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Development of a spherically focused phased array transducer for ultrasonic image-guided hyperthermia

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Abstract

A 1.5 MHz prolate spheroidal therapeutic array with 128 circular elements was designed to accommodate standard imaging arrays for ultrasonic image-guided hyperthermia. The implementation of this dual-array system integrates real-time therapeutic and imaging functions with a single ultrasound system (Vantage 256, Verasonics). To facilitate applications involving small animal imaging and therapy the array was designed to have a beam depth of field smaller than 3.5 mm and to electronically steer over distances greater than 1 cm in both the axial and lateral directions. In order to achieve the required f number of 0.69, 1-3 piezocomposite modules were mated within the transducer housing. The performance of the prototype array was experimentally evaluated with excellent agreement with numerical simulation. A focal volume (2.70 mm (axial) $\times$ 0.65 mm (transverse) $\times$ 0.35 mm (transverse)) defined by the –6 dB focal intensity was obtained to address the dimensions needed for small animal therapy. An electronic beam steering range defined by the –3 dB focal peak intensity (17 mm (axial) $\times$ 14 mm (transverse) $\times$ 12 mm (transverse)) and –8 dB lateral grating lobes (24 mm (axial) $\times$ 18 mm (transverse) $\times$ 16 mm (transverse)) was achieved. The combined testing of imaging and therapeutic functions confirmed well-controlled local heating generation and imaging in a tissue mimicking phantom. This dual-array implementation offers a practical means to achieve hyperthermia and ablation in small animal models and can be incorporated within protocols for ultrasound-mediated drug delivery.

1. Introduction

Focused ultrasound therapy has become more important in the past decades with more than 30 clinical indications now in trials (FUSFoundation 2015). As an important type of focused ultrasound therapy, ultrasound hyperthermia (Marmor *et al* 1979, Diederich and Hynynen 1999) utilizes thermal energy to enhance other therapies at moderate temperature. In ultrasound hyperthermia, a well-calibrated thermal dose is typically achieved through the control of the intensity and duration of insonation delivered to the region of treatment. The

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advantages and the clinical potential of ultrasound hyperthermia have resulted in intensive study for the treatment of cancers such as brain tumors (Britt *et al* 1983, Guthkelch *et al* 1991), breast cancer (Bin and Jian 2008, Wu *et al* 2014), cervical cancer (Wootton *et al* 2011), prostate cancer (Hurwitz *et al* 2001, Diederich *et al* 2011), liver cancer (Misra *et al* 2015) and lung cancer (Sekins *et al* 2004). Here, the development of a system optimized for scientific studies in small animals and superficial tumors is described. Such a development has unique challenges in limiting the depth of focus while facilitating steering and real time thermometry.

Ultrasound hyperthermia configurations have typically been implemented using a single element transducer that is mechanically scanned to deliver ultrasound throughout a volume of interest (Dickinson 1984). As the technology for phased array transducers has advanced, clinical ultrasound therapy has been increasingly realized by phased arrays where the focal size and position can be electronically controlled in the spatial and temporal domain (Ebbini *et al* 1988, Sharifi and Soltanian-Zadeh 2001, Kruse *et al* 2010, Lai *et al* 2010). As a result, controlled hyperthermia and ablation are feasible for deep targets (Diederich and Hynynen 1991) that were previously considered unreachable by focused ultrasound. Given the need to minimize the system channel count, most therapeutic arrays are designed with elements distributed over a 2D surface and with elements spaced at separation distances greater than the wavelength. The main drawback of such arrays is the presence of grating lobes in the resulting sound field. Among the techniques proposed to suppress the grating lobes, random element distribution has been proven to be able to effectively reduce the grating lobe levels (Goss *et al* 1996, Hutchinson *et al* 1996, Gavrilov and Hand 2000, Hand *et al* 2009, Bobkova *et al* 2010).

Integrated image guidance methods for targeting and monitoring treatment are required to improve the accuracy and efficiency of ultrasound hyperthermia. Accurate targeting allows the delivery of therapeutic energy to the treatment volume while avoiding biological effects in adjacent tissue. Monitoring methods provide an assessment of the tissue response to the delivered ultrasound energy facilitating the planning of further treatment (Vaezy, Andrew, *et al* 2001). Imaging modalities applied for guiding ultrasound therapy include Computer Tomography (CT) (Marquet *et al* 2009), Magnetic Resonance Imaging (MRI) (Hynynen *et al* 2001, Hazle, Diederich, *et al* 2002, Chopra *et al* 2005, McDannold *et al* 2006, Hynynen 2010, Siddiqui *et al* 2010, Feshitan *et al* 2012, Zhang *et al* 2015) and ultrasound (King *et al* 2003, Chan *et al* 2004, Ebbini and Ter Haar 2015). Compared with other imaging modalities, ultrasound imaging has the advantages of compactness, low cost, simplicity and high efficiency. For local hyperthermic and ablative treatments of small animals, the advantages of ultrasound guidance contrast with the existing technology for MR-guided (Hazle, Stafford, *et al* 2002, Chopra *et al* 2009, Hijnen *et al* 2012, Bing *et al* 2015) and PET-guided (Singh *et al* 2004) small animal treatments. While MRI provides three dimensional views of anatomy and well-established thermometry protocols, protocols for thermal treatments of small animals within the MRI are cumbersome, time consuming and relatively expensive. Such protocols require that the subject is positioned on the bed without image guidance, and maintaining a precise and constant body temperature within the MRI bore (particularly during hyperthermia) is challenging.

