The short-pulse subharmonic response of microbubbles based on a two-frequency approximation

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Abstract - The subharmonic response due to the nonlinear behavior of microbubble can be used to provide good discrimination between microbubble and surrounding tissue, especially in deep region. However, there is no proper analysis about the subharmonic response under short-pulse insonification. In this work, we extend the two-frequency approximated analytic solution of Newhouse et al. to derive the subharmonic response of microbubble under band-limited insonification. Based on Fourier theory, a band-limited signal can be synthesized by multiple sinusoids, with a two-frequency approximation being the simplest case. Our theoretical analysis illustrates that the amplitude of the subharmonics decrease with the transmitted fractional bandwidth. Moreover, under an applied pressure of 514 kPa, it approaches zero when the fractional bandwidth is increased to 8 %. In other words, this proves theoretically that only narrowband transmission can excite the microbubble to generate the subharmonics. The amplitude of low-frequency response can be derived to increase with the fractional bandwidth, which is different from that of subharmonics. The experimental data from free gas were used to verify the theoretical predictions. It can be shown that the amplitude of the subharmonics decrease with the transmitted fractional bandwidth being varied from 4 % to 18 % when the emitted frequency is 3.00 MHz and the acoustic pressure is 514 kPa. On the contrary, the low-frequency response increases with the transmitted bandwidth.

I. INTRODUCTION

The short-pulse responses of microbubbles to ultrasound excitation are of interest in the study of cavitation, transient responses, and contrast imaging. However, complete solutions are difficult to obtain due to the nonlinearity of bubble responses to such excitation. The solution comprises transient and steady-state components. Different analytic solutions and measurement techniques have been developed for different types of bubble responses. The nonlinear behavior is greatly influenced by the pulse length and pressure of the excitation signal.

Solving this equation analytically would improve our understanding of the complicated acoustic behaviors of microbubbles. In recent years, the harmonics, which was attributed to the nonlinear volume variation of the microbubble, has potential for detecting the small vessels, since the contrast between microbubbles and surrounding tissues for the harmonics is stronger than that for the fundamental, the subharmonics, which has been proved to have the strongest contrast with the tissues [1], especially. Past theoretical studies have shown that there exists threshold effect for microbubbles to generate subharmonics [2]. Prosperetti also indicated that a given bubble can hardly generate the subharmonics, except when the insonified frequency is in certain range and acoustic pressure should be over the onset threshold. Both the analytic and numerical onset thresholds presented in previous research are under such condition that the excited signal is sinusoids (i.e. continuous wave). In other words, there is no proper study about the threshold effect for the generation of the subharmonics under short-pulse transmission.

In this work, for a given bubble whose resonance frequency denoted as f_0 , the transmission is modeled as the composition of two-frequency (f_1, f_2, and $f_2 < 2f_0 < f_1$) under a constraint that the transmission has spectral continuity. Therefore, the bandwidth of the transmission can be approximated as the width of the spectral region spanned by theses two frequencies. Based on analytic solution of the amplitude of the subharmonics of Eller and Flynn

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[3], we found that if f_1 and f_2 are away from $2f_0$ (i.e. the bandwidth of the transmission is increased), the amplitude of the subharmonics will decrease rapidly.

II. PRINCIPAL

Analytic solution of subharmonic response

Several theories for the nonlinear emission of bubble have been developed. Microbubbles in fluid media exhibit several modes of vibration, among which the spherically symmetrical volume mode is the most important. The radius variation is sufficient for characterizing their nonlinear responses. The theory developed by Eller and Flynn seems relevant for our present study. Eller and Flynn develop the analysis using the well-known equation of motion for a radius of a spherical bubble driven by a external pressure $p_{ext}(t)$ in an incompressible liquid, which is given as

$$R\ddot{R}+\frac{3}{2}\dot{R}^2+\frac{p_0}{\rho}[1-(\frac{R_0}{R})^{3\gamma}]+\frac{p_{ext}(t)}{\rho}=0. \quad (1)$$

