Integrated Endoscope for Real-Time 3D Ultrasound Imaging and Hyperthermia: Feasibility Study

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The goal of this research is to determine the feasibility of using a single endoscopic probe for the combined purpose of real-time 3D (RT3D) ultrasound imaging of a target organ and the delivery of ultrasound therapy to facilitate the absorption of compounds for cancer treatment. Recent research in ultrasound therapy has shown that ultrasound-mediated drug delivery improves absorption of treatments for prostate, cervical and esophageal cancer. The ability to combine ultrasound hyperthermia and 3D imaging could improve visualization and targeting of cancerous tissues. In this study, numerical modeling and experimental measurements were developed to determine the feasibility of combined therapy and imaging with a 1cm diameter endoscopic RT3D probe with 504 transmitters and 252 receive channels. This device operates at 5 MHz and has a 6.3 mm x 6.3 mm aperture to produce real time 3D pyramidal scans of 60-120 degrees incorporating 64 x 64 = 4,096 image lines at 30 volumes/sec interleaved with a 3D steerable therapy beam. A finite-element mesh was constructed with over 128,000 elements in LS-DYNA to simulate the induced temperature rise from our transducer with a 3 cm deep focus in tissue. Quarter-symmetry of the transducer was used to reduce mesh size and computation time. Based on intensity values calculated in Field II using the transducer’s array geometry, a minimum $I_{\text{avg}}$ of 3.6 W/cm$^2$ is required from our endoscope probe in order to induce a temperature rise of 4°C within five minutes. Experimental measurements of the array’s power output capabilities were conducted using a PVDF hydrophone placed 3 cm away from the face of the transducer in a watertank. Using a PDA14 Signatec data acquisition board to capture full volumes of transmitted ultrasound data, it was determined that the probe can presently maintain intensity values up to 2.4 W/cm$^2$ over indefinite times for therapeutic applications combined with intermittent 3D scanning to maintain targeting. These values were acquired using 8 cycle bursts at a prf of 6 kHz. Ex vivo heating experiments of excised pork tissue yielded a maximum temperature rises of 2.3°C over 5 minutes of ultrasound exposure with an average rise of 1.8 ± 0.2°C over 5 trials. Modifications to the power supply and transducer array may enable us to reach the higher intensities required to facilitate drug delivery therapy.

Key words: 3D; endoscope; hyperthermia; imaging; ultrasound.

I. INTRODUCTION

The use of hyperthermia (HT) has been the subject of a wide variety of investigations in drug delivery. Small, sustained rises in temperature to 41-45°C for 30-60 minutes have been shown to increase cytotoxicity during radiation therapy and cancer therapy, increasing 2-year survival by more than 15% in some clinical trials. The low-level heating acts to increase radiation damage while inhibiting the ability of the target tissue to repair itself. In addition, hyperthermia is also cytotoxic, further assisting in the cancer treatment. Localized HT has been employed in studies that use thermally-responsive drug carriers for increased...
Hyperthermia treatments have also served as adjuvant therapies for the delivery of thrombolytic agents and the use of gene-based therapies. Typical methods of applying HT are through microwave, rf current and ultrasound devices.

Ultrasound has been used increasingly to generate hyperthermia for applications such as drug delivery. With the application of low level insonification, with intensities up to several watts per square centimeter, temperatures above 41°C can be achieved and sustained with relatively good spatial control over energy deposition compared with other delivery systems. The operating frequencies of ultrasound devices and the feature size of typical transducer arrays also enables diversity in fabrication shape and size for a number of different applications within drug delivery. Current research involves the development of multi-element cylindrical transducers and linear phased array devices for interstitial ultrasound hyperthermia. Such designs enable increased three-dimensional control of heating as well as higher control over penetration depth compared with rf and microwave systems.

In this paper, we explore the feasibility of a combined endoscopic real-time 3D ultrasound imaging and hyperthermia device. The dual functionality of such a device would enable the ability to visualize the volume of a target, such as a tumor, and control an HT beam in both azimuth and elevation using phased array scanning (Fig. 1). This technology could simplify implementation of radiation therapy, chemotherapy and other forms of drug delivery while improving target visualization and control of energy deposition. In particular, an endoscopic probe for 3D imaging and hyperthermia could be applicable to current research in the treatment of cancers of the cervix, prostate and esophagus. In addition, dual functionality probes could be applied to increase drug permeation across the blood-brain barrier for delivery to the central nervous system.