Two methods have been investigated to integrate ultrasound imaging and therapy. The most readily realized method is to combine ultrasound imaging and therapeutic systems that work independently (Vaezy, Shi, *et al* 2001, King *et al* 2003, Miller *et al* 2005, Held *et al* 2006). Alternatively, ultrasound imaging and therapy functions can be integrated in a single system and the transducer can include separate sections, layers and modes, or use interleaved elements. A dual section array combines distinct sections that realize the imaging and therapy functions (Jeong *et al* 2009, Kruse *et al* 2010, Lai *et al* 2010); a dual layer array has layers overlaid with each layer accomplishing one function (Azuma *et al* 2010); a dual mode array has one layer which works alternately for imaging and therapy (Ebbini *et al* 2006, Ballard *et al* 2010, Casper *et al* 2013) and an interleaved array has imaging and therapy elements positioned within the same array in an interleaved manner (Van Neer *et al* 2010).

This work aims to develop a therapeutic array to integrate with a commercial imaging array forming a dual-array system driven by a single programmable ultrasound platform to realize ultrasound hyperthermia and thermal strain imaging. In order to treat small animals or superficial lesions near sensitive structures such as nerves or blood vessels, a 128-element hyperthermia array (128EHYP) was designed to steer electronically by more than 1 cm with a depth of field defined by -6 dB intensity below 3.5 mm. In the following sections of this paper, design considerations to address functional requirements will be demonstrated first, followed by the experimental characterization of the therapeutic array and a performance evaluation of the ultrasonic image-guided therapeutic system.

2. Methods

2.1. A spherical array with a rectangular imaging opening

2.1.1 Basic design parameters—Among the system configurations available for ultrasonic image-guided focused ultrasound therapy, a combined system containing a commercial imaging array and a custom designed therapeutic array was chosen for its capability of providing both the high quality imaging and the customized therapeutic performance. The therapeutic array was defined by a spherical shell (due to its inherent beam focusing ability) with flat circular elements; the basic design requirements are summarized in Table 1. A 256-channel system is used to drive both the imaging and therapeutic arrays, and, therefore, the number of elements (channels) for each array is limited to 128. In small animal models the targets are tumors that are 1 mm to 10 mm in diameter and are typically located in superficial organs such as the mammary fat pad, pancreas or prostate. To protect the skin and organs of the small animals, the depth of field of the therapeutic beam is limited to 3.5 mm, which is on the order of the axial extent of sensitive organs such as the breast fat pad or pancreas. In order to treat tumors on the order of 1 cm in diameter, array steering is implemented in the lateral and axial dimensions. Further, in order to provide sufficient intensity for targets located mm or cm from the skin, a curved array and therapeutic aperture on the order of 8 or more cm are required. Finally, to provide flexibility in the choice of the target depth (mm or cm) and to constrain the f-number to a reasonable value, a focal depth of 55 mm was chosen for the therapeutic array. For mild hyperthermia of superficial tissue, a required focal intensity of ~ 30 W/cm² is anticipated (Fite *et al* 2012).

First, the f-number of the therapeutic array can be estimated using equation (1) (Cobbold 2007):

$$Z_F \approx 7.2\lambda \times (f\#)^2 \quad (1)$$

where Z_F is the depth of field corresponding to the -6 dB axial intensity profile, λ is the wavelength of the beam, and $f\#$ is the f-number of the array. Based on the parameters in Table 1 and a sound velocity of 1540 m/s, the f-number of the therapeutic array is below 0.69. This leads a lower limit for the array aperture of 80 mm. On a spherical shell with a radius of curvature of 55 mm, a reasonable element size can be estimated based on the following equation:

$$A_{element} = (A_{shell} - A_{opening}) \times \alpha_{coverage} \quad (2)$$

where $A_{element}$ is the total area of the active elements, A_{shell} is the area of the spherical shell, $A_{opening}$ is the area of the imaging opening, and $\alpha_{coverage}$ is the element surface coverage. According to the parameters in Table 1 and considering a minimum aperture of 80 mm, the minimum element diameter is 4.4 mm. In order to improve yield, a 5 mm diameter was utilized. To reduce crosstalk between elements a minimum inter-element distance of 0.5 mm was chosen (10% of the element diameter).

