Jan Helmerich*, Benedikt George, Stefan J. Rupitsch

Investigation of an Active Measurement Method to Detect Inertial Cavitation and the Presence of Potential Drug Carriers

Abstract: Drug carriers, such as nanoparticles, are capable of releasing pharmaceutically active ingredients, which can be initiated by focused ultrasound via the effect of inertial cavitation. This effect of inertial cavitation is often verified by passive measurement methods that rely on the analysis of emitted acoustic signals caused by the implosion of bubbles. However, a major issue of such methods is their inability to detect the presence of potential drugs in human vessels, complicating the implementation of a closed loop control for future medical therapies. Therefore, this contribution introduces an active measurement method to determine both inertial cavitation and the presence of potential drug carriers in a tissue mimicking phantom.

Keywords: Active Cavitation Detection, FUS, Inertial Cavitation, Drug Delivery

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1 Introduction

The diagnosis of cancer is often followed by therapeutic approaches such as chemotherapy. Unfortunately, there are several adverse reactions linked to this technique due to the toxic medication dosages circulating freely inside the body. Thus, Drug Delivery is emerging as a promising tool to minimize these side effects and guarantee high efficiency at the same time. For this purpose, drugs are incorporated into biocompatible particles, preventing any interaction with the human body until its release. The rough surfaces of these particles lead to the formation of gas bubbles on the surface area itself. Since these bubbles will tend to collapse via the

effect of inertial cavitation (IC), drug release can be initiated by applying focused ultrasound (FUS) from outside the body at the target area. The collapse of bubbles ruptures the particles and, hence, the presence of IC allows to draw a conclusion on the release of the drug. In addition, IC can increase the permeability of cells and, thus, supports the absorption of the medication [1].

The process of IC, in which bubbles collapse, is extremely fast and generates short sound pressure pulses. In comparison, stable cavitation (SC) describes the generation and oscillation of bubbles due to the exposure to an excitation signal. In both cases, the analysis of the frequency spectrum of a detected signal provides further information on the existence of SC and IC. In cases in which SC is present, harmonics and subharmonics of the excitation signal arise in the frequency spectrum. In contrast, IC causes a broadband noise as a result of the shortly emitted waves [2]. In addition, the voltage spectral density (VSD) S_r can be used to evaluate the cavitation activity [3]. In cases of a digitized signal, e.g. the hydrophone's output signal, the VSD can be determined by

$$S_r = \sqrt{\frac{\sum_{n=i_s}^{i_E} u(n)^2}{B}}, \quad (1)$$

whereas $u(n)$ describes the discrete frequency magnitudes of the Fast Fourier Transform (FFT) of the digitized measurement signal and B the investigated bandwidth, ranging from the frequency index i_s to i_E . In general, a higher value of S_r corresponds to a higher cavitation activity in the bandwidth of interest.

The process of IC and SC can either be detected actively or passively. These methods are referred to as active cavitation detection (ACD) and passive cavitation detection (PCD), respectively. PCD heavily relies on the emission of acoustic signals due to the collapse or oscillation of bubbles. ACD, in contrast, usually involves the insonification of the target area by an ultrasonic transducer [1]. The reflected or transmitted signal is then detected by either the same or a different transducer (e.g., hydrophone), respectively. As the emitted noise interferes with the sent signal, the analysis of either the

*Jan Helmerich: Department of Microsystem Engineering - IMTEK, Georges-Köhler-Allee 106, Freiburg im Breisgau, Germany, e-mail: jan.helmerich@imtek.uni-freiburg.de

Benedikt George, Stefan J. Rupitsch: Department of Microsystem Engineering - IMTEK, Georges-Köhler-Allee 106, Freiburg im Breisgau, Germany

transmitted or reflected signal allows to determine the process of IC and SC.

In this work, we concentrate on the evaluation of IC and SC at different points in time after and during cavitation excitation by applying a new active measurement method, for which pulses are sent to the cavitation field and transmitted to an oppositely located hydrophone. The proposed method will also provide us with the opportunity to determine the presence of potential drug carriers in a human vessel mimicking phantom.

2 Measurement

2.1 Experimental Setup

Figure 1 depicts the experimental setup, which is partly placed in a tank filled with degassed pure water. The temperature of the water is kept at 30 °C and an arbitrary 2-channel waveform generator (Agilent 33522 B) provides the electric excitation signal, which is then amplified by the RF power amplifier (ENI-1140LA) by 55 dB. The installed matching network maximizes the power transfer to the broadband FUS transducer (Sonic Concepts H231) by transforming the electrical impedance at the center frequency $f_0 = 750$ kHz to $50\ \Omega$.

