Ultrasound Therapy: Amplitude Modulation Technique for Tissue Ablation by Acoustic Cavitation

Fares A. Mayia, Mahmoud A. Yamany, Mushabbab A. Asiri

Abstract**—**In recent years, non-invasive Focused Ultrasound (FU) has been utilized for generating bubbles (cavities) to ablate target tissue by mechanical fractionation. Intensities >10 kW/cm^2 are required to generate the inertial cavities. The generation, rapid growth, and collapse of these inertial cavities cause tissue fractionation and the process is called Histotripsy. The ability to fractionate tissue from outside the body has many clinical applications including the destruction of the tumor mass. The process of tissue fractionation leaves a void at the treated site, where all the affected tissue is liquefied to particles at sub-micron size. The liquefied tissue will eventually be absorbed by the body. Histotripsy is a promising non-invasive treatment modality. This paper presents a technique for generating inertial cavities at lower intensities (< 1 kW/cm^2). The technique (patent pending) is based on amplitude modulation (AM), whereby a low frequency signal modulates the amplitude of a higher frequency FU wave. Cavitation threshold is lower at low frequencies; the intensity required to generate cavitation in water at 10 kHz is two orders of magnitude lower than the intensity at 1 MHz. The Amplitude Modulation technique can operate in both continuous wave (CW) and pulse wave (PW) modes, and the percentage modulation (modulation index) can be varied from 0 % (thermal effect) to 100 % (cavitation effect), thus allowing a range of ablating effects from Hyperthermia to Histotripsy. Furthermore, changing the frequency of the modulating signal allows controlling the size of the generated cavities. Results from *in vitro* work demonstrate the efficacy of the new technique in fractionating soft tissue and solid calcium carbonate (Chalk) material. The technique, when combined with MR or Ultrasound imaging, will present a precise treatment modality for ablating diseased tissue without affecting the surrounding healthy tissue.

Keywords**—**Focused ultrasound therapy, Histotripsy, generation of inertial cavitation, mechanical tissue ablation.

I. Introduction

THE destructive effect of micro-bubbles (cavities) in an ultrasound field is well known and has many industrial applications, such as in ultrasonic cleaning baths. However, it was not until recently that this effect was harnessed for medical applications: destruction of the tumor mass. Initially, acoustic cavitation is to be avoided when treating tumors by HIFU (high intensity focused ultrasound), which is an extreme form of hyperthermia. This is due to the difficulty in predicting the cavitation site.

In recent years, a research group at the Biomedical Engineering Dept., University of Michigan, reported generating controlled micro-cavitation cloud by applying the shock scattering technique with micro second-long pulses administered at 100 Hz to 1000 Hz, [1]. A second competing mechanism (Boiling Histotripsy) was reported by a group from the University of Washington and Moscow State University, [2]. Boiling Histotripsy (tissue heating by shocks) is achieved by employing millisecond-long pulses at a rate of 0.5 – 1 Hz. Both techniques utilize very high ultrasound power (order of 1000's of W) and < 1% of the wave duty cycle. It is noted that both techniques require high pressure (> 75 MPa) pulsed shockwaves for the generation and implosion of cavities and a minimal pulse rate to maintain cavitation.

The work of other research groups aiming to achieve controlled cavitation using different techniques is summarized below:

Liu HL et al. [3]., demonstrated a dual frequency approach for enhancing ultrasound-induced heating by the introduction of acoustic cavitation using simultaneous sonication with low- and high-frequency ultrasound. They used two transducers: a high frequency transducer (1.155 MHz) for thermal effect and a low frequency transducer for cavitational effect at 40 kHz. They reported increased lesion size with the cavitational enhanced thermal effect. However, the use of two transducers is not desirable in a clinical environment.

Ikeda et al. [4], investigated a method to control the collapse of high intensity FU induced cloud cavitation to fragment kidney stones. They developed a two frequency wave to generate and control cavitation; 1 MHz to 4 MHz high frequency pulse to generate cloud cavitation followed by 545 kHz low frequency trailing pulse to force the cloud into collapse. Their results showed the erosion of stones is enhanced by the combined high and low frequency waves over either wave alone. They confirmed that controlled cloud cavitation has potential for the lithotripsy applications.

