Feasibility Study of Noninvasive Tumor Treatment with Focused Ultrasound

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Abstract

This paper describes the design, construction, and evaluation of a three-dimensional (3D) ultrasound system to be used for tumor treatment using high-intensity focused ultrasound (HIFU). The system consists of two parts: an ultrasonic therapy part and a treatment planning part. The ultrasonic therapy part consists of an ultrasound bowl-shaped transducer made from lead zirconate titanate (PZT) and with a resonance frequency of 0.5 MHz. Electrical LC matching circuit built for maximum electrical power delivery to the transducer, a function generator, and a power amplifier. The ultrasonic therapy part is designed for generating a focus with high acoustical powers. The treatment planning part consists of three stepper motors (responsible for moving the setup in the x- y- and z-directions), three high-voltage high-current Darlington arrays (to supply the stepper motors with the required voltages and currents), and C# software to perform the treatment planning. To assess the movement of the treatment planner, each of the three stepper motors was moved forward and backward from end to end. Then the treatment planner was successfully driven to cover cubes of dimensions of 1 × 1 × 1 cm³, 2 × 2 × 2 cm³, 4 × 4 × 4 cm³, and 8 × 8 × 8 cm³, with step sizes 0.5 mm, 1 mm, 2 mm, and 4 mm, respectively. Ex vivo experiments were performed and indicated the capability of the system to generate lesions both on- and off-axis. Three different lesions, one on-axis and two off-axis, were successfully generated.

Keywords: Geometrically focused transducer, High-intensity focused ultrasound (HIFU), Lesion, Sonication, Treatment planning

1. Introduction

Cancer is a disease that can affect people of all ages, although the risk of having cancer increases with age. Cancer is responsible for more than 13% of all human deaths. According to the American Cancer Society, in the year 2007, about 7.6 million people died as a result of cancer worldwide [1]. Different techniques for treating cancer exist, such as surgery [2], chemotherapy [3], radiotherapy [3], microwave therapy [4-7], and high-intensity focused ultrasound (HIFU) therapy [8-12]. Surgery is an invasive procedure that may result in complications during the operation and some short- and long-term side effects. Chemotherapy destroys normal tissue besides destroying cancerous tissue, and radiotherapy is a costly, inconvenient procedure that may be accompanied by acute side effects (such as fatigue and skin reactions) and late complications (including cosmetic ones) [13]. Both microwave and HIFU therapies are noninvasive procedures that generate a focus at a pre-specified location determined by the operator, which results in killing all the cells at that location by raising their temperature above 60°C. However, with microwave, either a small penetration depth is achieved (at high frequencies) or less ability to generate a significant focus (at low frequencies) [14]. As a result, HIFU represents a good choice that can non-invasively target different kinds of tumors.

In the past two decades, HIFU has been receiving more attention by different research groups and companies as a non-invasive procedure to treat cancers in different organs, such as kidney [15-17], liver [15,18], brain [19,20], prostate [21], and breast [8-12]. Previous examples of HIFU devices that were designed specifically to treat breast cancer include a single-element spherical transducer with a focal distance of 6.8 cm and a frequency of 1 MHz, which was successfully used to treat breast cancer in sheep [8]. Another example is a 12-cm-diameter array (1~1.5 MHz) that used a mechanical system to move the array and was capable of generating lesions ex vivo [22]. Many HIFU devices have been tested with the guidance of magnetic resonance imaging (MRI) [8,9,23-25].
These HIFU devices either were unable to cover the whole cancerous volume due to limitations on the steering angle and the maximum depth of penetration (DOP), or used manual movements of single-element ultrasound transducers which resulted in inaccurate movements.

The purpose of this study was to build a complete and accurate ultrasound system for the treatment of different tumors without the use of any manual movement of the ultrasound transducer.