Due to its low cost, ubiquity and satisfactory image quality, the linear array L7-4 (Philips ATL, WA, USA) was chosen to be integrated as the initial imaging array. However, the designed arrays are modular, other imaging arrays can be substituted and the relative position of the two arrays adjusted in depth. The L7-4 has 128 active elements (imaging channels), a field of view of 38 mm, an aperture of 50 mm by 22.35 mm and an elevational focus of 25 mm. In the current design, a rectangular opening, rather than the circular opening that is common in many designs (Hand *et al* 2009), was chosen to accommodate standard imaging arrays without loss of surface area. This choice greatly reduces the gap between the therapeutic and imaging arrays, which not only simplifies the sealing of the gap for functioning in liquid environment, but also reduces the sidelobes that result from the imaging array void.

2.1.2 Random distribution of therapeutic array elements—Random element arrangements can greatly suppress grating lobes for undersampled array geometries and therefore significantly improve the intensity distribution of the array field (Hutchinson *et al* 1996, Gavrilov and Hand 2000). Since an array with elements arranged in circular pattern performs considerably better than other common regular distribution patterns such as square pattern and hexagonal patterns (Gavrilov and Hand 2000), it is reasonable to conclude that random distribution provides the best array performance in terms of element arrangement.

2.1.3 Array geometry—Compared with a conventional spherical array, introducing a rectangular void (designed to incorporate a conventional imaging array) increases the side lobe levels of the intensity field in an angle dependent fashion. Simulation of the intensity

field of a spherical array with the rectangular opening defined above shows that in the focal plane the first side lobes in the azimuthal direction (imaging array dimension of 50 mm) are ~5 dB higher than those in the elevation dimension. To balance the amplitude of the side lobes in each direction the therapeutic array design is modified. For example, extending the therapeutic array dimension with the incorporation of additional elements improves the symmetry of the therapeutic beam profile. Here, the aperture of the array was defined by the cross-section of a sphere of 55 mm in radius and a cylinder of 72 mm in radius with its axis 31 mm away from the center of the sphere. The design parameters are summarized in Table 2 and the 3D and 2D schematics of the modified array with randomly distributed circular elements are shown in Figure 1(a) and (b), respectively. With such a shape, the first side lobes are of similar height along each axis when the beam focus is on axis or steered off axis.

In many designs the f-number of a spherical array is larger than 1 (Gavrilov and Hand 2000), but here the f-number was reduced to 0.69 in order to reduce the depth of focus for the treatment of small animals (i.e. to avoid excessive skin absorption and collateral organ damage). In order to create a spherical array with this f-number, the 1-3 piezocomposite material (Cathignol et al 1999) was divided into two symmetric sections as shown in figure 1(c), and a 3 mm margin was added between these sections for convenience in fabrication. A fixture (figure 1(d)) was created to align the sections during assembly. The array was fabricated by Imasonic (Voray sur l'Ognon, France) as shown in figure 1(e) and its final parameters are listed in table 2.

2.2. Acoustic field simulation

Simulation of the ultrasound field of the therapeutic array was based on calculation of the pressure field of a single circular piston. The steady-state pressure p generated by a circular piston transducer was obtained from the frequency response H of the piston transducer according to

$$p(r, z; k) = -j\omega\rho v e^{j\omega t} H(r, z; k), \quad (3)$$

where r and z are the coordinates of a cylindrical coordinate system with its origin locating at the geometric center of the piston, k is the wavenumber, ω is the angular excitation frequency, ρ is the density of the medium, v is a constant normal velocity at the piston surface. Among the methods available, the frequency response was calculated using the Fast Nearfield Method (McGough *et al* 2004), which utilizes a spatially bandlimited single-integral expression for all field points, and was numerically obtained using:

$$H(r, z; k) = \frac{a}{jkN} \sum_{n=1}^N \frac{r \cos \psi_n - a}{r^2 + a^2 - 2ar \cos \psi_n} \times \left(e^{-jk \sqrt{r^2 + a^2 - 2ar \cos \psi_n + z^2}} - e^{-jkz} \right) \quad (4)$$

where a is the radius of the circular piston, ψ is the angle subtended by the ends of the arc elements for calculation (Archerhall *et al* 1979) and its discrete form ψ_n ranges from 0 to π ,

and N is the number of angle divisions considered in the calculation. The total pressure field was calculated by summing the contribution from each circular element of the array at the positions of interest. The (average) intensity was then obtained from converting the pressure at each point in space through the relationship:

$$I = \frac{|p|^2}{2\rho c_0} \quad (5)$$

where I is the average intensity, p the peak pressure at a point in space and c_0 the sound velocity of the medium. To facilitate the comparison between simulations and measurements, the medium was defined as water with a mass density of 1000 kg/m^3 , sound velocity of 1488 m/s and attenuation of $2.2 \times 10^{-3} \text{ dB/cm/MHz}^2$ (Kino 1987). All simulations were performed using the ultrasound simulation tool Fast Object-Oriented C++ Ultrasound Simulator (FOCUS).