It is clear from the above literature review that a controlled cloud cavitation can either be generated by pulsing high frequency ultrasound at high intensities or by multiplying dual high and low frequency ultrasound fields. In all cases, very high ultrasound intensities are required and for the dual frequency techniques two transducers instead of one were needed.

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We have developed a cavitation generation technique based on modulating the amplitude of the high frequency ultrasound wave. The modulating wave is of lower frequency than the modulated wave. We called this technique “the acoustic amplitude modulation (AAM) technique”. The AAM technique is similar to that used in modulating the Radiofrequency (RF) broadcast signal (carrier) with lower frequency (audible) modulating signal, Fig. 1.

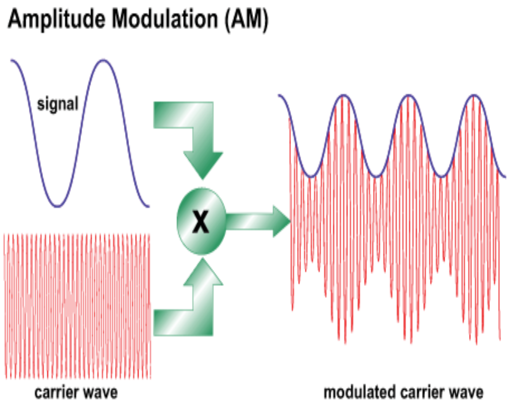


Fig. 1 Amplitude Modulation: low frequency signal modulates the amplitude of higher frequency signal (carrier)

The mechanism of generating cavities is such that the threshold of cavitation generation is lower at low frequencies [5]. Therefore, modulating the amplitude of the high frequency carrier wave by a lower frequency signal enables generating cavities at lower intensities than when the high frequency ultrasound wave is used alone. Fig. 2 shows the relationship between ultrasound intensity and threshold frequency for aerated and air-free water. In air-free water, the intensity that is required to generate cavities at 10 kHz is two orders of magnitude lower than the intensity required at 1 MHz.

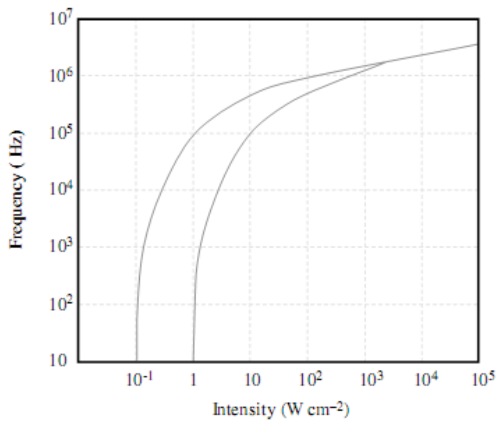


Fig. 2 Variation of intensity of sonication versus the threshold frequency: for aerated water (left-hand graph) and air-free water. Adapted from reference [5]

The AAM technique works in both continuous wave (CW) mode and pulsed wave (PW) mode. Another advantage of the AAM technique is that the percentage of modulation (modulation index) can be varied from 0 % (no modulation) to 100% (full modulation), Fig. 3, thus enabling a range of sonication effects from thermal (0 % modulation) to cavitation (100% modulation).

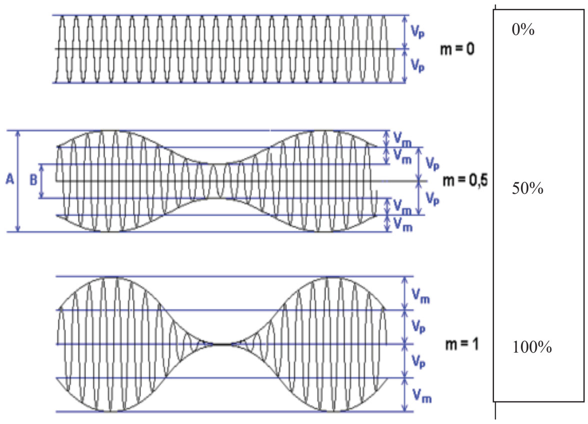


Fig. 3 Amplitude Modulation Index: 0% carrier (thermal) only, 50% (thermal and cavitational), 100% (cavitational)

An added advantage of the AAM technique is the ability to generate a range of cavity sizes. This is possible by varying the frequency of the modulating signal: lower frequencies generate larger size cavities. The AAM can be delivered in continuous (CW) mode. Working in CW mode overcomes the issue of minimal pulse rate required to maintain cavitation in PW mode, a drawback of all PW techniques.

