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Ex-vivo HIFU experiments using a 32 × 32-element CMUT array

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Abstract

High-intensity focused ultrasound (HIFU) has been used as noninvasive treatment for various diseases. For these therapeutic applications, capacitive micromachined ultrasonic transducers (CMUTs) have advantages that make them potentially preferred transducers over traditional piezoelectric transducers.

In this paper, we present the design and the fabrication process of an $8 \times 8\text{-mm}^2$, 32×32 -element 2-D CMUT array for HIFU applications. To reduce the system complexity for addressing the 1024 transducer elements, we propose to group the CMUT array elements into eight HIFU channels based on the phase delay from the CMUT element to the targeted focal point. Designed to focus at an 8-mm depth with a 5-MHz exciting frequency, this grouping scheme was realized using a custom application-specific integrated circuit (ASIC). With a 40-V DC bias and a 60-V peak-to-peak AC excitation, the surface pressure was measured 1.2 MPa peak-to-peak and stayed stable for

a long enough time to create a lesion. With this DC and AC voltage combination, the measured peak-to-peak output pressure at the focus was 8.5 MPa, which is expected to generate a lesion in a minute according to the temperature simulation. Following ex-vivo tissue experiments successfully demonstrated its capability to make lesions in both bovine muscle and liver tissue.

Index Terms

2-D array; capacitive micromachined ultrasonic transducers (CMUTs); dual-mode ultrasound; high-intensity focused ultrasound (HIFU); therapeutic ultrasound; thermal ablation

I. Introduction

HIGH-intensity focused ultrasound (HIFU) is an emerging medical technology for noninvasive surgery and therapy [1]–[3]. Compared to diagnostic ultrasound, HIFU uses significantly higher time-averaged acoustic intensity [3], [4]. This high acoustic intensity in tissue results in heat generation due to absorption of the acoustic energy, which rapidly raises the tissue temperature and destroys the tissue through thermal ablation [5]–[7]. Focusing the acoustic energy in a small focal region helps minimize the thermal damage in the intervening tissue [1], [7], [8]. Since the HIFU procedure accompanies no scar, the time of recovery is much shorter than open surgeries, resulting in fewer complications. Many advantages of HIFU led to recent researches expanding its clinical use to a wide variety of organs, including breast, prostate, liver, kidney, brain, bone, and pancreas [3], [4], [9]–[19].

Typical HIFU machines in the clinic employ an imaging system for guiding the HIFU procedure. The imaging system needs to provide temperature monitoring as well as anatomical location guidance. Magnetic resonance imaging (MRI) is a popular imaging modality to guide the HIFU procedure as it provides high-resolution anatomical images and thermal information [20]–[22]. MR-guided focused ultrasound systems (MRgFUSs) have been widely adapted for various HIFU applications [23]–[30]. Diagnostic ultrasound imaging is another modality capable of guiding the HIFU procedure in real-time [7]. In ultrasound-guided HIFU systems, a separate diagnostic transducer or a transducer array are aligned to the target region and used for imaging while the therapy transducer is in the ablation process.

For the focused ultrasound device used in therapy, piezo-electric transducers have been widely used. These are typically bowl-shaped single-element transducers for fixed focus operation, or phased transducer arrays for electronic focusing. One of the major drawbacks of the piezoelectric transducers in clinical systems is the transducer self-heating. To overcome the self-heating problem, piezoelectric transducers require a cooling system to protect both the transducers and the patients [31]–[36]. A cooling system is usually in the form of degassed circulating water or fluid located between the transducer and the skin. Especially, it is an important consideration in catheter-based HIFU transducers.

Capacitive micromachined ultrasonic transducers (CMUTs) are another type of ultrasonic transducers fabricated with silicon micromachining processes [37]. They have advantages over the conventional piezoelectric transducers in various ultrasound applications. Silicon

micromachining technology allows fabrication of CMUT arrays with various geometries and shapes, including but not limited to linear, rectangular, and annular arrays [38]–[40]. The unit cell size of a transducer, which determines the transducer characteristics, can vary in a wide range from tens of micrometers to several millimeters. Moreover, silicon micromachining enables flexible and seamless integration of CMUTs with integrated circuits (ICs), through either monolithic approach [41] or multi-chip approach [42].