2.3. Acoustic field measurements

The acoustic pressure field of the fabricated therapeutic array was measured in degassed water using a wide-band needle hydrophone (HNP-0400, Onda, CA, USA) with an active element diameter of 0.4 mm . The hydrophone was controlled by a universal motion controller/driver (ESP300, Newport, CA, USA), which allows for scanning motions in three perpendicular planes: x - y plane, x - z plane and y - z plane in a Cartesian coordinate system as illustrated in Figure 1(a). The pressure signals received by the hydrophone were first displayed on a digital oscilloscope (DPO4034, Tektronix, OR, USA) and then uploaded to a computer for further processing. The array was excited by a 10-cycle sine wave at 1.5 MHz generated by a programmable ultrasound system (Vantage 256, Verasonics, WA, USA). The pressure maps in the x - y , x - z and y - z planes were obtained for nine focal positions: geometric focus $(0, 0, 55) \text{ mm}$, foci steered along the x axis $(5, 0, 55) \text{ mm}$ and $(10, 0, 55) \text{ mm}$, foci steered along the y axis $(0, 5, 55) \text{ mm}$ and $(0, 10, 55) \text{ mm}$, foci steered along the z axis $(0, 0, 50) \text{ mm}$, axis $(0, 0, 60) \text{ mm}$ and $(0, 0, 65) \text{ mm}$. All scans were performed with a spatial resolution of 0.25 mm . For comparison with simulations, cubic interpolation was applied to the measurements to increase the spatial resolution four fold. Moreover, to check the spatial variation of the focal peak intensity of the array, the maximum pressure in the focal region was also measured as the focus of the array was steered along the x , y and z axes.

2.4. Acoustic power measurements

The output acoustic power of the array was measured using a radiation force balance (XS6002S, Mettler Toledo, Columbus, OH, USA) with a resolution of 0.01 gram . The array was fixed in place, immersed in degassed water of 20°C , pointed vertically downward to face an absorbing target. During the measurements, the array was excited at 1.5 MHz by a burst of 2 seconds. The applied electrical power was amplified using a single channel power amplifier with all elements excited in parallel, and recorded using a power meter (NAP, Rohde & Schwarz, Munich, Germany).

2.5. Imaging of the temperature elevation generated by the designed array

The functionality of the ultrasonic image-guided therapeutic system was tested by imaging the temperature elevation in a calibrated tissue-mimicking phantom (2% agar, 1.5% SiC powder) generated by the therapeutic array. The temperature measurement is based on the principle of ultrasonic thermal strain imaging (Seip and Ebbini 1995, Maass-Moreno and Damianou 1996) using the real-time measurement technique developed by our group (Foiret and Ferrara 2015). During the measurements both imaging and therapeutic arrays were driven by the same system (Vantage 256, Verasonics, WA, USA) and excited alternately. The imaging and therapeutic arrays were driven at 5.2 MHz and 1.5 MHz, respectively. To demonstrate the ability of the system to induce and monitor hyperthermia, the heating rate and maximum temperature elevation were chosen to generate a temperature increase of approximately 6°C after 20 s of sonication. Five experiments (I to V) were performed to monitor the temperature increase with the focus electronically steered within the imaging plane as shown in Figure 2(a). First, the therapeutic array was steered to (0, 0, 50) mm, (0, 0, 55) mm, (0, 0, 60) mm or (5, 0, 55) mm. Secondly, a measurement was performed with the focus rapidly alternating between the two positions ($\pm 5, 0, 55$) mm in order to generate two simultaneous heating spots (experiment V). As indicated in Figure 2(b), the excitation started at 0 s and ended at 20 s; the total imaging time was 80 s. For demonstration, temperature maps were recorded at 10 s, 20 s and 50 s. For the single-focus experiments (experiment I to IV), as the intensity gain decreases when steered away from the geometric focus, the input electrical power was adjusted according to the simulated intensity gain at the corresponding positions in order to achieve the same temperature elevation after 20 s of heating. For the double-focus excitation, the input power was the same as the single-focus excitation at (5, 0, 55) mm; the maximum temperature elevation was accordingly lower than the other four cases.

3. Results

3.1. Acoustic intensity fields

The simulations of the acoustic intensity in the x–y plane, the x–z plane and the y–z plane when the array is focusing at its geometric center (0, 0, 55) mm and the corresponding experimental measurements are shown in the left-hand and middle columns of Figure 3, respectively. In the 30 dB amplitude scale, the simulations are in excellent agreement with measurements. In order to compare the intensity distribution along three major axes, the intensity profiles of both simulations and measurements along the x, y and z axes were extracted from their corresponding intensity maps in the first two columns of Figure 3 and shown in Figure 3(c), (f) and (i). For the three axes, the main lobe and the first side lobes are similar, although the measured first side lobe for the y axis is ~1 dB higher than that estimated by the simulation.