We have described the development of real-time 3D ultrasound probes for endoscopic and laparoscopic applications. We have also previously investigated the development of integrated catheters for real-time 3D echocardiography and ultrasound ablation. In this paper, we explore the feasibility of using a 5 MHz endoscopic imaging probe with a 504 channel matrix array for hyperthermia treatment. We have developed a finite-element model to determine the minimum intensities necessary from the probe to achieve HT temperature rises, and we describe experiments to determine the optimum energy output using
our Model 1 real-time 3D ultrasound scanner (Volumetrics Medical Imaging, Durham, NC). We also detail our efforts to achieve *ex vivo* hyperthermia using the results of our finite-element model and our scanner optimization experiments. We compare our experimental and simulated results and address some of the problems we experienced achieving hyperthermia with a 3D imaging probe. Finally, we will discuss future possible work and other implications of achieving combined real-time 3D imaging and hyperthermia.

**II. MATERIALS AND METHODS**

*3D endoscopic probe and operating-frequency selection*

The transducer employed for this study is a 504 channel matrix array probe originally designed for transesophageal echocardiography,\(^{15}\) as shown in figure 2. A 4-directional bending sheath is incorporated into the tip of the probe. This steering function also provides quick orientation adjustment in any direction. The 3D endoscopic probe operates at 5 MHz using a 6.3 mm x 6.3 mm aperture. Its outer diameter at the probe tip is 1 cm. Using the Model 1 scanner, this device can produce real-time 3D pyramidal scans of 60-120° incorporating 64 x 64 = 4,096 image lines at 30 volumes per second. Its lateral imaging resolution at 3 cm is approximately 1.7 mm. Figure 3 illustrates the endoscopic probe’s imaging capabilities. The image shows a 4 cm volumetric scan of a water-filled, *in vivo* canine esophagus. In the azimuth view, the short axis of the esophagus is visible, with layers of smooth muscle under the esophageal lining. Similarly, the long-axis view of the esophagus is visible in the elevation B-scan. The volume-rendered image is acquired by spatially integrating information bounded by the white arrows.

Although the endoscopic probe was designed for imaging at 5 MHz, tests were performed in order to determine its optimal operating frequency on the Model 1 scanner for use in hyperthermia. This experiment was necessitated by the fact that the scanner has an operating passband with a peak frequency of approximately 3.5 MHz; thus, optimal transmit efficiency may not be attainable at the probe’s design frequency of 5 MHz. For this test, a digital oscilloscope (744A, Tektronix, Wilsonville, OR) was used to capture transmit pulses from a calibrated PVDF membrane hydrophone (Model 804, Sonic Technologies, Hatboro, PA) placed in a water tank 3 cm away from the face of the transducer. Through modifications to the FPGA’s modulating transmit timing, the scanner was programmed to fire 2, 4, 8, and 12 cycle bursts in a single scan line directed at the center of the hydrophone, using a pulse repe-
tion frequency (prf) of 2 kHz. Pulses were recorded on the oscilloscope and peak-to-peak voltage was used to determine the optimal frequency for hyperthermia experiments.

**Finite-element model**

A model simulating acoustic intensity and heat production from the 3D endoscopic probe was constructed using the Field II software package (version 3.0) and the FEA program LS-DYNA3D (Livermore Software Technology Corporation, Livermore, CA). First, a three-dimensional finite element mesh, consisting of over 128,000 individual nodes, was constructed in LS-PREPOST (Livermore Software Technology Corporation, Livermore, CA) as shown in figure 4; quarter symmetry of the volume and of the array was employed in order to reduce computation time. A 3 cm water layer was used between the transducer and the tissue layer in order to simulate the path through a water-filled balloon that would normally encapsulate the ultrasound device. Then, the array design of the endoscopic probe was simulated in Field II and used to calculate normalized ultrasound intensities at the nodal coordinates provided by LS-PREPOST. The periodic transducer array pattern is shown in figure 5a. The intensity field produced by this array when focused at 3 cm is displayed in figure 5b and 5c. Under the simulated conditions, this array has an approximate half-maximum (−6 dB) beam radius of 1.5 mm at 3 cm depth. The Field II simulation for the finite element model was performed utilizing a 3 cm focal depth and a Gaussian pulse impulse response input with a 25% fractional bandwidth, as detailed by the operating parameters of the probe. The resultant normalized intensities were thresholded at 2% of the maximum and scaled to intensities ranging from 1 W/cm$^2$ to 5 W/cm$^2$ in order to simulate varying levels of output.
from the transducer. The intensity for each element in the mesh was subsequently determined from the average of the values at each of its eight nodes.

