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# Tissue Ablation Using Multi-frequency Focused Ultrasound

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***Abstract*-In this study, experiments and simulations on tissue ablation were performed to investigate the effectiveness of multi-frequency focused ultrasound (FUS) with frequency differences more than 500 kHz (950 kHz, 1.5 MHz and 3.3 MHz FUS). In tissue ablation tests, temperature rise was recorded when chicken breast tissue was ablated by FUS with single-frequency and multi-frequency ultrasound, respectively, at controlled acoustic power and exposure time. Simulations have been performed to verify the temperature change and distribution in these tests. Distinct temperature rise differences were observed between single-frequency modes and dual-frequency modes, indicating that dual-frequency FUS is more effective on the rate of temperature rise. This finding is promising for ultrasound surgery.**

***Keywords*: HIFU, multi-frequency ultrasound, tissue ablation, focused ultrasound**

## I. INTRODUCTION

Scientific studies involving high-intensity focused ultrasound (HIFU) as a possible therapy option for several types of tumors have been published for about half a century. Ultrasound has the potential to provide a truly non-invasive target treatment option, which is not limited to the direct treatment of cancers, but may also be used in palliative setting for relief of chronic pain of malignant origin, for hemostasis, or even for the treatment of cardiac conduction or congenital anomalies [1].

In tissue ablation, HIFU causes tissue damage through two primary mechanisms. The first is considered to be thermal effects. Intense acoustic energy is delivered to a small region of tissue, where the absorption process raises the tissue temperature to a relatively high value and causes thermal coagulation and ablation of cells [2]. The second is through cavitation. Ultrasound can cause tissue vibration, resulting in compression and rarefaction at the molecular level. During rarefaction, gas can be drawn out of solution to form bubbles. When these bubbles collapse, it is accompanied by the release of a high concentration of energy which results in high local acoustic pressure and the propagation of shock waves. These manifest as high temperature within the insonated tissue. When the tissue temperature rises to over 60 ºC for 1 second, rapid thermal toxicity is introduced, causing irreversible cell death through coagulative necrosis. Hence, a tissue lesion is formed. Although there are still many on-going discussions on other possible HIFU ablation mechanisms, the broadly accepted tissue ablation theory is that biologic effects of FUS on the targeted tumor are the combination of both thermal effects and cavitation, and the main mechanism of damage is heat necrosis [1, 3].

Despite the success of HIFU for many tumor ablations, unwanted lesion volume has hindered the full realization of the benefits of FUS as a therapy option. In order to obtain tissue ablation with steeper temperature rise and enlarged lesion volume, dual-frequency FUS has been studied in recent years by a few groups [4-6]. The dual-frequency experiments were carried out by simultaneously irradiating porcine liver regions of interest with confocal ultrasound transducers at 1.563 MHz and 1.573 MHz [4]. It was found that dual-frequency FUS induces larger lesions than conventional single frequency FUS under the same power density. It was believed that the cavitation effect is more pronounced in the multi-frequency mode, which was well presented in the work done by Tatake et al [7]. Another possible explanation offered by Iernetti et al is the production of larger number of air bubbles by the introduction of the low-frequency (20 kHz) stimulating field, which aids in the cavitation effect [8]. Carpendo et al correlated the effect of dual-frequency excitation and the increase in heating effects to the combination resonance of the two ultrasonic fields [9]. It is noticed that these reported dual-frequency ablation experiments either used dual frequency with the lower frequency transducer in the 10-500 kHz range, or with the frequency difference less than 50 kHz.

In this paper, tissue ablation using multi-frequency FUS with frequency differences greater than 500 kHz was studied to investigate the effects of different governing parameters on the temperature rise during controlled therapeutic insonation. These parameters include the transmission frequency and the acoustic power exposure.