As an example of the lateral beam steering achieved with this design, the simulated and measured intensity maps at the focus (5, 0, 55) mm are shown in Figure 4 together with the intensity profiles along the x, y and z axes. The simulations and the measurements of the intensity maps and profiles are generally in good agreement, although the measured first side lobes along the y axis and the grating lobes along the x axis are ~1 dB higher than the

simulations. The major grating lobes are ~5 dB greater with 5 mm lateral steering as compared with the intensity fields at the geometric focus of the array; however, the sidelobes remain nearly 10 dB smaller than the first side lobes.

The features of the acoustic field of the array when steering along the z axis are demonstrated in Figure 5 using the field (0, 0, 60) mm as an example. The simulated and measured intensity maps are similar. The first side lobe and the peak grating lobe are about 9 dB and 19 dB below the main lobe.

3.2. Focal dimensions

For well-controlled treatments, a consistent effective focal volume is desirable at each location within the field of view. The -6 dB and -3 dB focal area of the array were calculated and measured at nine positions (Figure 6) and demonstrated to be closely matched. In addition, the amplitudes of first side lobes exceed -6 dB when the beam was laterally steered 10 mm in the focal plane ($z = 55$ mm) along the x and y axes.

In order to demonstrate the variation of the focal region of the array when the beam was steered along the x, y and z axes, the focal dimensions obtained from the measurements are shown in Figure 7. Within 5 mm lateral steering (Figure 7(a) and (b)) and 10 mm axial steering (Figure 7(c)) from the geometric focus (0, 0, 55) mm, the -6 dB and -3 dB focal dimensions along the x axis (lines with dots) and the y axes (lines with triangles) experience small changes, while the focal dimensions along the z axis (lines with squares) experience relatively large changes. For example, the -6 dB and -3 dB focal dimensions along the z axis both change ~0.25 mm during the 10 mm lateral steering (Figure 7(a) and (b)) and ~1.5 mm during the 20 mm axial steering (Figure 7(c)). In addition, at all nine positions the -3 dB and -6 dB focal dimensions along the x axis (line with dots) are 0.15 mm smaller than the dimensions along the y axis (line with triangles), and ~1 mm smaller than the z axis dimension (line with squares).

3.3. Focal peak intensity and -3 dB FPI volume

In order to characterize the intensity variation with respect to focal position, the focal peak intensity (FPI) was measured when the beam was steered along three perpendicular axes (x, 0, 53.5) mm, (0, y, 53.5) mm and (0, 0, z) mm at a spatial resolution of 0.25 mm. These measurements are shown and compared with those extracted from the simulations in Figure 8. As expected, the maximum FPI value of the array occurs at (0, 0, 53.5) mm, which is 1.5 mm away from the geometric focus towards the array, and therefore measurements for lateral FPI variation were performed in the plane of $z = 53.5$ mm. In addition, the simulations show that the current array has a FPI of 2077 W/cm² at the geometric focus and 2109 W/cm² at (0, 0, 53.5) mm given the surface intensity of the array elements being 1 W/cm². The intensity gain (2077) at the geometric focus obtained in this simulation differs by 0.1% from the theoretical estimate obtained according to the following equation (Oneil 1949, Stephens *et al* 2011):

$$G_I \cong \left(\frac{N\pi r^2}{\lambda R_c} \right)^2 e^{-0.2303\alpha_m R_c} \quad (7)$$

where N is the number of elements, r is the radius of the circular element, λ is the wavelength, R_c is the radius of curvature of the array in cm, and α_m is the absorption characteristics of the medium in unit of dB/cm.

Figure 8(c) shows that the measured and the simulated FPIs along the z axis are in agreement. For the FPIs along x and y axes as shown in Figure 8(a) and (b), the simulations and the measurements match well for the positions less than 5 mm away from the origin of the axes, while beyond the 5 mm position there is a small discrepancy. This discrepancy likely originates from the limited angle of acceptance of the hydrophone.

In practical applications the focus of the array is limited to the region where the FPI is within -3 dB of the maximum FPI of the array. To map this region for the current array, the boundary of the volume defined by -3 dB FPI was simulated (Figure 9). In both the x - y plane and the y - z plane the projections of the -3 dB volume are elliptical. The maximum dimensions of the -3 dB volume are 14.06 mm along the x axis, 12.12 mm along the y axis and 16.48 mm (from 46.27 mm to 62.75 mm) along the z axis.

3.4. Grating lobe level and -8 dB GLL boundary

Minimizing the grating lobe level is critical for the acoustic field of an array in order to eliminate off target effects. To safely deliver energy to the predefined treatment volume, the maximum intensity in the grating lobes is required to be 8 to 10 dB lower than that in the main lobe of the beam (Ebbini and Cain 1991, Hutchinson *et al* 1996, Gavrilov and Hand 2000). In this work we adopted -8 dB as the criterion for grating lobe level. Since the simulation and the measurement are similar, simulated intensity maps were used to find the -8 dB grating lobe level (GLL) boundary along the x , y and z axes. These boundaries are plotted in Figure 10 in comparison with those defined by -3 dB focal peak intensity. We observe a steering range of 18 mm, 16 mm and 24 mm along the x , y and z axes defined by -8 dB GLL criterion, which is larger than that defined by the -3 dB FPI.