2. Materials and methods

The block diagram of overall system proposed herein is shown in Fig. 1. The system consists of two parts, ultrasonic therapy and treatment planning. The ultrasonic therapy part consists of a single-element, geometrically focused ultrasound transducer that is driven by a function generator and a power amplifier and connects to a personal computer (PC). The treatment planning part includes three stepper motors, three Darlington arrays which connect to the PC through its parallel port, and a computer program (C#) to perform the planning.

2.1 Ultrasonic therapy part

2.1.1 Ultrasound transducer simulations

For a geometrically focused ultrasound transducer, the f-number is defined as the ratio of the focal distance to the aperture diameter. Since the geometrically focused ultrasound transducer used in this study has a diameter of 10 cm and a geometric focus (focal distance) of 10 cm, its f-number equals 1.

The pressure and intensity beam profiles of a single-element, geometrically focused ultrasound transducer were simulated using Huygen’s principle [26], which evaluates the overall generated pressure \( P(r, \theta) \) or intensity \( I(r, \theta) \) at a certain point in the medium (see Fig. 2) by dividing the ultrasound transducer into small point sources (known as simple sources) then adding the contributions of these sources to calculate the overall pressure or intensity. Matlab (MathWorks, Inc., USA) simulations were used to calculate both pressure and intensity distributions. Figure 3(a) shows the normalized intensity distribution calculated at an x-z plane \((y = 0)\); a focal point at \((x, y, z) = (0, 0, 10)\) cm is observed.
Using the simulated intensity field, the temperature distribution was calculated using the Pennes bioheat transfer equation (BHTE) [27]:

$$\rho C_v \frac{\partial T}{\partial t} = K \left( \frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} \right) - wC_b(T - T_a) + q(x, y, z)$$

where $C_v$ is the specific heat of the tissue (3770 J·kg⁻¹·ºC⁻¹), $K$ is the thermal conductivity (0.5 W·m⁻¹·ºC⁻¹), $T$ is the temperature at time $t$ at the point $x, y, z$ in ºC, $T_a$ is the arterial blood temperature (37ºC), $w$ is the perfusion in the tissue (5 kg·m⁻³·s⁻¹), $C_b$ is the specific heat of the blood (3770 J·kg⁻¹·ºC⁻¹), and $q(x, y, z)$ is the power deposited at the point $x, y, z$ [28]. The power was calculated from the intensity field distribution of the ultrasound transducer, while the BHTE was solved using a numerical finite difference method with the boundary condition temperatures set at 37ºC. Figure 3(b) shows the temperature distribution generated by the intensity waveform shown in Fig. 3(a). The temperature rise at the focal point was found to be around 60ºC, while outside the focus it was below 40ºC (safe).

2.1.2 Ultrasound transducer construction

Several parameters govern the selection of the ultrasound transducer to be used for HIFU, such as material type, geometry, and resonance frequency. The choice of the transducer’s material is crucial, since it has a direct impact on both the electrical and acoustical properties of the transducer. Among the different PZT (lead zirconate titanate) materials available in the market, PZT 8 and PZT 4 are the best candidates that can handle the high driving electrical powers needed for HIFU. PZT 8 has a low loss factor and a high quality factor compared to PZT 4. As a result, PZT 8 was chosen as the material for the transducer. Based on the simulation results mentioned earlier, a geometrically focused ultrasound transducer with a resonance frequency of 0.5 MHz was chosen in order to allow deep penetration of ultrasound wave to tissue since the DOP is inversely proportional to the resonance frequency. The geometric focus of the transducer was chosen to be 10 cm to allow the treatment of deep cancerous tissue.

The electrical impedance of the PZT-8 material alone was measured to be 1.3 kΩ ± 25º. This high impedance requires using a low-capacitance coaxial cable in order to have both the cable electrical impedance and the PZT-8 electrical impedance in the same range. A two-meter coaxial cable with a characteristic impedance of 75 Ω was found to be suitable. The soldering between the coaxial cable and the geometrically focused ultrasound transducer used a low-temperature soldering material (Indalloy #1E, Indium Corporation of America, USA) to ensure that the temperature during soldering did not exceed the curie temperature for the PZT-8 material, which is about 310ºC. Figure 4 shows the soldered transducer, as well as its housing.