## II. Experimental Design

### A. Temperature rise simulation

The simulations of the intensity field of transducers are done in Field II program, and temperature rise is calculated using inhomogeneous Pennes equation of heat conduction [10, 11]

$$\frac{\partial T}{\partial t} = k\Delta(T) - \frac{T - T_0}{\tau} + \frac{q_v}{c_v} \tag{1}$$

Here T is the tissue temperature, $T_0$ is the room temperature, $c_v$ is the heat capacity of a unit volume, k is the thermal diffusivity [10, 12], Δ is the Laplacian, τ is the characteristic time of the latter process which is not considered and will go infinite in this simulation with chicken breast tissue. So this equation is rewritten as

$$\frac{\partial T}{\partial t} = k\Delta(T) + \frac{q_v}{c_v} \tag{2}$$

where $q_v$ describes the field of thermal sources generated by the absorption of an ultrasonic wave and comes from the following equation

$$q_v = 2\sum \alpha(f_n) I_n \tag{3}$$

$I_n$ presents the intensity field of each transducer, and $\alpha(f_n)$ is the absorption coefficient under certain frequency. By solving this bio-heat equation with the calculated acoustic intensity field, tissue temperature rise versus exposure time can be obtained.

### B. Ablation experiments setup

Packaged frozen chicken breast tissue was brought to room temperature by leaving it in open air for about 30 minutes before being used for experiments. The tissue was cut to obtain a clean flat surface, and then mounted in a cylindrical PVC end cap with the diameter of 1.5 inches. The tissue was fixed in this position using needles. The schematic setup is shown in Fig. 1. HIFU transducers with significantly different center frequencies were mounted using a specially designed fixture such that the angle between their acoustic axes is 90º. The two transducers were held such that their axes were lying in the same horizontal plane, and their focal points were overlapped.

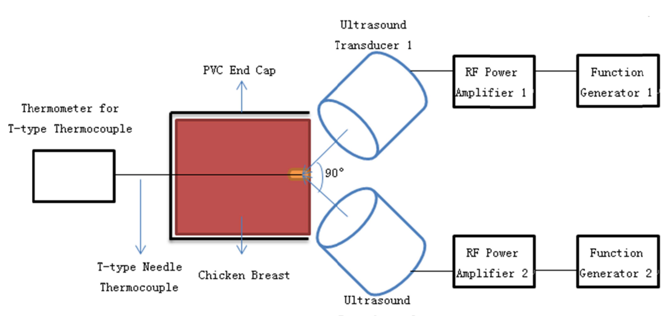


Fig. 1, Schematic diagram of dual-frequency tissue ablation test setup

### C. HIFU Transducers

Three transducers produced by Blatek (State College, PA) were used in experiments. The center frequencies of these FUS are 950 kHz, 1.5 MHz and 3.3 MHz, respectively. The aperture parameters and focal length of these transducers are given in Table. 1. Fig. 2 describes the schematic geometry of the focal zone. Output acoustic power of each transducer was measured under different input electrical power using an acoustic power radiation balance (Ohmic Instruments, UPM-DT-1AV).

For tissue ablation experiments, each transducer was driven by an amplified sinusoidal wave signal from a function generator (SRS PS355 and Tektronix AFG3101). The signals were amplified by RF power amplifiers (EN AP400B and EN 3100L). The input signal was set to match the resonance frequency of each corresponding transducer. The amplitude was then selected to adjust the output acoustic power designed for these experiments.

### D. Temperature measurement

An Omega HYP0 needle thermocouple probe with diameter of 0.2 mm was positioned inside tissue at the transducer focal point to measure temperature rise. Needle thermocouple was chosen to minimize acoustic field interference in tissue. This T-type (Copper-Constantan) thermocouple probe is enclosed in a 25-mm-long hypodermic needle. It has a fast response with a continuous temperature rating of 200 ºC. A digital temperature controller (Sestos P1S-2R-220) was used to temperature rise data acquisition.