3.5. Acoustic power

Figure 11 shows the acoustic power measurements of the array for 5 progressively increased electrical power inputs, demonstrating that the array has an efficiency of 62%.

3.6 Generation and measurement of temperature elevation

To demonstrate the combined imaging and therapeutic functionality of the array system, the phantom was heated by the therapeutic array and the temperature measured by the imaging array; the maps of the recorded temperature elevation (with a value higher than 1°C) were superimposed on their corresponding B-mode images as shown in Figure 12. The measurements performed at (0, 0, 55) mm, (0, 0, 50) mm, (0, 0, 60) mm, (5, 0, 55) mm, (± 5 , 0, 55) mm are shown in row (I) to row (V) of Figure 12, respectively. For each measurement,

the steered focus and the geometric focus of the therapeutic array are illustrated in column (A) of Figure 12, and the temperature elevation map recorded at 10 s, 20 s and 50 s were chosen to demonstrate the spatial and temporal elevation of temperature during the heating phase (column (B)), at the maximum temperature increase (column (C)) and during the cooling phase (column (D)). The -20 dB contours of simulated intensity maps were overlapped with the temperature elevation maps containing highest elevation values as shown in column (C). Column (C) shows that the heated areas were well defined with the maximum temperature increase arising at the steered focus position. For the single-focus studies (row I to IV of Figure 12), the adjustments in input electrical power (based on the simulated intensity gain) led to the same maximum temperature elevation after 20 s. The double-focus case demonstrates the ability of the array to efficiently deposit acoustic energy at several locations and to enhance the overall heated volume. Moreover, the grating lobes (the small dots in the -20 dB intensity contours of column (C) of Figure 12) elevate the temperature by 1.5 degrees, when the focus was steered laterally and axially away the geometric focus.

To check the effect of focal steering on the heat distribution, the total area of the temperature maps with an elevation higher than 1°C were obtained as a function of time (Figure 13). For the single-focus excitation studies, although the maximum temperature elevation remained consistent, the spatial extent of the heated region increased for lateral steering and extending the focus to a deeper region. For example, the heated areas measured at 20 s for the lateral steering at $(5, 0, 55)$ mm and the axially outward steering at $(0, 0, 60)$ mm increase by 79% and 65%, respectively, compared with that at geometric focus.

4. Discussion

4.1. Comparison of simulation and measurement

Numerical simulation of the acoustic field of the designed therapeutic array was performed throughout the process of development not only for refining the design, but also for evaluating the performance of the prototype array. As expected, the simulations are in agreement with the measurements. Therefore, the array characteristics obtained from the field simulations such as the intensity gain at geometric focus, the -3 dB FPI volume and -8 dB GLL boundary were realized as anticipated.

4.2. Steering ability of the array

3D beam steering is a crucial feature for future therapeutic arrays and can be evaluated using two acoustic field parameters: focal peak intensity (FPI) and grating lobe level (GLL). In the current work, both -3 dB FPI and -8 dB GLL were adopted as the criteria for steering evaluation. As shown in Figure 10 the -8 dB GLL boundary of the array is ~ 2 mm larger than the -3 dB FPI boundary along the three axes. In addition, the -3 dB FPI volume (Figure 9) defines a volume with maximum dimension of 12.12 mm in the x axis, 14.06 mm in the y axis and 16.48 mm in the z axis and therefore satisfy the design criteria of 10 mm.

4.3. Generation and monitoring of temperature elevation for hyperthermia application

As depicted in Figure 12 the five experiments performed in this study show successful generation and monitoring of temperature elevation in the tissue-mimicking phantom. In these experiments, a temperature elevation of $\sim 6^{\circ}\text{C}$ was achieved within 20 s meeting the requirements for a temperature increase for *in vivo* hyperthermia ($+5^{\circ}\text{C}$ from 37°C to 42°C). The maximum temperature increase can be controlled by excitation time and heating rate; the heating rate can be directly controlled by the input voltage and duty factor of the driving signal, which offers both flexibility and real time control of thermal dose. These experiments also demonstrate the steering capability of the array. The steering range tested here (± 5 mm laterally and ± 5 mm axially) is well suited for preclinical work and is currently used in rodent studies employing temperature sensitive liposomes. This array combined with the programmable ultrasound system is thus of great interest for spatial and temporal control of hyperthermia.

4.4. Distinct features of the array system

By integrating the imaging and therapeutic control in one programmable system (Verasonics Vantage 256), the imaging function and therapeutic function can effectively alternate. Compared with the existing image-guided ultrasound systems, in which imaging and therapeutic functions are supported by two separate driving systems, this system is more compact and efficient. Particularly when implementing ultrasound thermometry, a single imaging and therapy system is required.