Once intensity values were acquired for all elements in the mesh, volumetric heat generation rate was calculated using the equation:

\[ q_v = 2\alpha I_{td} \]  

(1)

where \( q_v \) is the volumetric rate of heat generation (W/cm\(^3\)), \( \alpha \) is absorption (Np/cm), and \( I_{td} \) is the time-average intensity (W/cm\(^2\)). In this simulation, we assume absorption to be equal to attenuation. The absorption coefficients for the materials used in the mesh are given in table 1.
With the volumetric heat generation rates calculated for each element in the finite element mesh, the induced temperature rise was found by solving the bio-heat transfer equation:

$$\dot{q} = \frac{K}{c_v} \nabla^2 T + \frac{q_v}{c_v}$$

(2)

where $K$ is the thermal conductivity (W/cm/°C) and $c_v$ is the volumetric heat capacity (J/cm$^3$/°C). In this model, the perfusion term has been omitted to simplify calculations. The ramifications of this omission are discussed in the Discussion section. Conductivity and heat capacity values for each medium are provided in table 1. This equation was solved in LS-DYNA neglecting any perfusions effects. LS-DYNA uses a time-domain explicit solver for calculating the temperature rise. Simulations were run for 300 seconds with 2 second time steps, and full mesh data was output to a file every 60 seconds in order to obtain temperature rise contours of the mesh.

**Intensity measurements**

In order to apply the results of the finite element model to experimental hyperthermia measurements, intensity measurements were acquired from the Model 1 Scanner, varying pulse repetition frequency, transmit cycle coun, and output power to determine the maximum sustainable power output from the 3D endoscopic probe.

As before, the face of the probe was placed in a water tank 3 cm away from the PVDF membrane hydrophone. The hydrophone was connected to a 1 MΩ-to-50 Ω preamplifier (AH2020, Onda Corporation, Sunnyvale, CA) which was, in turn, connected to a PC-mounted data acquisition board (Model PDA14, Signatec, Inc., Newport Beach, CA). Using the PDA14 board to acquire pulse data at a sampling rate of 50 MHz, 10$^6$ samples were recorded for varying scanner settings, providing 20 ms of data per acquisition. The Signatec board was set to monitor this much information in order to observe any possible power reduction or inconsistencies in the probe’s output. Intensities were calculated using the average pulse intensity integral across all recorded pulses during a single acquisition.

**Ex vivo measurements**

The 3D endoscopic probe was used to image and heat porcine muscle which was excised and degassed. The probe was first stationed in a water tank. Intensity measurements were recorded using a PVDF membrane hydrophone located 3 cm away using the method described above. Then, the hydrophone was replaced with a 3 cm thick sample of pork tissue, suspended in the tank as shown in figure 6. A 0.13 mm type-T thermocouple (STC-TT-T-36-72, Omega Engineering, Inc., Stamford, CT) was fed through the thickness dimension of the tissue so as to protrude from the front boundary of the sample. Using diagnostic settings (50% power, 2 cycle transmit bursts), the pork tissue was imaged, and the thermocou-

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**TABLE 1.** Material properties for finite element simulation.

<table>
<thead>
<tr>
<th>Material</th>
<th>Tissue absorption (dB/cm/MHz)</th>
<th>Thermal Conductivity (W/cm°C)</th>
<th>Heat Capacity (J/cm$^3$/°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.0165</td>
<td>0.006</td>
<td>4.2</td>
</tr>
<tr>
<td>Pork muscle</td>
<td>0.5</td>
<td>0.005</td>
<td>3.7</td>
</tr>
</tbody>
</table>
ple tip was located using B-scan and C-scan planes. The pork tissue was reoriented so that the thermocouple was located at the center of the volumetric scan.

Once alignment was achieved, the thermocouple was pulled back so as to rest just under the surface of the tissue. The scanner was then set to transmit down the center line of the volume using scanner settings as determined by the previous intensity experiments. The thermocouple was monitored using a multimeter (2700 Integra Series with 7708 40 Channel Multiplexer, Keithley Instruments Inc., Cleveland, OH) and the ExceLINX software package. Resultant temperature rises were recorded and compared with the finite element results.

III. RESULTS

Operating frequency selection

A graph of average pulse peak-to-peak amplitude in mV for various transmit cycle counts is given in figure 7. At 50% output power, the probe emits similar amplitude acoustic pulses
when the transmit cycle count is 4 or higher. From the graph, it is apparent that the endoscopic probe(scanner output is strongest at a frequency of 4 MHz.