2.1.3 Ultrasound driving source

Since the geometrically focused ultrasound transducer has a resonance frequency of 0.5 MHz, a sinusoidal signal generated from a function generator at this frequency was used. The sinusoidal signal was then fed into a 25-W power amplifier

Figure 4. The coaxial cable soldered on the transducer (a) and the transducer’s housing (b).

(Model 25A250, Amplifier Research, USA) to produce the high power required for HIFU treatments. Usually, in normal blood perfusion rates, a power of 6 W is enough to raise up the temperature at the focal point to 60ºC if the sonication time is set to 2 seconds.

2.1.4 Electrical matching circuit

The electrical impedance of the transducer, along with the coaxial cable connected to it, was measured to be 46.32 + j 13.07 Ω. Since this value is far from the optimal value of 50 + j 0 Ω, which is required for maximum power delivery to the load, an LC matching circuit with $L = 0.21 \, \mu H$ and $C = 1.88 \, nF$ was designed and built, as shown in Fig. 5.

![Image](image.png)

Figure 5. Transducer’s matching circuit.

2.2 Treatment planning part

The treatment planning part consists mainly of a three-dimensional (3D) translating system that consists of three stepper motors, named X, Y, and Z, and three Darlington arrays that connect to the PC through the parallel port, which is divided into three sub-ports: data, control, and status.

Two six-wire stepper motors (X and Z) and one eight-wire stepper motor (Y) were used to move the ultrasound transducer. Since the Y stepper motor is responsible for moving the whole setup, it was chosen to be larger to be able to generate the required torque. All the three stepper motors rotate with a step angle of 1.8º; thus one revolution (about 1 mm horizontal distance) needs 360/1.8 = 200 steps to be completed. Thus the distance resolution (minimum horizontal distance any of the three stepper motors can move) is 1 mm/200 = 5 µm.

Three high-voltage high-current Darlington arrays (ULN2003A, Allegro MicroSystems, Inc., USA) were used because of their ability to provide the stepper motors with high voltages (up to 50 V) and high currents (up to 500 mA). Each
Darlington array was driven with a 5 V transistor-transistor-logic (TTL) signal. The three Darlington arrays were connected to the X, Y, and Z motors from one side and to the PC through its parallel port interface from the other side. Figure 6 shows a front view of the built translating system.

Figure 6. Front view of the translating system.

C# code was written to move any of the three stepper motors either forward or backward. After each movement, a command instructs the moved stepper motor to stop for a pre-determined period of time, which represents the time delay required to cool down the tissue that lies in front of the transducer after each sonication.

A treatment planning starts by defining a cubic volume that contains the cancerous volume inside. A computer program is written to perform the treatment planning, which starts by ablating a single cigar-shaped volume with a single sonication of 2 seconds using a driving signal of 6 W electrical power, then turning the transducer off for 10 seconds to cool down the volume the lies between the transducer and the focal point. The transducer is then moved to a nearby location and the on and off times are applied again. This process is repeated until the whole cancerous volume is ablated. It is important to mention here that the ablation starts with the most distal tissue first then moving progressively to the most proximal; this is because the acoustical properties of tissue are changed by lesioning. Figure 7 shows a treatment planning for ablating a cubic volume using movements in the x, y, and z directions. Furthermore, although the transducer’s movement covers a 3D cubic volume, it is turned only when the center of the focal point lies inside the tumor; in other words, some of the cigar-shapes inside the cube are ablated (transducer is on) and some are not (transducer is off).