Figure 1: Experimental Setup of the Active Cavitation Detection.

The selected ultrasound signal for cavitation excitation comprises a sinusoidal burst signal of a peak-to-peak

amplitude $U_{\text{Peak-to-Peak}} = 102.80$ V and the frequency $f_0 = 750$ kHz. Since this frequency enables the generation of a focused ultrasonic beam due to the concave shape of the transducer, sound energy is strongly concentrated in an ellipsoid shaped focal volume, which features the size of only a few millimeters. Thus, high sound energy levels can be achieved in a particular target area where it is required for the release of the drug via the effect of IC. As the sound pressure decreases outside the focal zone, the process of IC can be exclusively restricted to tumorous tissue [3].

A tissue mimicking phantom, which consists of 10 % polyvinyl alcohol and 90 % ultra-pure water, is placed inside the center of the tank. Its 3 mm canal, which imitates a blood vessel, is placed in the focal zone of the FUS transducer. The phantom is 100 mm high, 63 mm wide and 63 mm deep. The peristaltic pump (Boxer 15KS) provides the opportunity to realize a perfusion through the phantom's canal, similar to the human circulatory system. Since vessels can provide nutrients and oxygen, which are crucial for the tumor cell's proliferation, the canal might be considered as a blood vessel to which the tumorous tissue has grown to.

The ultrasonic transducer (Olympus V306 - plane), arranged perpendicular to the FUS transducer H-231, emits pulsed signals $u_p(t)$ (center frequency $f_c = 2.5$ MHz, pulse length $l_p = 2 \mu s$) via a pulser (Olympus 5900PR) through the canal of the phantom. These transmitted signals $u_T(t)$ are then received by the opposite hydrophone (Onda HNC-1500), pre-amplified by 20 dB and measured with a digital oscilloscope (Agilent DSO7014B). Depending on whether cavitation activity or the presence of potential particles as drug carriers is evaluated, a passive high-pass filter is placed after the amplifier of the hydrophone.

2.2 Experimental Procedure

Due to the limited availability of nanoparticles as drug carriers, talcum micro particles are used as a substitute, which are produced by mixing talcum powder and pure water. The flow velocity of the talcum-water-concentration (*TWC*) pumped through the canal is kept constant at 10 cm/s at all times and is therefore similar to velocities in a 3 mm blood vessel [5]. The pulser's settings are set to 4 μ J and 50 Ω damping.

2.2.1 Investigation of Cavitation Activity

The mixture ratio of the *TWC* is kept constant at 1.0 g talcum powder by 50 ml pure water. The excitation signal comprises a sinusoidal burst with the frequency $f_0 = 750$ kHz and a duration length of 0.6 ms. Synchronization between cavitation

excitation and emitting ultrasonic pulses through the V306 is realized via the external trigger of the pulser, which is controlled by the second channel of the arbitrary waveform generator.

For each cavitation excitation, eleven pulses are sent through the canal of the phantom via the transducer V306, the time interval between two successive pulses being approximately $67 \mu\text{s}$ ($T = 1/15 \text{ kHz}^{-1}$) and the duration of each pulse $2 \mu\text{s}$. The voltage signal $U_{C,p}(t)$, consisting of the detected cavitation noise and pulses, is depicted in Fig. 2. The first pulse ($i = 1$) is received just before broadband noise can be detected by the hydrophone ($t = 0.155 \text{ ms}$). In addition, depending on the time the pulses are sent, they will interfere slightly differently with the broadband noise (see Fig. 2). In total, cavitation is triggered $N = 200$ times, each placed 3 s apart, and each of the eleven pulses is analyzed via FFT. The average amplitudes A of each pulse i are determined by adding the amplitudes of the same frequency of each excitation, divided by the number of measurements. For instance, the average amplitude of the 2nd pulse ($i = 2$) and the frequency 750 kHz is calculated by

$$A_{\text{Pulse2-750 kHz}} = \frac{\sum_{k=1}^N A_{\text{Pulse2-750 kHz-k}}}{N}, \quad (2)$$

whereas N represents the number of excitations. Furthermore, the average VSD

$$\bar{S}_r(i, \tau) = \frac{1}{N} \sum_{k=1}^N S_r(i, \tau), \quad (3)$$

of each pulse i , starting at its corresponding time $\tau = 0.155 \text{ ms} + (i-1) \cdot T$, is determined. The VSD is calculated for the bandwidth 6 – 6.5 MHz, which had proven to be an excellent indicator for IC [3].

Figure 2: Received Signal $U_{C,p}(t)$ by the Hydrophone (1.0g/50ml).