Mechanical tissue fractionation (Histotripsy) has many clinical applications. It can fractionate the tumor mass, fragment solid objects such as kidney stones, and emulsify blood clots. The ability to generate, control and precisely position these cavities by an ultrasound beam is key to this new therapy. The ultrasound beam is generated outside the human body and aimed at the target area inside the body: guided by either B-mode ultrasound imaging or MR imaging. This makes the new treatment totally non-invasive. Unlike other forms of cancer radiotherapy or chemotherapy, ultrasound is non-ionizing radiation that does not harm the tissue in the beam path which makes it a safe treatment modality.

II. Method

A sinusoidal RF amplitude modulated signal is generated by a Function Generator (Agilent 33521A) and the signal is fed to an RF Amplifier (Electronics & Innovation, RF Power Amplifier A150). The output of the RF amplifier is fed directly to the HIFU transducer (Precision Acoustics) and the signal is displayed on an oscilloscope (Agilent DSO-X 3024A Digital Storage Oscilloscope). An ultrasound imaging scanner GE LOGIQe was used for imaging the fractionation process. The HIFU transducer operates at 1 MHz (carrier frequency) and the modulating frequency was 10 kHz. Fig. 4 shows the HIFU transducer, the ultrasound imaging probe and the video camera.

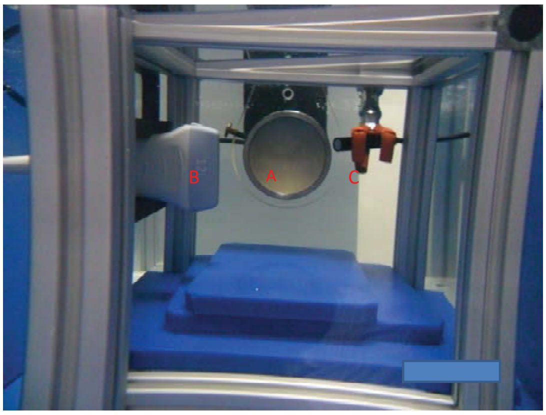


Fig. 4 Experimental setup showing, HIFU transducer (A), imaging probe (B), and video camera (C) in degassed and deionized water

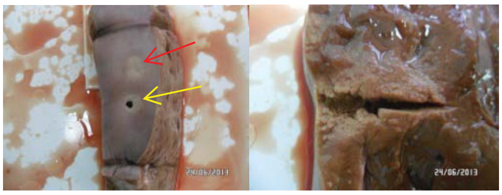
All experimental work was performed in a water tank (supplied by Precision Acoustics, Dorchester, UK). The tank was filled with deionized/degassed water at room temperature. To demonstrate the ability of the AAM technique to fractionate tissue and solid material, animal soft tissue samples (bovine liver and chicken breast) and hard material (Calcium Carbonate) chalk samples were placed at the focus of the HIFU transducer (75 mm from the transducer face). Samples were sonicated by a sinusoidal 1 MHz FU wave that is amplitude modulated by 10 kHz. At 100 W power levels, cavitation cloud can be visually observed at the focus of the high intensity ultrasound transducer by the video camera and also by the B-mode ultrasound imager. The effect of cavitation implosion generates a micro jetting force at the liquid/material interface resulting in tissue fractionation to sub-micron level. A video camera is used to record this effect on the surface of the material and an ultrasound imaging scanner records the effect inside the tissue samples.

An experiment was set up to determine the inertial cavitation threshold. A needle thermocouple was inserted in the chicken breast at 0.5 mm beneath the surface of the tissue sample at right angle to the direction of the HIFU beam. The tissue/thermocouple assembly was placed at the focus of the HIFU transducer. The power to the transducer was increased from zero to 130 W and the temperature of the tissue was recorded at power intervals by a Fluke meter (digital thermocouple thermometer 50 series II).