2.3 Exposimetry

To measure the acoustic intensity generated by the ultrasound transducer, a 0.5-mm diameter needle hydrophone (Precision Acoustics, UK) was used. Both submerged in water, the hydrophone and the ultrasound transducer were placed such that the tip of the hydrophone needle was placed and fixed, at the location of the geometric focus of the ultrasound transducer (i.e., coordinates x, y, z = 0, 0, 10 cm). The ultrasound transducer was then moved to cover cubes of dimensions 1 × 1 × 1 cm³, 2 × 2 × 2 cm³, 4 × 4 × 4 cm³, and 8 × 8 × 8 cm³, with step movements of 0.5 mm, 1 mm, 2 mm, and 4 mm, respectively. For each movement of the ultrasound transducer, the fixed hydrophone recorded the generated voltage, and thus intensity, at that position. For each cubic volume, fifteen exposimetry experiments were performed. The exposimetry system was controlled using a laptop connected to the treatment planner via the RS232 serial port. The fixed hydrophone was connected to a digital oscilloscope (Agilent DSO3062A, Agilent Technologies, USA) via the general purpose interface bus (GPIB) to record voltages at the required locations. From the recorded voltages, pressures were calculated and used to calculate the normalized intensities as the mean and standard deviation of the results (mean ± s.d.) and compared against the simulated values.

2.4 Ex vivo experiments

To ensure the capability of the system to generate on- and off-axis lesions ex vivo, a fresh bovine liver (thickness about 4 cm) was obtained and submerged in a 40 × 40 × 60 cm³ water tank. The bovine liver was placed such that its proximal surface was 6 cm away from the transducer and its distal surface was about 10 cm away from the transducer. The coordinate (0, 0, 0) was set at the center of the ultrasound transducer. The transducer was aimed at a point that lay exactly on the distal liver’s surface (to have a visible lesion), then turned on for 2 seconds. The transducer was then moved off-axis to the locations (1, 1, 10) cm and (-1, -1, 10) cm, and was turned on at each location for 2 seconds.

To indicate that the heating system was capable of treating different depths of tumors, fresh bovine tissue was obtained and placed in front of the ultrasound transducer. Three separate
experiments were performed to generate two, four, and ten lesions deep inside the bovine tissue. For these three experiments, the theoretical distances between any two consecutive lesions were made 1 cm, 0.5 cm, and 0.45 cm, respectively.

3. Results

The electroacoustic efficiency, which is defined as the output acoustic power divided by the input electric power, was first measured to ensure that the therapeutic ultrasound transducer was capable of delivering enough power to the tissue. The radiation force technique [29] was used to measure the electroacoustic efficiency, which was found to be 52%. This efficiency can be increased by adding a matching layer to the design.

The movement of the 3D translating system was tested first by moving each of the three stepper motors forward and backward from end to end. Then, cubes of dimensions $1 \times 1 \times 1$ cm$^3$, $2 \times 2 \times 2$ cm$^3$, $4 \times 4 \times 4$ cm$^3$, and $8 \times 8 \times 8$ cm$^3$, were scanned using step sizes of 0.5 mm, 1 mm, 2 mm, and 4 mm, respectively. For a cube of dimensions $1 \times 1 \times 1$ cm$^3$ (i.e., $x_c = y_c = z_c = 1$ cm), the ultrasound transducer was moved with a step size of 0.5 mm to cover the whole volume. After each step movement of the ultrasound transducer, the fixed hydrophone recorded the voltage, and thus the intensity, generated by the ultrasound transducer. This experiment was repeated fifteen times, and the resultant intensities (mean ± s.d.) were plotted as a function of $z$ ($x = 0$, $y = 0$, $z = 9.5$ to 10.5) and as a function of $x$ ($x = -0.5$ to 0.5, $y = 0$, $z = 10$), as can be seen in Figs. 8(a) and 8(b). The same procedure was repeated for three more cubes with dimensions $2 \times 2 \times 2$ cm$^3$, $4 \times 4 \times 4$ cm$^3$, and $8 \times 8 \times 8$ cm$^3$. The step sizes of the movement of the ultrasound transducer was set to 1 mm, 2 mm, and 4 mm, respectively. Plots for the normalized intensities along the $z$ and $x$ axes are shown in Figs. 8(c) and 8(d) for the case of the $2 \times 2 \times 2$ cm$^3$ cube, in Figs. 8(e) and 8(f) for the case of the $4 \times 4 \times 4$ cm$^3$ cube, and in Figs. 8(g) and 8(h) for the case of the $8 \times 8 \times 8$ cm$^3$ cube. Figure 8 indicates the capability of the 3D translating system to cover different volumes with different step sizes.