Moreover, additional passive recordings with the hydrophone HNC-1500 serve as a reference and allow to evaluate the influence of the ACD on the cavitation activity. For these $N = 200$ passive measurements, the V306 transducer was not driven. Furthermore, the VSD $\bar{S}_r(i, \tau)$ is only calculated for

time periods $l_p = 2 \mu\text{s}$, previously defined with the start of a pulse i at the time τ by employing ACD.

In all these mentioned procedures in which IC activity is evaluated, the received signal is filtered by a high-pass filter before being measured with the digital oscilloscope in order to suppress the FUS signal $u_s(t)$.

2.2.2 Investigation of Presence of Particles

In order to evaluate the proposed measurement method on its ability to prove the presence of potential drug carriers, the mixing proportion of the TWC were varied between 0g/50ml (pure water), 0.25g/50ml, 0.5g/50ml, 1.0g/50ml and 3.5g/50ml. Note that for these experiments no cavitation is initiated. Moreover, the high-pass filter was removed, and the peak-to-peak voltage of the transmitted pulses was determined. Pure water serves as a reference, representing no potential drug carrier in the canal. Thus, evaluating the average peak-to-peak voltage

$$U_{PP}(TWC) = \frac{U_{PP-TWC}}{U_{PP-Water}} \quad (4)$$

provides information on the setup's capability of detecting the presence of talcum particles. U_{PP-TWC} represents the average peak-to-peak voltage of 200 pulses for a particular talcum water suspension, $U_{PP-Water}$ the average peak-to-peak voltage of 200 pulses for pure water.

3 Results

3.1 Investigation of Cavitation Activity

Figure 3: Average Amplitudes A of different pulses (1.0g/50ml).

First, we investigated SC and IC activity both by employing Eq. 1, Eq. 2 and Eq. 3. Figure 3 depicts the average amplitudes A in the frequency spectrum for the first, second, third and eleventh pulse, whereby all spectra are normalized to the

maximum amplitude value of the second pulse. Since the pulses three to ten have similar frequency spectra, only one pulse is shown for the sake of clarity. It can be recognized that the first and the eleventh pulse do not show any frequency characteristics for SC or IC. Starting with the second pulse, frequencies close to the excitation frequency ($f_0 = 750$ kHz) and the second harmonic ($2f_0 = 1.5$ MHz) are present and interharmonic frequencies are more pronounced as a result of SC and IC. In all frequency spectra, the frequency $f_c = 2.5$ MHz is dominant since it is the center frequency of the transducer V306 and close to the third harmonic ($3f_0 = 2.25$ MHz). As only the first and the eleventh pulse do not indicate

Figure 5: Average Cavitation Activity at Different Times, starting at $\tau = 0.155$ ms + $(i-1) \cdot T$, (1.0g/50ml).

SC or IC activity, it clearly shows that IC and SC are processes that arise quickly after cavitation excitation but also disappear as quickly as no burst signal is applied to the target area. The same is indicated by the VSD of ACD and PCD. Figure 4 depicts the average VSD $\bar{S}_r$ for each pulse one to eleven (ACD) or the corresponding time period (PCD). As the passive VSD are similar to those of the active measurement method between pulse two ($i = 2$) and ten ($i = 10$), one can conclude that the ACD has almost no impact on IC in the frequency range of 6 - 6.5 MHz. As stated before, the emitted pulses do impact the frequency spectrum, particularly at the center frequency of the transducer V306. However, this will not be further discussed and be part of a future investigation.

3.2 Investigation of the Presence of Talcum Particles

Figure 5 shows the measured $U_{pp}(TWC)$ (see Eq. 4) and its approximated progress. The TWC of 0.25g/50ml is hardly distinguishable from pure water. However, with an increasing ratio of talcum powder, the peak-to-peak voltage $U_{pp}(TWC)$ decreases. A TWC of 3.5g/50ml already results in a $U_{pp}(TWC)$

Figure 4: Voltage $U_{pp}(TWC)$ of different concentrations.

being almost 12 % less pronounced than the one of pure water. Thus, the method provides a good possibility to prove the presence of talcum particles in the vessel.

4 Conclusion

This study confirmed a new ACD method to prove both IC activity and the presence of talcum particles and, therefore, provides the opportunity of accomplishing a closed loop control. In addition, we investigated the course of IC activity and showed that this process arises as quickly as it disappears.

However, as the hydrophone HNC-1500 and the transducer V306 are positioned oppositely, the setup is only suitable for medical applications to a limited extent. A future approach might involve the detection of inertial cavitation and the presence of particles by means of a pulse-echo method.

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