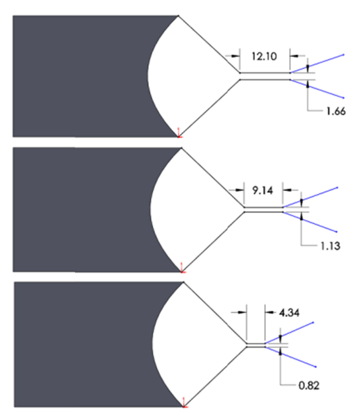


Fig. 2, Schematic of -6dB focal beam length and diameter (units of mm) of ultrasound transducers: 950 kHz transducer (top), 1.5 MHz transducer (middle) and 3.3 MHz transducer (bottom)

Table 1, Ultrasound transducers used in tissue ablation experiments.

| Center Frequency | Aperture Diameter | Focal Length |
|---|---|---|
| 950 kHz | 29.5 mm | 28 mm |
| 1.5 MHz | 29.5 mm | 30 mm |
| 3.3 MHz | 29.5 mm | 30 mm |

### *E. Tissue ablation*

Tissue samples were exposed to single-frequency ablation and dual-frequency ablation for the same period of time, e.g. up to 45 seconds. Temperature data was recorded at an interval of three seconds during each ablation. The total input electrical power of 10-20 W was introduced for both single-frequency and multi-frequency modes to compare the rise in temperature. Each test was conducted twice to obtain the average value of the temperature rise.

## III. RESULTS AND DISCUSSION

### *A. Temperature rise simulation*

By solving this bio-heat equation with the calculated intensity field, temperature rise at the focal point versus exposure time for ablation using the 950 KHz transducer and 1.5 MHz transducer is shown in Fig. 3.

The results can be explained by he following equation

$$\mathrm{T} = \frac{q_v t}{c_v} \frac{1 - e^{-t/\tau}}{t/\tau} \tag{4}$$

which is an approximate solution of bio-heat equation suitable for simple analytic study by assuming that all tissue properties are spatially uniform, constant in time, and unchanged by the thermal treatment as explained by Mast et al [4]. Here, the quotient $(1 - e^{-t/\tau})/(t/\tau)$ reduces to unity for $t/\tau \to 0$. At any certain time, the temperature rise is approximately directly proportional to $q_v$, so it also has a linear relation to the acoustic intensity. The acoustic intensity is determined by the input power to the ultrasound transducer. As can be seen, due to the simulation results with inhomogeneous assumption of acoustic waves, temperature rise has an approximately linear relation to the incident acoustic power at a given time under both single and dual-frequency ultrasound exposures.

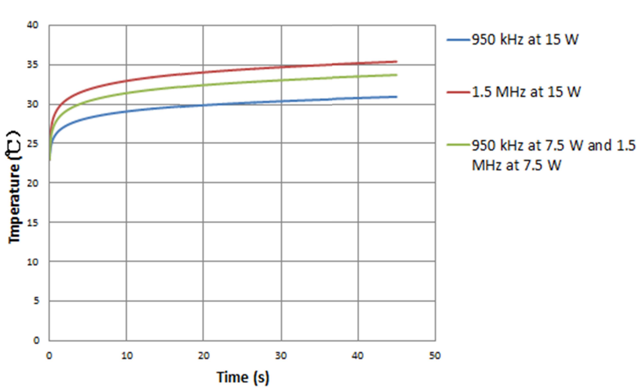


Fig. 3, Temperature simulations for single frequency and multifrequency with 950 kHz and 1.5 MHz transducers under 15 W total input power during ultrasound exposure

### *B. Experimental results*

Temperature rise vs. time of tissue ablation using single frequency and dual frequency modes with total power of 15 W are shown in Fig. 4, 5 and 6. The average of the two single-frequency tests is also plotted against the exposure time. The total input power is kept constant for all measurements. For example, Fig. 4 plots the case when the total input power is maintained at 15 W. Thus, either transducer is given an input power of 15 W for single-frequency tests, or each is given 7.5 W in the dual-frequency mode. Fig. 5 and Fig.6 are the graphs for the cases with different groups of transducers. For all the above measurements, the depth of focus (DOF) was maintained at 5mm below the tissue surface. As can be seen, higher