Here, R is instantaneous bubble radius, and R_0 is the equilibrium value of R. The quantity ρ is the density of the liquid, p_0 is the hydrostatic pressure, γ is polytropic exponent. $p_{ext}(t)$ ($=p_1\cos 2\pi f_1 t$) represents the applied sinusoidal pressure. A solution of Eq. (1) that does not contain subharmonic components and ignore higher order terms, can be found to be

$$\frac{R}{R_0}=A_0+A_1\cos 2\pi f_1 t+A_2\cos 4\pi f_1 t, \quad (2)$$

with

$$A_1=p_1\left\{3\gamma p_0[(f_1/f_0)^2-1]^2\right\}^{-1}, \text{ and} \quad (3)$$

where f_0 is the resonance frequency corresponding to the bubble radius R_0. When the acoustic pressure and driving frequency are within certain ranges, subharmonic components at half the driving frequency are generated and Eller and Flynn drive the subharmonic response $y(t)$ to be

$$y(t)=e^{\mu_1 2\pi f_1 t/2}\sin(\pi f_1 t+\theta_1), \quad (4)$$

where θ_1 is phase angle, and μ_1 can be approximated to be

$$\mu_1=\sqrt{\frac{1}{4}\{(\frac{P_A}{6P_0})^2-[\frac{(f_1/f_0)^2-4}{4}]^2\}}. \quad (5)$$

Based on Fourier theory, a band-limited signal can be synthesized by multiple sinusoids, with a two-frequency approximation being the simplest case. In the double frequency methods [4], a second acoustic field of frequency f_2, named as $p_2\cos 2\pi f_2 t$ is applied. Therefore, Eqs. (2)—(4) are therefore modified to be

$$\frac{R}{R_0}=A_0+A_1\cos 2\pi f_1 t+A_2\cos 4\pi f_1 t+A_3\cos 2\pi f_2 t+A_4\cos 4\pi f_2 t, \quad (6)$$

with

$$A_3=p_2\left\{3\gamma[(f_2/f_0)^2-1]^2\right\}^{-1}, \text{ and} \quad (7)$$

$$y(t)=B_1\sin(\pi f_1 t+\theta_1)+B_2\sin(\pi f_2+\theta_2), \quad (8)$$

where $B_1=e^{\mu_1 2\pi f_1 t/2}$, and $B_2=e^{\mu_2 2\pi f_2 t/2}$.

We can assume that $f_1=2f_0+\Delta f/2$, and $f_2=2f_0-\Delta f/2$. To construct the external pressure as a pulse train with a period large enough such that it approximates a short-pulse waveform, we need $p_1\approx p_2(=p)$ and $\Delta f(=f_1-f_2)$ not so large as to cause spectral discontinuity of the transmitted waveform. The fundamental responses (A_1, and A_3) are combined into a mixed response $A_F(t)$ around $2f_0$, which is defined as the band-limited fundamental response, given by

$$A_F(t)[\cos 2\pi(2f_0)t+\theta_F] = A_1\cos[2\pi(2f_0+\Delta f/2)t]+A_3\cos\left[2\pi(2f_0-\Delta f/2)t\right]. \quad (9)$$

According to non-coherence summation, the peak amplitude of $A_F(t)$ is given to be

$$A_F=\sqrt{A_1^2+A_3^2}\approx\frac{p}{3\gamma p_0}\sqrt{\frac{18}{81-576B_e^2}}, \quad (10)$$

where $B_e=\Delta f/2f_0$ is named the equivalent fractional bandwidth. As the bandwidth is not so large as to cause spectral discontinuity of the transmitted waveform, the term of $81-576B_e^2$ is always positive under this restriction, eg. B_e is smaller than 35 %.

In addition, the subharmonic responses (B_1, and B_2) are combined into a mixed response $B(t)$ around f_0, which is defined as the band-limited subharmonic response, and the amplitude of $y(t)$ is given to be

$$B=\sqrt{B_1^2+B_2^2}=\sqrt{e^{\mu_1 2\pi(2f_0+\frac{1}{2}\Delta f)t}+e^{\mu_2 2\pi(2f_0-\frac{1}{2}\Delta f)t}}, \quad (11)$$

where

$$\mu_1=\sqrt{\frac{1}{4}\{(\frac{p}{6p_0})^2-[\frac{\Delta f}{2f_0}+\frac{1}{4}\cdot\left(\frac{\Delta f}{2f_0}\right)^2]^2\}},$$

and

$$\mu_2=\sqrt{\frac{1}{4}\{(\frac{p}{6p_0})^2-[-\frac{\Delta f}{2f_0}+\frac{1}{4}\cdot\left(\frac{\Delta f}{2f_0}\right)^2]^2\}}.$$

Omitting the term $(\Delta f/2f_0)^2$, then $\mu_1\approx\mu_2(=\mu)$ and it can be approximated to be

$$\mu = \sqrt{\frac{(p/6p_0)^2 - B_e^2}{4}} . \tag{12}$$

The value of μ determines the bandwidth-threshold ($B_e = p/6p_0$) of the subharmonic signal under band-limited transmission. If the pressure p increases, the fractional bandwidth B_e could be achieved within larger range.

