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Controlled positioning of microbubbles and induced cavitation using a dual-frequency transducer and microfiber adhesion techniques

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ABSTRACT

We report a study on two methods that enable spatial control and induced cavitation on targeted microbubbles (MBs). Cavitation is known to be present in many situations throughout nature. This phenomena has been proven to have the energy to erode alloys, like steel, in propellers and turbines. It is recently theorized that cavitation occurs inside the skull during a traumatic-brain injury (TBI) situation. Controlled cavitation methods could help better understand TBIs and explain how neurons respond at moments of trauma. Both of our approaches involve an ultrasonic transducer and bio-compatible Polycaprolactone (PCL) microfibers. These methods are reproducible as well as affordable, providing more control and efficiency compared to previous techniques found in literature. We specifically model three-dimensional spatial control of individual MBs using a 1.6 MHz transducer. Using a 100 kHz transducer, we also illustrate induced cavitation on an individual MB that is adhered to the surface of a PCL microfiber. The goal of future studies will involve characterization of neuronal response to cavitation and seek to unmask its linkage with TBIs.

1. Introduction

Cavitation refers to the spontaneous growth and collapse of MBs in low pressure regions. This process is currently used in a variety of areas, to mix fluids and eliminate impurities [1], as well as in specific drug delivery [2], gene therapy [3], and thrombolysis [4]. Previous research has also linked cavitation as a contributing factor in the exfoliation of graphene [5,6]. Additionally, cavitation has been shown to produce shock waves that have erosive effects on objects such as turbines and propellers [7–9]. Cavitation has also shown to produce a wide range of bioeffects. Previous studies sought out to identify cell damage that occurs in the midst of ultrasound therapy via calcium signaling processes [10]. On top of this, interested parties suspect that cavitation occurs inside the skull of TBI victims and its aftermath is leaving a profound impact [11–14]. Generation and characterization of controlled cavitation is critical to understand the cellular mechanisms of TBIs. These understandings can lead to better treatment that improves the quality of life for TBI victims, or it can even help launch preventative techniques that reduce the chance of a TBI altogether. In this study we use capillary tubing and an ultrasonic transducer to create two cost-effective methods for controlled cavitation. Our expectation is that these methods will be advantageous and applicable in future studies that focus on studying and understanding on the effects that cavitation has on nearby surfaces, like neurons in a TBI situation.

Acoustic cavitation occurs when the instantaneous pressure is negative, and a process of nucleation takes place [15]. Upon collapse of these MBs, micro jets form, localizing impact and force, causing damage to nearby surfaces [16]. This phenomenon is most visible in propellers, where the turbulent force of moving water creates areas of extreme low pressure, and over a period of time the blades experience significant erosion due to the repetitive impact of the cavitation shock waves [17]. There has been various techniques used in previous studies to study cavitation.

Acoustic, hydrodynamic, and optical methods have been implemented in previous studies to generate cavitation. In acoustic cavitation, ultrasonic waves are used to create cavitation, however previous methods do not have arbitrary control in the quantity of produced MBs and the specific location of their collapse is variant [18]. In hydrodynamic cavitation, fluid flows through an orifice, which increases the velocity and subsequently lowers threshold pressure so that nucleation occurs at the point of entry. With this method, vast amounts of MBs are generated, preventing the ability to analyze the effects of finite cavitation [19]. In optical induced cavitation, an intense energy is introduced to the system (laser), creating a stream of MBs in the beam of the laser. While this method is practical in creating controlled amounts of MBs, lasers are expensive and not accessible for a lot of research

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groups. Our approach is economical and offers a modification to the acoustic method to ultimately create a controlled environment to observe the effects of cavitation.

We introduced MBs into a water tank at a controlled size by pushing air through capillary tubing. We implemented two separate techniques to arbitrarily trap and position the MBs before induced cavitation. Our first method involves the use of a dual-frequency transducer [20]. The second method involves the MBs adhering to the surface of finely positioned PCL microfibers as they rise in solution. Using these techniques we were able to create, position, and collapse a finite number of MBs, as well as successfully illustrate live cavitation. These approaches are reproducible as well as affordable, providing more controlled and efficient techniques for cavitation studies.

2. Materials and methods

2.1. MB production

Capillary tubing with an inner diameter of 5 μm and an outer diameter of 360 μm (Molex, Lisle, IL), was used to produce the MBs. The tubing was attached to a 3 mL luer-lock syringe filled with air using a tubing adapter (Idex, Lake Forest, IL). A syringe pump (GenieTouch, Kent Scientific, Austin, TX) was used to plunge the syringe at a constant rate, allowing for the constant release of consistent sized MBs. The accuracy of all measurements were within ~2.7 μm due to the resolution of our imaging techniques. Sections 2.2 and 2.3 overview controlled cavitation via the dual-frequency method and via adhesion and resonant frequency, respectively. This orientation is followed throughout the Materials and Methods, Results, and Discussion sections.