CMUTs experience less self-heating than piezoelectric transducers that have higher dielectric loss [43], [44]. In addition, CMUTs are composed of MR-compatible materials with susceptibility close to water and human tissue [45]. Therefore, CMUTs are ideal for MR-guided ultrasound therapy applications. Another important feature of CMUTs is their wide bandwidth because the mechanical impedance of the vibrating plate is much smaller than that of water or tissue near its resonant frequency [46]. The wide transducer bandwidth is beneficial in dual-mode operations where a single transducer is used for both imaging and therapy, as it is desirable to operate the transducer at higher frequency for imaging than for therapy to achieve high image resolution [47], [48]. With these advantages, CMUTs are promising candidates for therapeutic ultrasound applications.

The feasibility of HIFU using CMUTs has been reported in [49], [50]. An unfocused single-element CMUT was tested for thermal ablation with a water-mimicking phantom while being monitored by MR thermometry [49]. The tested CMUT was operated at 2.5 MHz, producing a peak-to-peak output pressure of 1.4 MPa (16.3 W/cm²). Based on the design of this CMUT, a concentric annular CMUT array was fabricated to realize focused ultrasound with high intensity at the focus [50]. These reports demonstrated the feasibility of HIFU using CMUTs, and showed that a concentric annular array can be used to treat an on-axis target. However, electronic focusing or beam-steering is not possible with these devices. A 2-D transducer array enables electronic focusing and steering in any direction in real-time by applying appropriate time delays to the array elements [51]–[53]. Real-time volumetric imaging based on the electronic beam steering was demonstrated using the 2-D CMUT arrays [46].

The purpose of this work is to develop a 2-D CMUT array and present the capability of HIFU using this array. We designed and fabricated a fully-populated 32×32-element 2-D CMUT array using the sacrificial release process with through-wafer via interconnects [37], [54], [55]. This array successfully demonstrated real-time volumetric imaging, and the imaging results were presented in [56]. In this study, we developed a multi-channel excitation system for HIFU operation and characterized the output pressure of this CMUT array. Then, we experimentally showed thermal ablation using this device.

Section II explains the methods we used to manufacture a 2-D transducer array and to develop the operating system to address this array. In Section III, we discuss the temperature simulations in tissue. Section IV presents the pressure characterization of the array and the *ex-vivo* tissue experiments. In section V, we discuss the issues we found in this study.

II. Methods

A. CMUT Design Parameters and Assembly

The transducer array has 32×32 elements with a pitch of $250 \mu\text{m}$ in both directions. With 64 ground elements at one edge of the array as shown in Figs. 1 (a) and (b), its total size is $8 \text{ mm} \times 8.5 \text{ mm}$. The CMUT cells are designed to operate at a 5-MHz center frequency in immersion. Their radius and the thickness of the CMUT plates are $19 \mu\text{m}$ and $0.7 \mu\text{m}$, respectively. The gap height is designed to be $0.2 \mu\text{m}$, for a collapse voltage of 96.1 V. The specifications of the CMUT array and its cells are summarized in Tables I and II, respectively.

The 2-D CMUT array is integrated with a custom designed application-specific integrated circuit (ASIC) using flip-chip bonding technique [42], and then wire-bonded in a pin-grid array (PGA) package [42], as shown in Figs. 1 (c) and (d). The custom ASIC flip-chip bonded underneath the CMUT array groups the 1024 array elements into eight excitation channels to implement the grouping scheme discussed in the next subsection.

B. Grouping Scheme

Ideally, the 32×32 -element CMUT array can be driven by a 1024-channel continuous wave (CW) excitation system for electronic focusing and beam steering. As in the ultrasound imaging [57], each CW channel can be individually delayed based on the distance from the array element to the targeted focus. However, this scheme makes the system complex, especially for HIFU excitation that requires a bank of AC generators, amplifiers, and matching inductors [50].