**Finite-element model**

As determined by the previous results, the finite element simulations were performed at 4 MHz. The results are shown graphically in figure 8. For exposures 5 minutes or greater, it was found that an $I_{sptA}$ of at least 3.6 W/cm$^2$ is necessary in order to reach a 4°C temperature rise and achieve the hyperthermia region of 41°C. A contour map of the simulated heat generation for this intensity is shown in figure 9. The main focal region of heating that reaches...
4°C is approximately 1-2 mm wide in the lateral dimension, compared with the 3 mm -6 dB beam diameter calculated from simulations. In the axial dimension, the size of the main heated region is 4-5 mm deep. This region of heating is present at approximately 3.3 cm away from the transducer face, indicating that most of the temperature rise occurs just under the surface of the tissue in this model. Near-field heating in the water layer is not observed. Based on these simulations, delivered intensities ranging from 3.6 W/cm² to 7.2 W/cm² should maintain a state of hyperthermia in the target tissue. Beyond this range, prolonged exposures could cause excessive heating above 45°C.

Intensity measurements

Measured intensities from the 3D endoscopic probe are shown in figure 10 for various transmit cycle counts while varying pulse repetition frequency. Data points indicated by circles are stable and can be maintained indefinitely. Plot points marked by black squares indicate a peak $I_{SPTA}$ measurement recorded under unstable conditions. In these situations, either significant power reduction would be observed or the scanner reverted back to diagnostic settings due to internal thermal safety interlocks. Using 50% power (Fig. 10a) on the Model
1 scanner, the probe cannot produce intensities exceeding 3 W/cm². At 100% power (Fig. 10a), using 12 cycles at 6 kHz or 8 cycles at 10 kHz, intensities greater than 3.6 W/cm² were achieved; however, these settings could not be sustained for longer than 30 s before significant decreases in power were experienced due to scanner overheating. As seen in figure 10b, maximum stable output intensity is 2.4 W/cm² at 100% power with 8 cycles and a prf of 6 kHz. Under these conditions, the 3D endoscopic probe produces acoustic pulses as shown in figure 11. These are the settings we chose for experimental heating of pork tissue *ex vivo*.

**Ex vivo measurements**

The image acquired for targeting the thermocouple during the *ex vivo* hyperthermia experiment is shown in figure 12. The short axis of the tissue sample is shown in the azimuth B-scan and the long axis of the sample is visible in the elevation B-scan. The tip of the thermocouple is shown protruding from the proximal surface of the pork at the center of both B-scans. It is also visible in the bottom left C-scan, taken at the plane indicated by the white arrows in the B-scan images.

The measured temperature rise *ex vivo* is shown in figure 13, compared with that of the desired minimum 3.6 W/cm² simulation. In addition, the finite element model simulation was repeated for the experimentally acquired 2.4 W/cm², and the results are included in the figure. After 300 seconds, the 3D endoscopic probe heats the tissue sample an average of 1.8 ± 0.2°C over 5 trials with a maximum temperature rise of 2.3°C. In contrast, simulations predict a 2.7°C rise at the focus after 5 minutes.

**IV. SUMMARY AND DISCUSSION**

A number of problems were encountered during these experiments to determine the feasibility of combined 3D ultrasound imaging and hyperthermia. The finite element simulations predicted that delivered intensities of at least 3.6 W/cm² over prolonged exposures should induce a temperature rise in tissue of at least 4°C. This amount of energy deposition should be
sufficient for hyperthermic assistance in drug delivery. However, although the Model 1 scanner was able to achieve peak intensities greater than 3.6 W/cm², these settings were not sustainable. At a stable 2.4 W/cm², a peak temperature rise of 2.3°C and an average temperature rise of 1.8 ± 0.2°C were achieved. Simulations predict that at this intensity level, the induced temperature rise should be approximately 2.7°C, a difference of 33%.

**FIG. 12** 6 cm, 60° scan of *ex vivo* hyperthermia target. The 0.13 mm T-type thermocouple used for monitoring heating is shown protruding from the proximal surface of the pork tissue in both B-scans and in the C-scan. This thermocouple was retracted just under the surface of the pork for heating.

**FIG. 13** Results from *ex vivo* hyperthermia experiment compared with simulated results from the finite element model. For a simulated 3.6 W/cm², the model predicts a temperature rise of 4°C after 5 minutes. The experimental results at an average 2.4 W/cm² yielded an average temperature rise of 1.8 ± 0.2°C, a 33% difference from the 2.7°C predicted by the model at the same output power level.
There are a few factors that may be involved with this discrepancy between simulated and experimental results. Convective losses from the tissue surface due to acoustic streaming may have been a source of heat loss at the position of the thermocouple. Another common issue with similar finite element models is that the tissue property values may be inaccurate. While the values for absorption, conductivity and heat capacity were taken from experimental findings in the literature, small degrees of error could have noticeable effects on the simulated outcome. Furthermore, the intensity field calculation performed in FIELD II neglects any inconsistencies or nonuniformity particular to the 3D endoscopic probe. To maintain quarter symmetry and simplify calculations, the defined transducer array in the simulation does not account for any missing or dead elements. For example, our esophageal probe has a documented functionality of 92% of the total number of elements. Additional simulation studies including randomized apodization and the removal of documented nonfunctioning elements may be necessary to achieve a more accurate simulation model.