From Eqs. (11) and (12), the amplitude of $y(t)$ could be rewritten as

$$B = e^{\mu 2\pi f_0 t}\sqrt{e^{\mu\pi\Delta f t} + e^{-\mu\pi\Delta f t}} . \tag{13}$$

Therefore, the peak power ratio of subharmonics to fundamental responses based Eqs. (10) and (13) is given by

$$\frac{B^2}{A_F^2} = \frac{e^{\mu 4\pi f_0 t}(e^{\mu\pi\Delta f t} + e^{-\mu\pi\Delta f t})}{(\frac{p}{p_0 3\gamma})^2 \cdot \frac{18}{81 - 576 B_e^2}} . \tag{14}$$

From Eq. (13), the peak power ratio is proportional to e^p, and inverse proportional to p^2. Therefore, it would increase exponentially with p, which is also shown as the growth stage of subharmonics from the research of Shi et. al. [5].

Numerical result of subharmonic response

The peak power ratio of subharmonics to fundamental responses contain time factor, and we can choose some large value $2f_0 t$ to determine the properties of the peak power ratio under steady-state condition. According to the derivations in previous section, the center frequency of the transmitted waveform should be at twice the resonance frequency of microbubbles. In the simulation work, we could assume that the radius of microbubbles is 2.27 μm, and the center frequency at twice its resonance frequency is about 3 MHz. The fractional bandwidth is from 1% to 20%, and peak pressure is from 10 kPa to 200 kPa. The peak power ratio of subharmonic to the fundamental response calculated from Eq. (14) is displayed as contour plot in the Fig. 1(a). The black zone in the left-upper part where is larger fractional bandwidth, as well as shorter pulse length, at the same applied pressure denotes that subharmonic signal cannot be generated. On the contrary, peak power ratio of low-frequency to fundamental response increases with the transmitted bandwidth [4]. Figure 1(b) shows the peak power ratio versus the fractional bandwidth under different peak pressure. The peak power ratio increases with the applied pressure exponentially under the same fractional bandwidth. As the applied peak pressure increases, subharmonic could be generated within larger range of the fractional bandwidth.

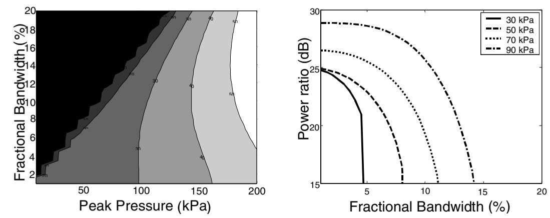

Fig. 1(a) Fig. 1(b)

Fig.1 The peak power ratio of subharmonic to the fundamental response is displayed as contour plot (a) where bubble radius is 2.27 μm and center frequency is at 5 MHz, and versus the fractional bandwidth under different peak pressure (b).

Ⅲ. EXPERIMENTAL STUDIES

The transmitted waveforms were generated by an arbitrary-function generator (TAG 1242, TTi), and fed to a power amplifier (Model 75A250, Amplifier Research). The received signals were amplified by a pulser/receiver (Model 5072PR, Panametrics). Experimental data were recorded on a PC using a PCI-based A/D converter (PCI-9812, NuDAQ, ADLink) at a sampling rate of 20 MHz. The experimental setup is shown in Fig. 2.

