



## Ultrafast monitoring and control of subharmonic emissions of an unseeded bubble cloud during pulsed sonication

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### ABSTRACT

In the aim of limiting the destructive effects of collapsing bubbles, the regime of stable cavitation activity is currently targeted for sensitive therapeutic applications such as blood-brain barrier opening by ultrasound. This activity is quantified through the emergence of the subharmonic component of the fundamental frequency. Due to the intrinsically stochastic behavior of the cavitation phenomenon, a better control of the different (stable or inertial) cavitation regimes is a key requirement in the understanding of the mechanisms involving each bubble-induced mechanical effect. Current strategies applied to stable cavitation control rely on the use of either seeded microbubbles or a long-lasting pulse to reinitiate subharmonic emission. The present work aims at developing an ultrafast (inferior to 250  $\mu$ s) monitoring and control of subharmonic emissions during long-pulsed (50 ms) sonication. The use of a FPGA-based feedback loop provides reproducible level of subharmonic emissions combined with temporal stability during the sonication duration. In addition, stable cavitation events are differentiated from the broadband noise characterizing inertial cavitation activity, with perspectives in the discrimination of the involved mechanisms underlying bubble-mediated therapeutic applications.

### 1. Introduction

Sustaining small amplitude oscillations of bubbles in an ultrasound field refers to stable cavitation, a cavitation regime for which bubbles can exhibit weakly nonlinear oscillations, far from the regime of large oscillations and collapses commonly known as inertial cavitation. Such stable cavitation regime is currently the aim of intensive research for sensitive therapeutic applications such as blood-brain barrier opening by ultrasound [1], ultrasound-enhanced thrombolysis [2] or chemotherapeutic drug delivery [3], where destructive side effects of collapsing bubbles (cell lysis) have to be limited. Current passive acoustic detection of stable cavitation activity relies on the detection of subharmonic emission [4,5]. Indeed the latter constitutes the first nonlinear frequency component that arises uniquely from the bubble oscillations opposite to harmonics possibly induced by nonlinear propagation in tissues. It is worth noting that the origin of strong subharmonic emission from a cavitating bubble cloud is not yet elucidated, as several single or collective bubble mechanisms can induce period-doubling such as (i) the presence of large bubbles with radii close to twice the resonant radius [6,7], (ii) bubble surface mode

emission through parametric driving [8], (iii) chaotic bubble oscillations [9], (iv) collective behavior of an oscillating [10] or (v) periodically-collapsing [11] cloud.

Regardless of the considered source of subharmonic emission, the onset of stable cavitation activity is achieved above a certain threshold intensity. Even above this threshold, subharmonic emission can be weak and have an intermittent behavior due to the complexity of the cavitation phenomenon. To overcome this drawback, ultrasound contrast agents are commonly used, allowing to control both bubble presence and size in the treatment zone. However, it requires maintaining a continuous supply of agents during the sonication duration [12], without knowledge of the time-varying microbubble concentration that would naturally impact the global response of the cloud. The control of the fluctuation requires real-time monitoring of subharmonic emission, temporally integrated with a cavitation dose for quantifying induced bioeffects [5]. However, for sufficiently large acoustic pressures providing substantial stable cavitation activity, inertial regime stochastically coexists with soft bubble oscillations, making the full discrimination of ultrasound-induced bioeffects [12] difficult.