Instead of implementing a 1024-channel CW excitation system, we propose a grouping method to minimize the system complexity without significant loss of the focusing gain. Fig. 2 (a) presents the sorted phase delays from all array elements to the targeted focus. The array elements are grouped based on their phase delays, with 45° steps, to make eight phase groups. For example, the array elements with a phase delay between 0° and 45° are assigned to channel 1 (0°), and those with a phase delay between 45° and 90° are assigned to channel 2 (45°). This channel assignment scheme is depicted in Fig. 2 (a). Fig. 2 (b) plots the grouping configuration of the 2-D CMUT array for an on-axis focus at an 8-mm depth.

We simulated the output pressure field using an ultrasound field simulation software, Field II [58], [59]. The simulated pressure field distribution and focusing gain in a lossless medium of the 8-channel grouped array were compared to those of the same array driven by the ideal 1024-channel excitation system. Table III lists important simulation parameters, and Fig. 3 shows the simulated pressure fields for the two array configurations. The simulated focusing gain of the grouped array is 15.2, which is not significantly lower than the focusing gain of 15.6 for the ideal case. Decreasing the number of phase groups, or the number of excitation channels, helps reduce the system complexity at the cost of lowered focusing gain, as shown in Fig. 4. This figure confirms that eight is a good number for the number of excitation channels to reduce the system complexity without significant loss of focusing performance.

C. Experimental Setup

A plastic tank was attached to the PGA package and it was plugged onto a custom interface printed circuit board (PCB) designed to provide the 8-channel pre-phased AC inputs as well as the DC bias voltage to the CMUT array. Then, vegetable oil was filled in the tank to immerse the CMUT array. Vegetable oil has a higher attenuation coefficient than that of water, and 1.57 dB/cm attenuation is expected at 5-MHz frequency in vegetable oil [51]. However, vegetable oil was chosen as a medium instead of water because this CMUT array assembly was not passivated from electrical conduction. To generate eight 5-MHz CWs for the eight channels of the array, a pair of direct digital synthesizers (DDS9m, Novatech Instruments, Inc., Seattle, WA), each of which generates 4 phases, were used. An external pulse from an arbitrary waveform function generator (Agilent 33250A, Santa Clara, CA) was applied to the two direct digital synthesizers to synchronize their clocks. The eight phased CWs were then amplified by 1-W amplifiers (ZHL-3A-S, Mini-Circuits, Brooklyn, NY) followed by another custom amplifier stage. For impedance matching, an inductor was connected to each channel of the CMUT array in series as depicted in Fig. 5 (a).

Fig. 6 (a) is a drawing of the experimental setup. The interface board and the CMUT package were placed on a PC-controlled XY-stage to align the acoustic focus in the horizontal directions, and a separate Z-stage with a microcontroller adjusts the location of the experimental target in the vertical direction.

A hydrophone (HGL-0200, Onda Corporation, Sunnyvale, CA) was attached to the Z-stage for the output pressure measurement, and a tissue holder shown in Fig. 6 (b) was attached to the Z-stage for *ex-vivo* tissue experiments. The tissue holder has a window at the center, on which the target tissue is placed.

III. Simulations

We performed temperature simulations with HIFU Simulator [60]. The medium was defined in two layers, a layer of water (Medium 1) followed by a layer of tissue (Medium 2). In the simulations, the 2-D transducer array was approximated to an equivalent spherical bowl-shaped single-element transducer that generates a focus with the same focal spot size as that of the 2-D transducer array at the same distance. First, the acoustic field was simulated with attenuation and nonlinear propagation in the medium using the Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation

$$\frac{\partial \hat{p}_k}{\partial z} + \frac{ic_0}{2} \nabla_r^2 \hat{p}_k + \alpha_k \hat{p}_k = 0, \quad k=1, 2, \dots, K, \quad (1)$$

where $\hat{p}_k$ is the complex pressure field of the k^{th} harmonic, K is the total number of harmonics, z and r are the axial and radial coordinates, c_0 is the small-signal speed of sound,

$\nabla_r^2 = \frac{\partial^2}{\partial r^2} + \frac{\partial}{r \partial r}$ is the axisymmetric transverse Laplacian, and the real part and the imaginary part of α_k are the absorption and dispersion coefficients, respectively [61]. The simulation parameters for the pressure field simulations are summarized in Table IV.

