ultraharmonic content, despite the rather high driving acoustic pressures of several tens of atmospheres and the tremendous radial excursions developed by the bubbles. An explanation for this observation may be that those bubbles happened to nearly always be driven well below their natural frequencies, theoretically predicted (under the Gilmore model) to range from 4.52 MHz at a 1-μm equilibrium radius down to 336 kHz at 10 μm. A cavitation classification system for sonothrombolysis should probably be tuned to account for this fact.

An example of a bubble which did radiate more complex sub- and ultraharmonic sound is given in Figure 1. Up to about 0.7 ms, or a mean driving acoustic pressure of 700 kPa in amplitude, only integer harmonics of the driving frequency can be clearly seen in the spectrogram; once the forcing function exceeds that general threshold amplitude, however, the 1/2 subharmonic and its associated ultraharmonics remain present throughout the oscillations. Furthermore, short-time sliding windows near 3 ms (mean drive around 3 MPa) show very sharp quarter ultraharmonics (62.5n kHz, n = 3, 5, 7, . . .), a feature we could only clearly detect in some of the simulated bubbles. The highly energetic horizontal artifacts in the spectrograms correspond to unusually strong peaks (positive or more often negative) in radiated pressures, as shown in Figure 2.

Even more exotic sub- and ultraharmonics were seen in selected cases, such as the sixth fractions (250n/6 kHz, n = 2, 4, 5, 7, 8, 10, 11, . . .) shown in Figure 3 (short-time

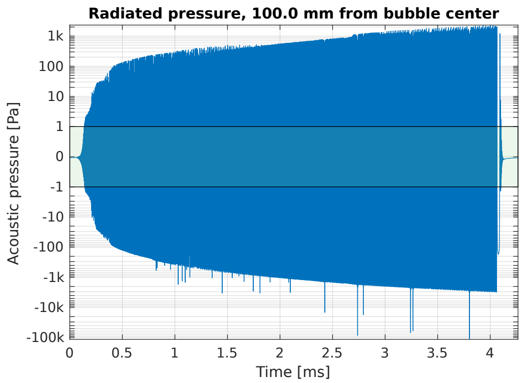


Figure 2: Log–lin–log plot (for lack of a better name) of the pressure radiated by the same 3.5-μm-radius bubble, showing logarithmic space above 1 and below -1 Pa, and linear space in between (shaded in light green). Abrupt, extreme values occur at instants compatible with the horizontal artifacts in the spectrograms of Figure 1.

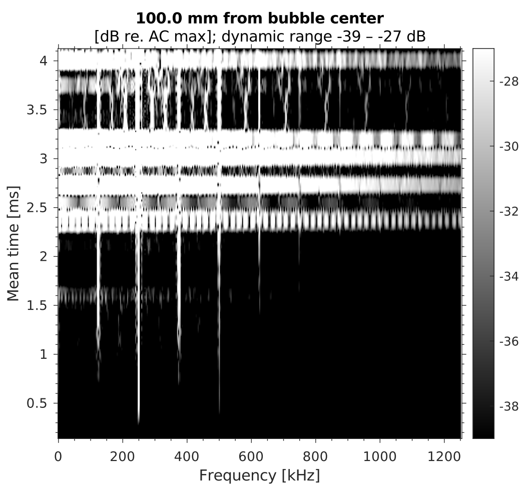


Figure 3: Sound radiated by another Gilmore bubble (4.5-μm equilibrium radius), simulated under otherwise identical conditions.

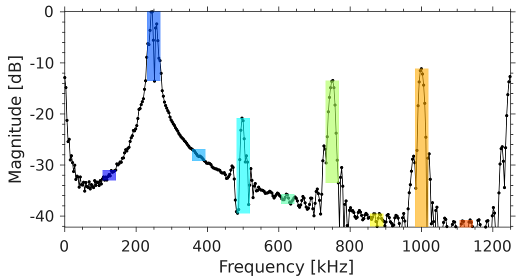
windows of mean time around 3.5 ms).

Our choice of a fairly low frequency for the driving ultrasound seems to have accomplished its goal: comparing the two spectrograms of Figure 1, one can notice how the intervening myocardium-like tissue attenuates higher frequencies more strongly, but not to the point of compromising the visualization of a significant width of the frequency spectrum even at a distance of 10 cm, which may be a reasonable estimate of the typical distances to a transthoracic transducer used in a sonothrombolysis procedure.