2.2. Controlled MB positioning through a dual-frequency transducer

Fig. 1A represents the experimental setup for controlled MB positioning through the incorporation of a dual-frequency transducer. A 1.5 gallon tank filled with deionized water was used to house the existing components. This method was established through a developed study [20] which involves a point-focused, donut-shaped, (inner diameter of 14 mm and outer diameter of 30 mm, focal distance of 48 mm) ultrasound transducer with a center frequency of 1.6 MHz (ndtXducer, LLC, Northborough, MA). The transducer emitted brief ultrasound pulses to trap the MBs at the focus without collapsing them. The dual-frequency transducer is suspended in mid-solution through the attachment with a 3-axis adjustable stage (MT1, Thor Labs, Newton, New Jersey). This stage allows three-dimensional (3D) arbitrary movement of the transducers, which ultimately leads to 3D spatial control over MBs after they are trapped. PCL microfibers (Hashemi Lab, Iowa State University, Ames, IA) were placed above the capillary tubing and at the focal point of the transducer. There are three main reasons that the PCL microfibers were chosen to be used for this method. First, they have a delicate nature [21], allowing minimal disruption to the MBs and pressure field induced by the transducer upon entrapment. Second, they are used as a point of reference during the characterization of MB positioning. Lastly, these microfibers are known for their biocompatibility and potential in many future studies [22]. When not in simulation, the microfibers were preserved in ethanol to prevent infection and swelling. With the transducer focused at the level of the PCL microfibers and in line with the rising MBs, we were able to consistently trap and isolate individual MBs next to the PCL microfibers.

The central transducer induces oscillation on the MBs which ultimately leads to their collapse. The resonant frequency of a MB refers to the frequency at which it oscillates at a relative maximum amplitude [23]. When a MB oscillates with enough magnitude, it begins to fragment into smaller MBs, creating cavitation [24]. Eq. (1) represents the necessary calculation to find the resonant frequency of a MB with a known radius:

$$f_0 = 2\pi\sqrt{\frac{3\gamma P_0 + \frac{2\sigma}{R_0}}{\rho R_0^2} - \frac{2\sigma}{R_0}} \tag{1}$$

In this calculation, f_0 represents the first resonant frequency, R_0 designates the nominal bubble radius, ρ is the suspending mass density, γ denotes the gas phase polytropic constant, P_0 is the ambient pressure, and σ symbolizes the surface tension [25]. The size of the MBs generated through the capillary tubing ranged from 50 to 100 μm in diameter throughout our study. Plugging in the necessary parameters for Eq. (1), a MB with a 60 μm diameter will oscillate at a resonant frequency of ~100 kHz. We decided to use a 100 kHz transducer (diameter of 45 mm, unfocused) (Olympus, Waltham, MA) to achieve dramatic oscillation near the resonant frequency for 50–100 μm MBs. Since prior studies have shown the effectiveness of simultaneous dual-frequency functionality [20], it was ignored in this study. Our motivation is to demonstrate that a dual-frequency transducer would be effective through the combination of our positioning and cavitation results. The transducers were driven by a power amplifier (RAM-5000, Ritec, Warwick, RI). The magnified high-speed analysis was achieved by using

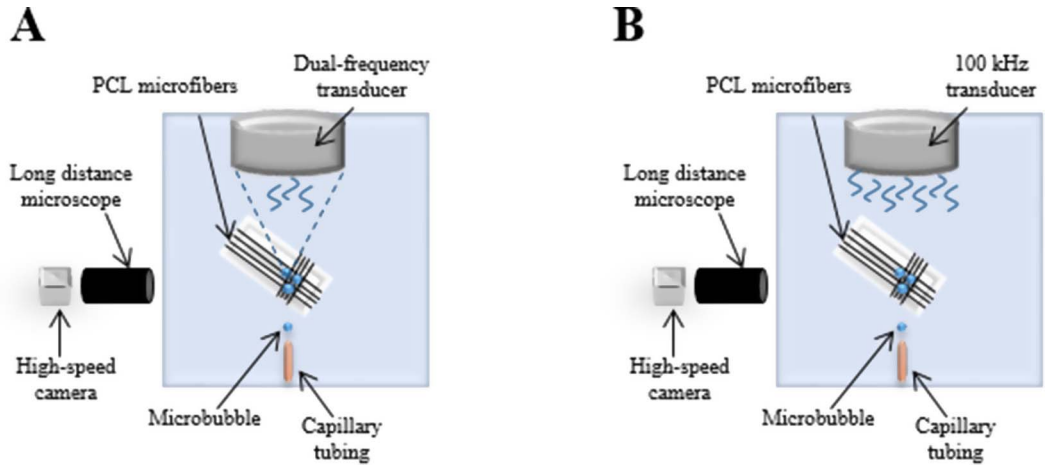

Fig. 1. (A) Apparatus for controlled MB positioning and collapse through using a dual-frequency transducer. The gap between the tip of the capillary tubing and the ultrasonic transducer was 70 mm. The gap between the PCL fibers and the ultrasonic transducer is 48 mm. The MBs are trapped at the focus of the 1.6 MHz outer-transducer (lowermost tip of the dotted lines). The 100 kHz central transducer is unfocused and is emitting sinusoidal waves. (B) Apparatus of controlled MB positioning and cavitation through adhesion and resonant frequency. The gap between the tip of the capillary tubing and the ultrasonic transducer is 70 mm. The gap between the PCL fibers and the transducer is 22.5 mm. The MBs are trapped through adhesion to the surface of the PCL microfibers.