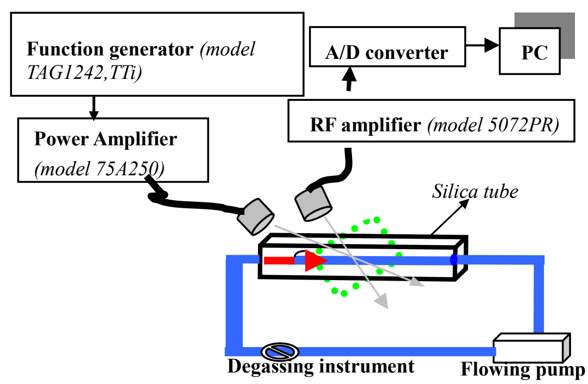

Fig.2 The diagarm of the experimental set-up

The setup includes a hollow tube with an inside diameter of 15 mm that is covered by silicon. This phantom serves as a window for observing flowing bubbles, and is totally immersed in water during experiments. In addition to the silicon phantom, the system includes a degassing system, a roller pump, and flow tubes. Two piston probes (V325: center frequency, 2.25 MHz; V309: center frequency, 5.00 MHz; focal distance of both pistons is, 20 mm) are utilized as transmitting and receiving transducers. The angle between the flow tube and the beam direction for both probes is about $45°$, and both probes are focused at the same point in the middle of the flow tube.

Sixteen waveforms whose center frequency at 3 MHz, and fractional bandwidth changed from 4 % to 18 % in steps of 2 %, were transmitted alternately. There are three kinds of peak pressure, 411, 463, 514 kPa, are selected. Fig. 3 displays the contour plot of frequency responses of microbubbles where the fractional bandwidth is from 4 % to 18 %. Applied peak pressure is 411 kPa (a) and 514 kPa (b), respectively. The subharmonic resides at the frequency of 1.5 MHz. The bandwidth-threshold is about 5 % under applied peak pressure of 411 kPa as shown in Fig. 3(a). The bandwidth-threshold would increase to 8 % under applied peak pressure of 514 kPa. The low-frequency response resides near DC, however, it could be generated under increasing fractional bandwidth.

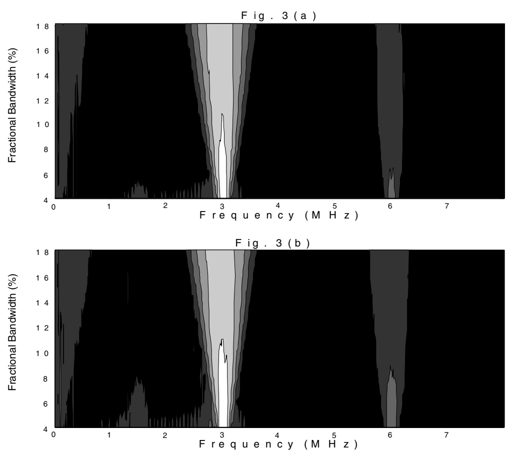

Fig.3 Frequency responses of microbubbles under different fractional bandwidth displayed as contour plot where transmitted pressure are 411 kPa (a) and 514 kPa (b) respectively.

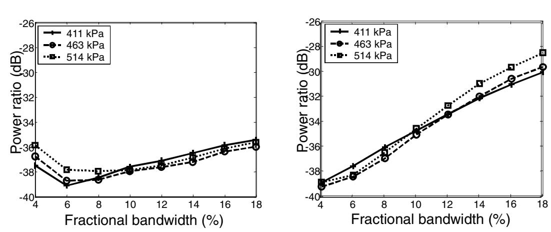

Fig. 4(a) Fig. 4(b)

Fig.4 Power ratio of subharmonics to fundamental response and that of low-frequency to fundamental response are displayed in (a) and (b) respectively.

Figures 4(a) and 4(b) display the power ratio of subharmonics to fundamental response (a) and that of low-frequency to fundamental response (b) under different fractional bandwidth and peak pressure. As the fractional bandwidth increases from 4 % to 8 %, the peak power ratio decreases gradually. As peak pressure increases, the range where subharmonic response could be generated increases. As the fractional bandwidth increases over 8 %, the intensity of subharmonic response is lower than noise level, however, the power ratio increases owing to decreasing fundamental response as Fig 4(a) displayed. On the contrary, the peak power ratio between low-frequency and fundamental response increases gradually as Fig 4(b) displayed.

IV. CONCLUSION

From numerical and experimental results, the peak power ratio of subharmonics to fundamental response increases with the applied peak pressure. More than this, the threshold of subharmonics increases with the fractional bandwidth. Therefore, narrowband transmission can excite microbubbles to generate the subharmonics more easily. The peak power ratio of low-frequency to fundamental response increases with the applied pressure also. However, it increases with the fractional bandwidth, this is different from the subharmonics. Both of range resolution and contrast to surrounding tissues can be improved if the by low-frequency and subharmonic responses are used alternatively in imaging.

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