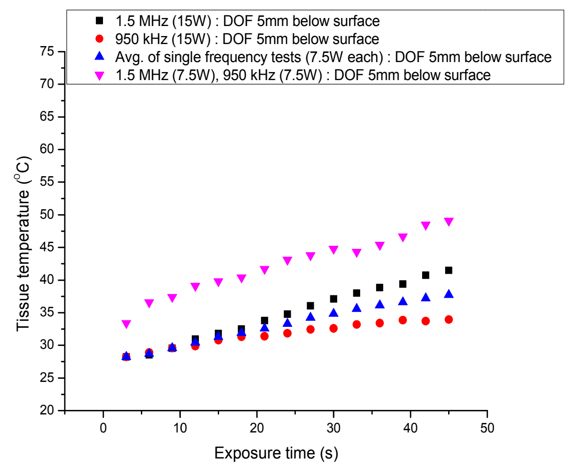


Fig. 4, Measured change in chicken tissue temperature with exposure time for single frequency and multifrequency (950 kHz and 1.5 MHz) tests under 15 W total input power, and 5 mm DOF

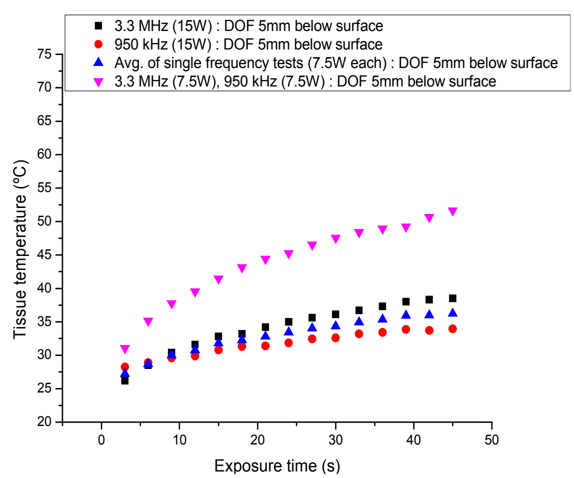


Fig. 5. Measured change in chicken tissue temperature with exposure time for single frequency and multifrequency (950 kHz and 3.3 MHz) tests under 15 W total input power, and 5 mm DOF

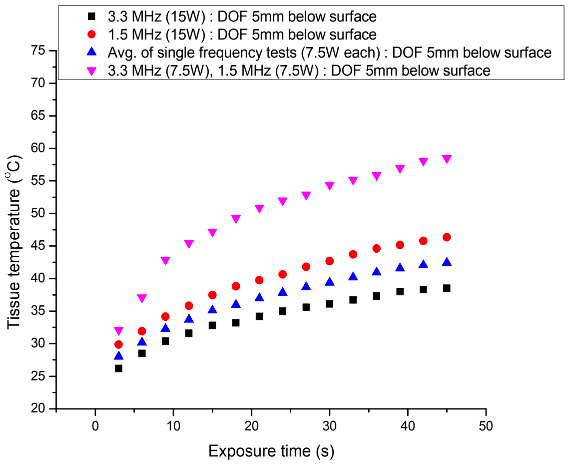


Fig. 6. Measured change in chicken tissue temperature with exposure time for single frequency and multifrequency (1.5 MHz and 3.3 MHz) tests under 15 W total input power, and 5 mm DOF

temperature and faster temperature rise can be obtained by using a dual-frequency mode.

Similar to the previous observation from multifrequency ablation using different frequencies and tissue materials [4], dual-frequency ultrasound can generate higher temperatures under the same exposure condition may be attributed to the cavitation yield at different frequencies, even when frequency difference is greater than 500 kHz. The frequency differences in multi-frequency mode may result in a low-frequency homogeneous acoustic wave, which will enhance the cavitaion effect, according to Iernetti and Feng [13,14]. A combination of two different frequencies may even result in the formation of constructive and destructive interference patterns that composed of waves with a wide range of different frequencies and pressure amplitudes. Cavitation is a random frequency dependent phenomenon, and thus the generation of waves of width different frequencies increases the chance of more efficient energy dissipation during cavitation.

## IV. Conclusion

Tissue ablation using multi-frequency FUS can generate higher temperature rise and larger lesion volume when compared with ablation using single frequency under the same exposure condition, which will lead to a more effective FUS ablation approach. Furthermore, the multi-frequency ultrasound ablation using FUS with a larger frequency difference may lead to promising imaging guided therapy using one multi-frequency probe.

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