Soft tissue fractionation was demonstrated in *in vitro* animal samples: chicken breast and bovine liver. The bovine liver samples were degassed by vacuum in deionized/degassed water to remove air pockets. Solid material samples were calcium carbonate (chalk) in standard cylindrical shape 8x14 mm.

III. Results

The amplitude modulation technique was operated in CW mode to fractionate the animal tissue samples *in vitro*. Bovine liver and chicken breast samples were sonicated at 100 W (RF power). Cavitation occurred at the focal volume, 75 mm from the face of the transducer. Fig. 5 shows surface void created by histotripsy (A, yellow arrow) and longitudinal section of the fractionated liver (B). The modulation index (% modulation) can be varied from 0 % (no modulation, full thermal effect), red arrow in Fig. 5 (A) to 100 % modulation for cavitation generation with minimal thermal effect, Fig. 5 (A), yellow arrow. The void (yellow arrow) is created by the implosion of the inertial cavities.



(A) (B)

Fig. 5 (A) fractionated (surface void, yellow arrow) in bovine liver and (B) longitudinal section showing depth of the void. Also shown in (A) thermal effect (red arrow)

The threshold of generation of inertial cavitation was determined by monitoring the heating effect of HIFU sonication in soft tissue. The experimental set up is explained in the method section II. The sonication power of the HIFU transducer was gradually increased from zero to 130 W while monitoring the temperature rise of the chicken breast tissue by a needle thermocouple. Fig. 6 shows initial increase of tissue temperature with increasing the HIFU power from zero to 50 W. The temperature increased from 26 °C (room temperature, zero HIFU power) and peaked at 70 °C at 50 W HIFU power. As the HIFU power is increased further from 50 W to 60 W, tissue temperature dropped significantly (57 %) from 70 °C to 40 °C. Cavitation cloud was seen on the surface of the tissue at this power level. Further increase in power caused less temperature decrease to level around 35 °C. Series 1 and 2 data were from repeating the experiment two times.

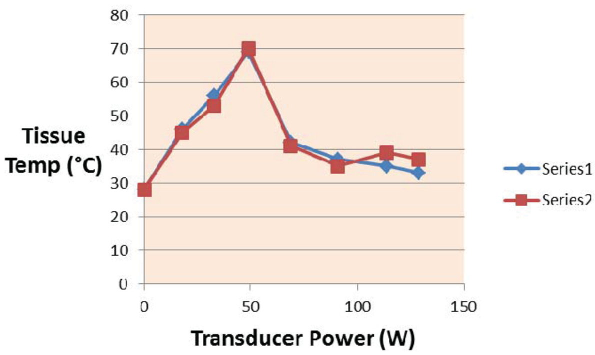
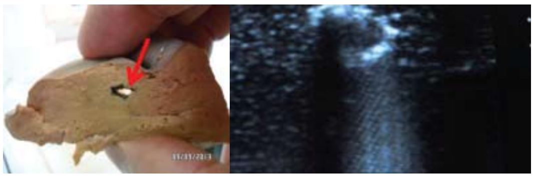


Fig. 6 Cavitation threshold: the relationship between transducer power and tissue heating/cavitation effect

To demonstrate the ability to generate various void sizes, the modulating signal was varied from 10 kHz to 100 kHz and this has resulted in the various void sizes in chicken breast shown in Fig. 7. Higher modulating frequencies produced smaller void diameter.

Fig. 7 Various void sizes in chicken breast created by varying the frequency of the modulating signal: higher frequencies generated smaller void diameters

Tissue fractionation inside liver sample is shown in Fig. 8. In figure 8 (A), a section through the fractionated tissue clearly shows a void (red arrow), and in (B) the void as seen on a B-mode ultrasound image. Cavities appear bright in the B-mode image making it easy to demarcate the boundaries of the fractionated tissue. The void created by the fractionated tissue appears dark (hypoechoic) in the B-mode image as it is filled with water.