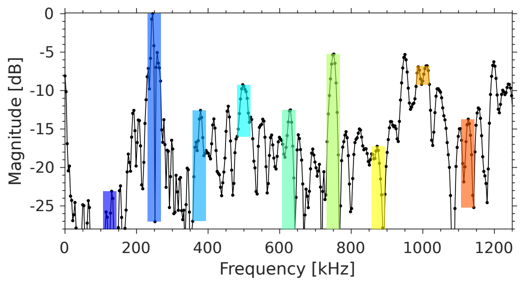
In the second batch of simulations, which prioritized more realistic wave propagation and transducer operation, computational constraints hampered the identification of the same level of detail in the results. Nonetheless, characteristic patterns could be found according to the amplitude of the ultrasound that reached the bubble. For a 3.5-μm-radius Gilmore bubble similar to that of the previous batch of simulations, at drive amplitudes below 1 atm (Figure 4a), there was a predominance of the fundamental frequency in the reradiated sound, bordering on a linear behavior at pressures on the order of 0.1 atm or less and tending toward marked nonlinearity, with progressively more important contributions from integer harmonics, as the drive approached the atmosphere. Having the drive go slightly above 1 atm (4b) then led to a rather sudden development of significant noninteger harmonic (sub- and ultraharmonic) components. Further increases in amplitude, going into the high hundreds (4c) and mid thousands (4d) of kilopascals, did not have quite as dramatic an effect as the crossing of the atmosphere, although some of the noninteger harmonics seemed to become more sharply defined against the background.

At the highest drive amplitude shown in the figure (-3.5 peak negative and 5.3 MPa peak positive acoustic pressure), the transmitted ultrasound already reached the bubble (about 12 cm away from the phased array) with a significant amount of nonlinear distortions, with second, third and fourth harmonics about -10, -16 and -20 dB of the fundamental, respectively. We speculate very high drive amplitudes, besides their intrinsically higher energy content, may have had the additional effect of helping excite the bubble (natural frequency of nearly 1.0 MHz, in the case under consideration) at more favorable frequencies.

In general, as the amplitude increased, so did the broadband noise reradiated by the bubble, a characteristic of high-energy cavitation. However, this broadband radiation increased only in absolute terms, comparing the magnitude of Fourier transforms directly across scenarios. Once the spectra were normalized by their respective intra-scenario maxima (as was done in the figures presented here), this upward trend seemed to vanish, and in fact to paradoxically become reversed, with broadband noise *decreasing* slightly (in relative terms) with drive amplitude for amplitudes past 1 atm: in the figure, the general broadband level (loosely defined as the perceived trend of the background continuum) on an intra-scenario decibel scale seemed to be around -35 or -40 dB at the lowest amplitude (Figure 4a), followed by -20 dB (b), -25 dB (c) and -32 dB (d). This fact can be seen as an enhancement of the signal-to-noise ratio of the spectra, if the background continuum is interpreted as noise. In any event, some form of normalization of the spectra seems to be necessary for a practical sonothrombolysis device, as this procedure increases the robustness of the system against variations in the number and distance of bubbles, as well as variations in tissue attenuation.



(a)



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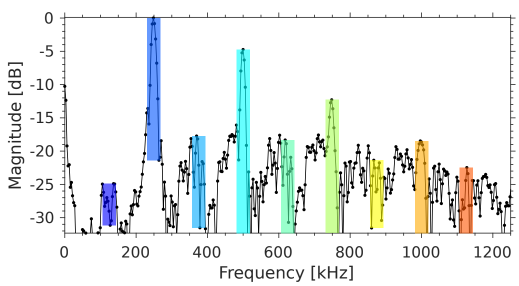

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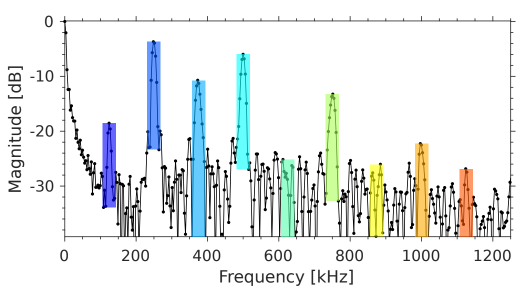

(d)

Figure 4: Frequency spectrum of sound beamformed by phased array, representing the detectable emanations of a Gilmore bubble (3.5-μm equilibrium radius) driven for 32 cycles at 250 kHz with an amplitude of (a) -72 to 72 kPa, (b) -127 to 129 kPa, (c) -690 to 750 kPa, and (d) -3.5 to 5.3 MPa. Colored regions represent bands of interest, centered at $125n$ kHz, $n = 1, 2, 3, \ldots$, and their vertical span indicates the range of the spectral components that fell within the band.

4. Conclusion

Our findings are in general agreement with qualitative descriptions from the literature. An observation that may have bearing on the development of a cavitation reporting system is the fact that energy concentration at noninteger harmonics other than the half subharmonic and its multiples was found to be relatively uncommon and not wholly predictable. A cavitation detector might thus be better off considering the spectral content at such frequency bands as part of the background continuum by default, unless there is strong evidence of some sort to suggest otherwise.

We also conjecture that nonlinear sound propagation through biological tissues may play an important role in the excitation of bubbles smaller than the resonant size, a situation that may be quite frequent when small UEA bubbles, low frequencies and high ultrasound amplitudes are combined in a sonothrombolysis procedure.

Further developments in the way of encapsulated bubble models are expected to yield more realistic results for the period of time the encapsulation remains intact. Still, as soon as the UEA shell is fractured (which may occur rather early under a strong acoustic field), the bubble is expected to behave in a fashion not unlike that described here.

Acknowledgments

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