Another distinct feature of the current design of the therapeutic array is its small f-number and therefore highly curved geometry. This feature leads to both a small -6 dB (intensity) focal size and a high intensity gain. At the geometric focus the -6 dB focal volume of the array is as small as 2.70 mm (axial) $\times$ 0.65 mm (transverse) $\times$ 0.35 mm (transverse), and this is advantageous for accurate energy delivery while avoiding heating the sensitive organs surrounding the region of interest.

High intensity gain is highly desirable for deep penetration in hyperthermia applications (Ebbini and Cain 1991). According to the simulations, the therapeutic array has an intensity gain of 2077 at its geometric focus (0, 0, 55) mm and maximum intensity gain of 2109 at (0, 0, 53.5) mm. Although the array is designed for ultrasound hyperthermia, this high intensity gain also facilitates its use in ablation.

4.5. Comparison between the designed array with two commercial transducers

To further demonstrate the performance of the designed array (128EHYP), it is compared with two commercial single-element transducers applied in ultrasonic image-guided HIFU treatment for enhancing drug delivery in a small animal model (Li *et al*/2015). Both of these transducers (Commercial 1 and 2) have an aperture of 64 mm and a circular central opening of 38 mm in diameter, and their radius of curvature and working frequency are 64 mm and 1.1 MHz, and 45 mm and 1.5 MHz, respectively. The intensity fields of all three transducers working in their respective center frequencies were simulated and compared in Figure 14. The comparison of -6 dB and -3 dB focal regions in Figure 14(a) and (b) shows that the intensity field of 128EHYP is smaller than the commercial transducers, and therefore

suitable for small animal applications. The 128EHYP also reduces the lateral lobe levels (Figure 14(c)) and axial lobe levels (Figure 14(d)).

4.6. Summary of the contributions and potential and future applications

As expected, beam calculations provide high confidence that axial lobes, side lobes, and grating lobes can be accurately assessed by a-priori calculations. Here, a short axial focus was combined with a larger steering range. In particular, we find that the metric of the -3dB beam steering volume along the three axes provides a useful summary of the steering capability of the array (Figure 9). In this case, the therapeutic array performs well within a range of depths between approximately 48 and 60 mm. The imaging array used in our initial studies and the skin line can each be offset in the axial dimension to provide high quality imaging within this region.

The importance of evaluating the focal dimensions of the array as a function of steering was emphasized (Figure 7). For small animal therapy, low intensity, high duty cycle ultrasound can be problematic when the target organ is near the gut (due to local gas bodies). Therefore, careful estimation and measurement of the focal dimensions are required.

Further, we established that thermal strain imaging is a useful tool to monitor temperature dynamically using such an array. Maps of thermal strain are shown to be useful both in the assessment of the peak temperature at the focus, but also in the assessment of the temperature increase that results from grating and side lobes. Such lobes are unavoidable when a void is created for a dedicated imaging array. Row V within Figure 12 demonstrates the use of the electronically steered therapeutic array to insonify multiple foci to spread the temperature increase over the field of view. Here, the beam was dithered between two positions; however, alternative operating modes include the simultaneous transmission of energy to multiple focal regions. The current system has now been successfully implemented within studies of *in vivo* image-guided hyperthermia involving small animal models (data not shown). Compared with a similar array (G4) developed by our team (Stephens *et al* 2008) and interfaced with the Siemens Antares (which combines imaging and therapeutic functions in a triple-row linear array system), the current array format has improved 3D steering of the therapeutic beam, improved heat dissipation and tolerance, and an integrated imaging and therapy capability. Moreover, an algorithm for compensating physiological motion (Foiret and Ferrara 2015) has been applied using the new array, which facilitates effective real-time temperature monitoring. The array provides many new opportunities for image-guided therapy including the implementation of multiple focal zones, 3D beam steering and cavitation generation and detection. Such studies will be the subject of future work.

5. Conclusions

This work presents the development of a spherical therapeutic array that can be integrated with a commercial imaging array (L7-4) to realize real-time ultrasonic image-guided therapy for small animals. A distinct feature of the image-guided therapeutic system is that both imaging and therapeutic functions can be achieved with a single control system (Verasonics Vantage 256). To facilitate small animal applications, the therapeutic array can maintain a

depth of field below 3.5 mm while the focus is scanned over a region larger than 1 cm along the x, y and z axes. We verified the capability of the transducer and system to control imaging and mild hyperthermia in a tissue mimicking phantom. Moreover, the intensity gain of the array (2077 at the geometric focus) not only suggests its suitability in the designed application of mild hyperthermia, but also its application in tissue ablation.

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Figure 1.