(A) (B)

Fig. 8 (A) Bovine liver section showing void remaining after fractionated tissue (arrow). (B) The image of the void on a B-mode ultrasound scanner

For the experiment involving solid material (chalk), the chalk sample was placed at the focal point of the HIFU transducer and sonicated at 70 W (RF power). The result is shown in Fig. 9. Fragmentation by cavitational effect has created a hole (red arrow), and other holes of different shapes and sizes can also be created as seen in Fig. 9. The chalk material was fragmented to a powder like material. This method is potential for fragmenting kidney stones.

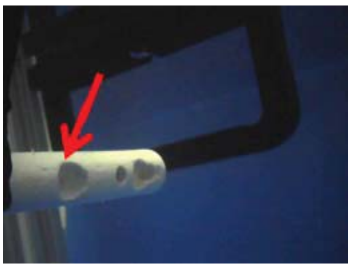


Fig. 9 Fragmentation of solid material (chalk)

IV. Discussion and Conclusion

The rapid growth and implosion of cavities in an ultrasound field in aqueous solution generates micro-jetting which is capable of fragmenting biological soft tissue and some hard material such as chalk. Data from the literature [5] indicates that the cavitation threshold is lower in low frequency ultrasound fields. In the current work, lower cavitation threshold was achieved by oscillating the amplitude of a high frequency (1 MHz) ultrasound wave by a lower frequency (10 kHz) modulating wave. According to published data [5] the cavitation threshold is two orders of magnitude lower in 10 kHz field compared to 1 MHz field.

In the current work a sinusoidal high frequency (1 MHz), high intensity, FU field was modulated by a lower 10 kHz frequency signal. At cavitation threshold power levels, stable (non-inertial) cavitation appeared to be confined to the focal volume region where intensity is highest. These cavities will be forced to oscillate due to the applied acoustic field. If the acoustic power is sufficiently high, the cavities will first grow in size and then collapse releasing large amount of energy.

The relationship between the acoustic power and tissue heating is demonstrated in Fig. 6: as the power is increased from zero to 50 W, tissue heating occurs leading to temperature rise. This is due to transfer of energy from the acoustic wave to overcome frictional forces in tissue. Further increase in power beyond 50 W caused rapid temperature drop. This is the power level at which cavitation occurs and the energy from the acoustic wave transfers to the medium to generate the cavities, hence the rapid drop in tissue temperature. The power at which cavitation occurs is the cavitation threshold level (> 50 W in Fig. 6). The generated cavities will be forced to oscillate in the acoustic wave at the range of powers from 50 W to 65 W, thus forming stable cavities, and their size will increase by a process called rectified diffusion. Further increase in power above 65 W leads to the cavities growing rapidly in size over few cycles of the wave followed by rapid implosion, the unstable inertial cavities. In the range of energies above 65 W, the process of generating, growing, and implosion of the inertial cavities is maintained. This implies that most of the energy in the wave is taken by the inertial cavities, and that less energy is available to heat the tissue. Hence the tissue temperature is leveling at around 35 °C, Fig. 6.

The Acoustic Amplitude Modulation (AAM) technique presents a potential method for generating controlled cavities at acoustic intensities at least an order of magnitude lower than other methods that are based on shock waves. High power techniques risk tissue thermal injury in the ultrasound beam path. In the AAM technique, further control of the thermal effect can be achieved by increasing the percentage of modulation (modulation index), Fig. 3. This allows flexibility in choosing between thermal ablation (low index, heating) and mechanical ablation (high index, cavitation). An added advantage of the AAM technique is the ability to generate cavities of different sizes by varying the frequency of the modulating signal: higher frequencies generate smaller cavities leading to smaller voids diameter, Fig. 7.

Tissue fragmentation by acoustic cavitation has many applications in medical therapy, this includes: destruction of the tumor mass, removal of blood clot, and fragmentation of kidney stones. The AAM technique has potentials in removing unwanted tissue non-invasively; thus providing a new treatment modality without surgical intervention.

V. Future Work

Further work is needed to test the AAM cavitation technique in life animal model. This will provide evidence of *in vivo* tissue fractionation. Based on this evidence, the AAM technique can be tested on patients in clinical trials.

It is envisaged that a totally non-invasive clinical device that can fractionate diseased tissue and fragment solid objects can be accomplished by this AAM technique.

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