The acoustic intensity, I , is calculated by

$$I(r, z) = \frac{1}{2\rho_0 c_0} \sum_{k=1}^K |\hat{p}_k|^2, \quad (2)$$

where ρ_0 is the mass density.

To calculate the temperature in the tissue, the intensity is converted to the heating rate, Q , by

$$Q(r, z) = \frac{1}{\rho_0 c_0} \sum_{k=1}^K \text{Re}(\alpha_k) |\hat{p}_k|^2. \quad (3)$$

The heating rate is used as a heat source for Pennes's bio-heat equation,

$$\rho_0 C \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) - \omega C T + Q, \quad (4)$$

where T is the temperature rise, t is time, κ is the thermal conductivity, C is the heat capacity, and ω is the perfusion rate [62]–[64].

Table V lists the parameters for temperature simulations. The pressure field simulation showed that the focal spot size was tiny when the sonication time is short. Therefore, to show a visible lesion size, a long-time sonication was used for the temperature simulations, instead of a sequence of short pulses. Fig. 7 (a) plots the expected peak temperature at the focus for a 1-min sonication.

After the temperature calculation, the ablated region can be determined using the cumulative equivalent minutes referenced to 43 °C [65]. This method determines the biological death of the cell by estimating the thermal dose accumulated during the exposure. The equivalent time referenced to 43 °C (CEM_{43}) is mathematically described as

$$CEM_{43} = \sum_{t=0}^{t=\text{final}} R^{(43-\bar{T})} \Delta t, \quad (5)$$

where t is the sufficiently small duration in time, $\bar{T}$ is the average temperature during time t , and $R = 0.5$ above 43 °C and $R = 0.25$ below 42 °C. With a threshold of 240 CEM_{43} for muscle tissue [5], [66], the colored area in Fig. 7 (b) represents the tissue region that exceeds the threshold.

IV. Results

A. Pressure Measurements

The output pressure at the surface of a single transducer element of the array was characterized in vegetable oil. Fig. 8 (a) presents the surface pressure under various DC and 5-MHz AC input combinations. The long-term measurement with a 40-V DC and a 60-V peak-to-peak AC in Fig. 8 (b) shows that the array is capable of generating a constant peak-to-peak pressure over 1 MPa for 8 min, which is long enough to create a lesion. Both measurements were performed with a hydrophone at a 2.4-mm distance from the transducer array surface, and the surface pressure was back calculated from this pressure by propagating back through the vegetable oil to the transducer surface. The attenuation of the oil for this propagation length is 0.37 dB [51].

All transducer elements of the array were excited by the 8-channel HIFU system, with each channel tuned by a series inductor for efficient power delivery at 5 MHz. Fig. 9 shows the measured peak-to-peak pressure at the focus with increasing DC bias voltage. The peak-to-peak AC input voltage was 40 V and 60 V for the two curves in the figure, and a 5-cycle burst wave was used for the AC excitation. The pressure at the focus increases with the DC input bias voltage until it reaches 58 V, and then decreases as the CMUT array elements start to collapse.

B. Ex-vivo Experiments

For *ex-vivo* experiments, the array was biased at a 40-V DC, and excited by 8-channel 60-V peak-to-peak 5-MHz AC inputs. This combination produced a peak-to-peak pressure of 8.5 MPa (645.1 W/cm^2) at the focus as presented in Fig. 9. Ultrasound propagated upward as shown in Fig. 6 (a), and was focused at the surface of a 2.5-mm thick bovine muscle slice placed on the tissue holder, which was 8-mm distant from the surface of the array. The experimental parameters are summarized in Table VI.