Ex vivo experiments were performed to prove the capability of the overall system to generate lesions both on- and off-axis. Three sonifications were aimed at $(0, 0, 10)$ cm, $(1, 1, 10)$ cm, and $(-1, -1, 10)$ cm, with the time of each sonication set to 2 seconds and the time between two consecutive sonifications (off time) set to 10 seconds. The result is shown in the unmarked (Fig. 9(a)) and marked (Fig. 9(b)) versions of Fig. 9, which indicate the generation of three different lesions. The two off-axis lesions (at $(1, 1, 10)$ cm and $(-1, -1, 10)$ cm) coincide exactly at the intended locations, while the on-axis lesion $(0, 0, 10)$ cm was shifted a little bit from its intended location; which might be due to the curvature of the distant liver’s surface.
Figure 9. Three lesions (one on-axis and two off-axis) generated: (a) unmarked (b) marked.

More ex vivo experiments using bovine tissue were performed to ensure the capability of the system to generate lesions at different depths. In one experiment, the geometric focus of the ultrasound transducer was aimed at a deep location inside the bovine tissue and the transducer was turned on for 2 seconds. After a cooling period (transducer was off) of 10 seconds, the ultrasound transducer was moved such that its geometric focus was 1 cm away from the previous position, then was turned on for 2 seconds. The result, shown in Fig. 10(a), indicates the generation of two lesions inside the bovine tissue. In another experiment, four consecutive sonications were aimed at four locations deep inside the bovine tissue with the intended distance between any two consecutive lesions set to 0.5 cm. Figure 10(b) indicates the generation of four lesions as required. In a third experiment, ten locations were targeted with the separation between any two consecutive locations set to 0.45 cm. As planned, ten lesions were generated at the intended locations, as shown in Fig. 10(c). Figure 10 indicates the capability of the system to generate lesions at different depths deep inside tissue.

One more ex vivo experiment was made to observe the temperature profile inside and outside the lesion. One thermistor was placed inside the intended location of the lesion and one thermistor was placed outside the intended location of the lesion (about 1 cm away from the lesion’s intended location). To protect the thermistors from being damaged, the electrical driving power was set to 3 W rather than 6 W, while the sonication time was increased from 2 seconds to 5 seconds to compensate for the reduction in power. The temperature recordings (Fig. 11) indicate an increase in temperature inside the lesion from 37ºC to about 61ºC in 5 seconds, while the temperature outside the lesion remained around 38.5ºC.

Table 1. Lesions dimensions (length and diameter) and their deviation from the simulated locations summarized for experiments with an electrical driving power of 6 W and sonication times of 3, 6, 9, 12 and 15 seconds.

<table>
<thead>
<tr>
<th>Number of experiments</th>
<th>15</th>
<th>15</th>
<th>15</th>
<th>15</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonication time (sec)</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Electrical driving power (Watt)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Lesion length (cm)</td>
<td>1.01±0.04</td>
<td>1.47±0.07</td>
<td>2.1±0.03</td>
<td>2.71±0.06</td>
<td>3.14±0.02</td>
</tr>
<tr>
<td>Lesion diameter (cm)</td>
<td>0.35±0.09</td>
<td>0.51±0.07</td>
<td>0.69±0.12</td>
<td>0.92±0.13</td>
<td>1.22±0.07</td>
</tr>
<tr>
<td>Average deviation of lesion from intended location (mm)</td>
<td>0.1</td>
<td>0.4</td>
<td>0.3</td>
<td>0.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>
More \textit{ex vivo} experiments were performed to study the lesions’ dimensions and their deviation from the intended locations. For each of these \textit{ex vivo} experiments, the sonication time was varied in steps of 3 seconds while the driving electrical power was kept constant at 6 W. For each sonication time, fifteen \textit{ex vivo} experiments were carried out. The dimensions of the lesions and the deviation of the lesions from their simulated positions were recorded as shown in Table 1.