In addition, the model employed for these simulations does not include factors such as convection and blood perfusion. For this preliminary feasibility model, perfusion was removed from calculations. In the validation experiment, treatment was performed \textit{ex vivo}; thus, significant means of active heat loss were not present. However, over the duration of an actual 30-60 minute hyperthermia treatment, it is likely that, even in regions of low-density vasculature, heat loss in the system will necessitate a higher delivered intensity from the probe. For future studies, factoring perfusion into the model could be implemented by calculating heat loss tables based on the perfusion time constants of the tissue.

Another possible source of error is incomplete alignment with the thermocouple during the experimental measurements. While the image in figure 11 shows the thermocouple at the center of all scan planes, a slight alignment error on the order of a millimeter could affect the measured temperature rise by a few tenths of a degree. Based on the simulations, the highest temperature rise occurs in a region only 1 mm in diameter.

Heating from the face of the transducer was considered to be negligible. During the \textit{ex vivo} experiments, the array temperature reached a temperature of $3.5 \pm 0.5^\circ\text{C}$. Given an approximate 4 cm$^2$ pork tissue surface area and assuming radial propagation of heat, the array is only contributing an estimated 3.5% to the overall temperature rise detected by the thermocouple in the tissue sample. For further study, though, this face heating can be incorporated into the finite-element model as a continuous source of heat production.

Other obstacles associated with achieving hyperthermia with the 3D endoscopic probe were the limitations of the Model 1 scanner and the transducer itself. While intensity measurements at higher transmit cycle counts and higher pulse repetition frequencies initially yielded high energy pulses that, if sustained, could produce sufficient time average intensities for hyperthermic temperature rises, significant power reduction from the scanner power supply during extended operation prevented these settings from being applied to the experimental setup. It is apparent that the diagnostic scanner in its current state is incapable of meeting the high demands of a 504 channel transducer operating at levels outside the standard imaging range. A successful 3D imaging/hyperthermia system must exhibit a higher level of efficiency and be able to handle higher average power transmission in order to sustain a hyperthermia beam over 30 minutes. Another obstacle is the design of the 3D endoscopic probe. Because the piezoelectric elements of the transducer array have a small feature size, their electrical impedance is high in comparison to elements in standard linear arrays. Coupled with the scanner, this decreases the transmit efficiency of the system. Modifications to the scanner and 3D endoscopic probe, such as electrical matching, additional capacitance in the power supplies, or transducer acoustic matching layers could improve transmit efficiency and enable the system to operate at a higher prf and transmit cycle count for sustained periods of time.
One issue presented by the results is the relatively small heating zone predicted by simulations. For hyperthermia-assisted drug delivery, heating must be applied uniformly over the entire target region, such as a tumor. If peak heating is only occurring within a 1 mm diameter region, dispersion of hyperthermia treatment will not be adequate. Future experiments monitoring \textit{ex vivo} heating with an array of thermocouples will be necessary. However, one solution to the small focal region is to use scanning in both azimuth and elevation. By steering over a small angle volume, hyperthermia treatment with a 3D probe could effectively distribute heat over the entire target area and it may enable a greater degree of control over energy deposition when compared with current techniques.

While our \textit{ex vivo} feasibility study was unable to reach the temperatures predicted by our simulations, the ability to combine 3D ultrasound imaging and hyperthermia still holds promise. At present, current systems of hyperthermia often encounter problems achieving thorough heating of an entire targeted area. In particular, phased-array steering of a hyperthermia beam in both azimuth and elevation could offer greater control over energy deposition and enable more uniform heating in a targeted tumor. Intensity measurements indicate that the 3D endoscopic probe can endure producing focal intensities of greater than 3.5 W/cm$^2$; therefore, future work involves modifications to the Model 1 scanner and improvements in 2D array design and fabrication to increase transmit efficiency and ensure system stability under these demanding operating conditions.

ACKNOWLEDGEMENTS

The authors would like to thank Carl Herickhoff for his assistance programming the data acquisition equipment and Mark Palmeri for his help with LS-DYNA. This research was supported by NIH grants HL 72840 and HL 64962 and NSF grant DMR313764.

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