We performed three consecutive experiments with the bovine muscle tissue. First, we planned to use a thermocouple to measure the temperature-rise of the tissue near the focus during the sonication. Fig. 10 (a) shows the result after a 30-sec sonication. During this experiment, the temperature at the focus increased up to 97.8°C rapidly and made a lesion marked with a dotted circle. The measured temperature of 97.8°C was higher than the simulated temperature of 74.4°C presented in Fig. 7 (a). It is because the acoustic beam is partially reflected by the tip of the thermocouple thus leading to a higher temperature rise. In the second experiment, the array was repositioned to target a fresh part of the tissue. The thermocouple was removed to avoid its effect on the acoustic pressure at the focus, and a 1-min sonication was applied to the tissue at the same pressure level. As shown in Fig. 10 (b), a small lesion was created. To show a more visible lesion, a 2-min sonication was used in the third experiment. As more energy deposited for a longer duration, the lesion size became bigger compared to that from the 1-min sonication. Fig. 10 (c) shows the lesion created with the 2-min sonication.

After these experiments that proved the capability of creating lesions, we wrote a letter S on the tissue using a sequence of 1-min sonication, with the same input voltages and the same

distance to the target. Figs. 11 (a) and (b) show bovine muscle tissue and bovine liver tissue, respectively, after the sequence of sonication, which started from the top of the letter S and progressed toward the bottom.

V. Discussion

In Fig. 11, the lesions on the upper part of the S are less clear than those on the lower part. It is because of the drift in the ambient temperature. The attenuation in oil increased the ambient temperature in each sonication event. Therefore, for the lesions created later in time, the initial temperature before sonication was higher, leading to higher temperature at the end of sonication with the same thermal dose. For more accurate experiments, a constant temperature bath would be useful to eliminate the effect of ambient temperature.

In clinical situations, the initial sonication temperature is around 37 °C, which is the human body temperature. The ambient temperature in our experiments was mostly below 37 °C, as shown in Fig. 12. However, the experimental results show that HIFU is feasible using the CMUT array, even with initial temperature lower than the body temperature.

The drift in the ambient temperature was due to the acoustic energy absorbed by vegetable oil, which has relatively high attenuation coefficient. To verify, we measured the ambient temperature and the temperature of the CMUT array during sonication in water medium, which has a lower attenuation coefficient. As shown in Fig. 13, the drift of the ambient temperature was not observed in water while the array temperature increased by less than 3 °C. This temperature rise at the surface of the transducers, which could be from either the CMUT array itself or the ASIC, is not significant enough to cause a safety issue without cooling circulation.

VI. Conclusion

In this study, we demonstrated the first ex-vivo HIFU experiments using a 32×32-element CMUT array. These results show that we can make lesions with the presented array, which was designed for both imaging and HIFU operations, not optimally for HIFU applications. The same CMUT array already demonstrated volumetric imaging successfully [56]. Currently, we are developing the two-dimensional electronic beam-steering capability in HIFU operation, as well as a dual-mode system to support both HIFU and imaging with a single 2-D CMUT array [67]–[69].