4. Discussion and conclusions

HIFU is gaining more attention as a noninvasive (sometimes minimally invasive, such as for the case of the prostate) approach to treating cancer in different organs such as liver, kidney, brain, prostate, and breast. Different HIFU devices have been proposed in the past to treat cancer. Some of these devices used complex and expensive arrays yet with limited steering angles and DOPs, while others used single-element transducers that needed to be moved manually (inaccurate) to generate different lesions.

The design described herein consists of an ultrasonic therapy part and a treatment planning part. The ultrasonic therapy part includes a geometrically focused ultrasound transducer (material = PZT-8 and frequency = 0.5 MHz) that was manufactured according to some simulated design parameters. An electrical impedance matching circuit was designed and built to ensure maximum electrical power delivery to the load and to prevent the loss of electrical power as a result of impedance mismatch between the source and the load. A power amplifier was also used to provide the high powers required for this kind of treatment. The treatment planning part includes two 6-wire stepper motors and one 8-wire stepper motor. Three high-voltage high-current Darlington arrays were used to provide the stepper motors with the required voltages and currents.

Exposimetry experiments were performed to ensure the capability of the system to move the ultrasound transducer to different locations with different step sizes. The ultrasound transducer was successfully moved to cover cubic volumes of dimensions $1 \times 1 \times 1 \text{ cm}^3$, $2 \times 2 \times 2 \text{ cm}^3$, $4 \times 4 \times 4 \text{ cm}^3$, and $8 \times 8 \times 8 \text{ cm}^3$, with step sizes of 0.5 mm, 1 mm, 2 mm, and 4 mm, respectively, as indicated by the results of the exposimetry experiments.

\textit{Ex vivo} experiments on bovine liver and bovine tissue were carried out to test the capability of the system to generate lesions. These experiments indicate that the system is indeed capable of generating lesions both near the surface (as for the case of the bovine liver experiments) as well as deep inside tissue (as for the case of the bovine tissue experiments). The deviation of the generated lesions from their simulated locations was recorded to be very small.

To move from this design to an actual clinical design that can be used to treat humans with HIFU, some important design issues must be taken into consideration. These issues are described below:

(1) Image guidance of the treatment can be achieved by adding an ultrasound imaging transducer to the design. The ultrasound imaging transducer can be placed in a small hole (around 1 cm in diameter) especially made at the center of the therapeutic ultrasound transducer. The ultrasound imaging transducer must be synchronized with the ultrasound therapeutic transducer; however, it should be driven separately using a negative high voltage pulse.

(2) A matching layer must be designed, built, and placed at the transmitting face of the therapeutic ultrasound transducer. The matching layer is important to eliminate the mismatch between the high acoustic impedance of the PZT-8 material (about 33 MRayl) and the low acoustic impedance of the human tissue (about 1.5 MRayl). This mismatch may result in the destruction of the PZT-8 material as a result of the ultrasound waves being reflected back and forth inside the PZT-8 material.

(3) After placing the matching layer on the transmitting face of the therapeutic ultrasound transducer, acoustic coupling between the transducer and the skin can be made in two ways: either water is used for coupling by performing the treatment inside water, or a coupling gel with an acoustic impedance of around 1.5 MRayl is used to fill the distance between the transmitting face of the transducer and the skin.

(4) Mechanical support for both the therapeutic system and the patient to be treated must be considered.

References