(a) 3D and (b) 2D (top view) schematics of the spherical therapeutic array with 128 randomly distributed circular elements and a rectangular opening for inserting the imaging transducer. (c) Symmetric sections of the array. (d) Rear aspect before element patterning. (e) Top view of the integrated array system for ultrasound imaging and therapy: (A) The imaging array ATL L7-4; (B) the therapeutic array with elements underneath the black matching layer; (C) housing of the therapeutic array; and (D) plastic support.

Figure 2.

(a) The focal positions for generating and measuring temperature elevation in five experiments: Experiment I to IV in single-focus mode (ellipse) and experiment V in double-focus mode (pentagram). (b) The temporal control of the therapeutic array excitation and time points (star) for temperature map recording.

Figure 3.

Comparison of simulations (left-hand column) with lab measurements (middle column) of the one way acoustic intensity field at the geometric focus (0, 0, 55) mm in three orthogonal planes: the x–y plane (a, b), the x–z plane (d, e), and the y–z plane (g, h). The simulated and measured intensity profiles along the x, y and z axes were extracted from the corresponding intensity maps and compared in (c), (f) and (i), respectively.

Figure 4.

Comparison of simulations (left-hand column) with lab measurements (middle column) of the one way acoustic intensity field at (5, 0, 55) mm in three orthogonal planes: the x–y plane (a, b), the x–z plane (d, e), and the y–z plane (g, h). The simulated and measured intensity profiles along the x, y and z axes were extracted from the corresponding intensity maps and compared in (c), (f) and (i), respectively.

Figure 5.

Comparison of simulations (left-hand column) with lab measurements (middle column) of the one way acoustic intensity field at (0, 0, 60) mm in three orthogonal planes: the x - y plane (a, b), the x - z plane (d, e), and the y - z plane (g, h). The simulated and measured intensity profiles along the x , y and z axes were extracted from the corresponding intensity maps and compared in (c), (f) and (i), respectively.

Figure 6.

Comparison of simulations with lab measurements of the -6 dB and -3 dB focal intensity contours at nine positions (a) in the x-y plane for $z = 55$ mm, (b) in the x-z plane for $y = 0$ mm, and (c) in the y-z plane for $x = 0$ mm.

Figure 7.

Experimentally measured focal dimensions at nine focal positions as the array was steered along the (a) x, (b) y and (c) z axes.

Figure 8.

Comparison of simulation with lab measurement of the focal peak intensity along (a) the axis ($x, 0, 53.5$) mm, (b) the axis ($0, y, 53.5$) mm, and (c) the z axis.

Figure 9.

Projections of the simulated -3 dB beam steering volume in the (a) x-y plane, (b) x-z plane and (c) y-z plane are defined by all focal positions whose focal peak intensity (FPI) are greater than -3 dB of the maximum FPI of the array.

Figure 10.

The intensity field boundaries defined by -8 dB grating lobe level (GLL) along the x, y and z axes compared with the boundaries defined by -3 dB focal peak intensity (FPI).

Figure 11.
Measurements of the output acoustic power of the array as a function of the applied electrical power.

Figure 12.

Generation and measurement of temperature elevation at different positions in the tissue-mimicking phantom. Row (I) to (V) correspond to the tests at (0, 0, 55) mm, (0, 0, 50) mm, (0, 0, 60) mm, (5, 0, 50) mm, and (± 5 , 0, 55) mm, respectively. Column (A) illustrates the positions of electronically steered focus (ellipse) with reference to the geometric focus of the therapeutic array (dot). Column (B), (C) and (D) show the temperature maps recorded at 10 s, 20 s and 50 s, respectively. Only the temperature change higher than 1 °C is displayed. The -20 dB simulated intensity contour is overlapped with temperature map obtained at 20 s.

Figure 13.
Temporal evolution of the total area of the temperature map with the temperature elevation larger than 1 °C for five measurements.

Figure 14.

Comparison of the performance of the designed array (128EHYP) with two commercial transducers (Commercial 1 and 2): -6 dB and -3 dB focal intensity region (a) in the x-y plane and (b) in the x-z plane; intensity profiles along (c) the x axis and (d) the z axis.

Table 1

General requirements for the therapeutic array.

Working frequency (MHz)	1.5
Number of elements	128
Depth of field (mm)	3.5
Minimum electronic steering range (mm)	+/- 5
Nominal focal depth (mm)	55
Imaging aperture (mm)	50×22.35
Element surface coverage ($\alpha_{coverage}$)	0.4
Focal intensity for mild hyperthermia (W/cm^2)	~ 30

Table 2

Summary of the final design parameters of the therapeutic array.

Working frequency (MHz)	1.5
Number of elements	128
Element diameter (mm)	5
Minimum inter-element distance (mm)	0.5
Element area (fraction of surface)	0.37
Imaging opening size (mm)	50×22.35
Radius of curvature (mm)	55
Dimension in the x and y axes	104×74
Depth of field at geometric focus (mm)	2.7
Total range of steering in the x, y and z axes (mm)	$18 \times 16 \times 24$