An interesting alternative consists in inducing, and real-time

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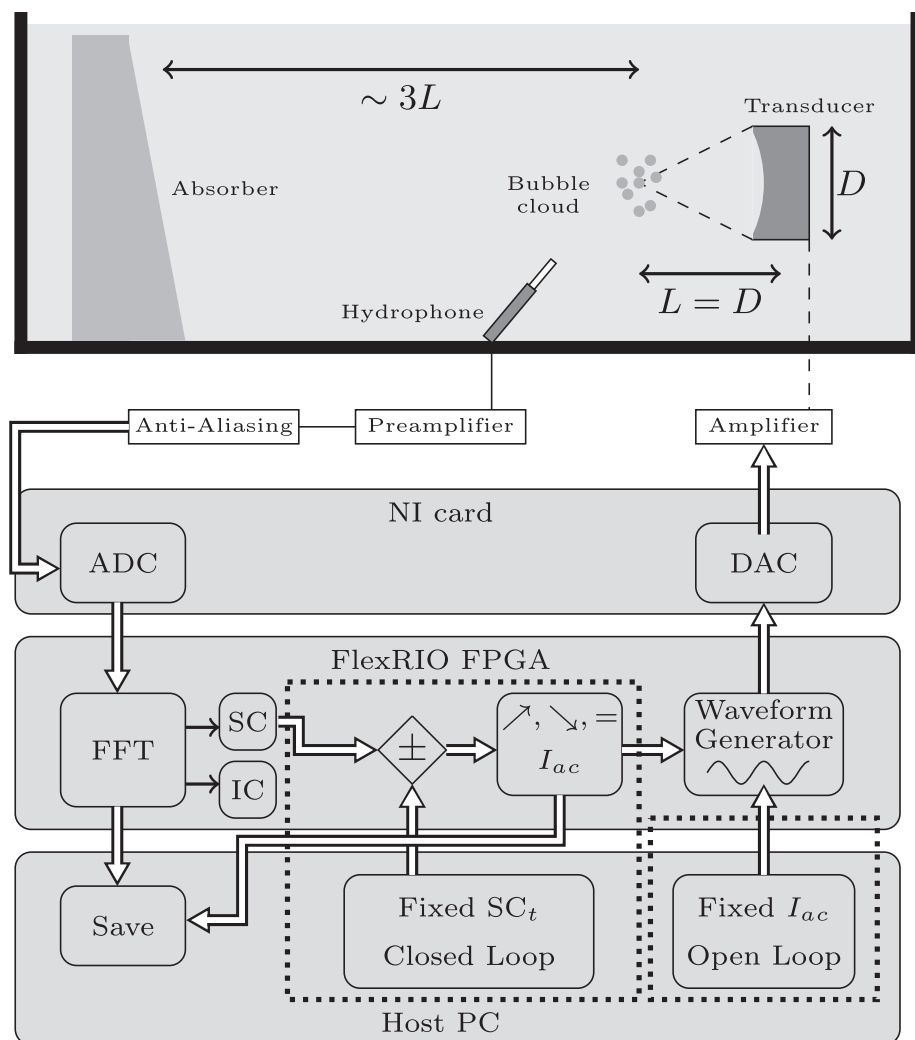


Fig. 1. Schematic representation of the sonication system combined to the description of the signal processing chain.

controlling, stable cavitation activity of an unseeded bubble cloud. Such technique relies on the possibility of successively creating free bubbles from diffused gas in the medium and maintaining bubble oscillations at a given cavitation activity. Maintaining cavitation has already been performed for the control of inertial cavitation activity [13] and its induced bioeffects [14,15]. Moreover real-time control strategies allow counterbalancing the presence of seeded microbubbles [16] and still to achieve high transfection efficiency [17]. We therefore propose to investigate the feasibility of real-time subharmonic emission control of an unseeded bubble cloud during pulsed sonication, and to evaluate (i) how stable cavitation activity can be maintained over the duration of the sonication shot at a given and constant level and (ii) how cavitation activity fluctuations can be limited.

## 2. Material and methods

A schematic representation of the experimental setup is presented in Fig. 1. Experiments are carried out in a rectangular tank ( $500 \times 250 \times 240$  mm) filled with air-saturated tap water ( $O_2$  concentration  $\sim 8$  mg/L). The ultrasound waves are generated by a spherical piezoceramic transducer (diameter 100 mm, focal length 100 mm), operated at its resonance frequency  $f_0 = 550$  kHz (corresponding wavelength in water  $\lambda = 3$  mm at  $25^\circ\text{C}$ ). The signal supplied to the transducer is synthesized by a FPGA system (Field-Programmable Gate Array, NI PXIe-7965R card, Austin, TX) and is provided by the Digital-to-Analog Converter of the FPGA module (14-bit, 100 MHz sampling frequency, NI-5781R module), and subsequently amplified by a power

amplifier (PRANA, GN 1000, 1000 W). The transducer generates sinusoidal pulsed ultrasonic waves with a 50 ms pulse duration and a 20% duty cycle. The cavitation noise emitted from the bubbles is measured with a needle hydrophone (Onda, HNC C1500) located at a distance of 73 mm from the focal point, and an absorber is placed at the end of the tank for reducing the reflexion within the cavity. The measured signal is pre-amplified (Müller preamplifier, 40 dB) before anti-aliasing filtering, and acquired by the Analog-to-Digital Converter device of the FPGA module.

The FPGA core is built to synthesize the output wave, to acquire the signal, and to make all the required signal processing operations [windowing, Fast Fourier Transform (FFT) calculation, cavitation indicator calculations and regulation process]. The programming is based on arrays of logic blocks within the FPGA core (100 MHz clocking) and all these operations execute themselves continuously until the end of the sonication (typically during 60s). The acoustic pressure signal of 2048 values is acquired at a sampling rate of 10 MHz, before hanning windowing, FFT calculation and dB conversion of the spectrum. Stable and inertial cavitation activities are then quantified through a particular signature of acoustic emission for each cavitation regime. The inertial cavitation regime is evaluated by the broadband noise level, given by the arithmetic mean of the signal magnitudes over the frequency range of [0.1–5] MHz. This indicator will be referred to as IC from now on. Considering that the spectral width of each line frequency is low, the contribution of stable cavitation activity within this signature of strong collapses is relatively negligible. The quantification of stable cavitation activity is performed by evaluating the subharmonic

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