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References

1. Kennedy JE, ter Haar GR, Cranston D. High intensity focused ultrasound: surgery of the future? *Br. J. Radiol.* 2003; 76(909):590–599. [PubMed: 14500272]
2. Sanghvi NT, Fry FJ, Bihle R, Foster RS, Phillips MH, Syrus J, Zaitsev AV, Hennige CW. Noninvasive surgery of prostate tissue by high-intensity focused ultrasound. *IEEE Trans. Ultrason., Ferroelect., Freq. Control.* 1996; 43(6):1099–1110.
3. Dubinsky TJ, Cuevas C, Dighe MK, Kolokythas O, Hwang JH. High-intensity focused ultrasound: current potential and oncologic applications. *Am. J. Roentgenol.* 2008; 190(1):191–199. [PubMed: 18094311]
4. Kennedy JE, Wu F, ter Haar GR, Gleeson FV, Phillips RR, Middleton MR, Cranston D. High-intensity focused ultrasound for the treatment of liver tumours. *Ultrasonics.* 2004; 42(1):931–935. [PubMed: 15047409]
5. Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. *Int. J. Hyperther.* 2003; 19(3):267–294.
6. Chen W-S, Lafon C, Matula TJ, Vaezy S, Crum LA. Mechanisms of lesion formation in high intensity focused ultrasound therapy. *Acoust. Res. Lett. Onl.* 2003; 4(2):41–46.
7. ter Haar GR, Coussios C. High intensity focused ultrasound: physical principles and devices. *Int. J. Hyperther.* 2007; 23(2):89–104.
8. ter Haar GR. Ultrasound focal beam surgery. *Ultrasound Med. Biol.* 1995; 25(5):1089–1110.
9. Wu F, Wang Z-B, Chen W-Z, Wang W, Gui Y, Zhang M, Zheng G, Zhou Y, Xug G, Lih M, Zhang C, Ye J, Feng R. Extracorporeal high intensity focused ultrasound ablation in the treatment of 1038 patients with solid carcinomas in China: an overview. *Ultrason. Sonochem.* 2004; 11(3):149–154. [PubMed: 15081972]
10. Wu F, Wang Z-B, Zhu H, Chen W-Z, Zou J-Z, Bai J, Li K-Q, Jin C-B, Xie F-L, Su H-B. Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer. *Breast Cancer Res. Treat.* 2005; 92(1):51–60. [PubMed: 15980991]
11. Madersbacher S, Pedevilla M, Vingers L, Susani M, Marberger M. Effect of high-intensity focused ultrasound on human prostate cancer in vivo. *Cancer Res.* 1995; 55(15):3346–3351. [PubMed: 7542168]
12. Gelet A, Chapelon JY, Bouvier R, Rouviere O, Lyonnet D, Dubernard JM. Transrectal high intensity focused ultrasound for the treatment of localized prostate cancer: factors influencing the outcome. *Eur. Urol.* 2001; 40(2):124–129. [PubMed: 11528187]
13. Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. *BJU Int.* 2006; 97(1):56–61. [PubMed: 16336329]
14. Yang R, Reilly CR, Rescorla FJ, Faught PR, Sanghvi NT, Fry FJ, Franklin TD, Lumeng L, Grosfeld JL. High-intensity focused ultrasound in the treatment of experimental liver cancer. *Arch. Surg.* 1991; 126(8):1002–1010. [PubMed: 1863205]
15. Wu F, Wang Z-B, Chen W-Z, Zhu H, Bai J, Zou J-Z, Li K-Q, Jin C-B, Xie F-L, Su H-B. Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. *Ann. Surg. Oncol.* 2004; 11(12):1061–1069. [PubMed: 15545506]
16. Illing RO, Kennedy JE, Wu F, ter Haar GR, Protheroe AS, Friend PJ, Gleeson FV, Cranston DW, Phillips RR, Middleton MR. The safety and feasibility of extracorporeal high-intensity focused ultrasound (HIFU) for the treatment of liver and kidney tumours in a Western population. *Br. J. Cancer.* 2005; 93(8):890–895. [PubMed: 16189519]
17. Chen W, Zhu H, Zhang L, Li K, Su H, Jin C, Zhou K, Bai J, Wu F, Wang Z. Primary Bone Malignancy: Effective Treatment with High-Intensity Focused Ultrasound Ablation 1. *Radiology.* 2010; 255(3):967–978. [PubMed: 20501734]
18. Wang X, Sun J. High-intensity focused ultrasound in patients with late-stage pancreatic carcinoma. *Chin. Med. J.* 2002; 115(9):1332–1335. [PubMed: 12411106]
19. Kennedy JE. High-intensity focused ultrasound in the treatment of solid tumours. *Nat. Rev. Cancer.* 2005; 5(4):321–327. [PubMed: 15776004]

20. Cline HE, Schenck JF, Hynynen K, Watkins RD, Souza SP, Jolesz FA. MR-guided focused ultrasound surgery. *J. Comput. Assist. Tomo.* 1992; 16(6):956–965.
21. Rieke V, Pauly KB. MR thermometry. *J. Magn. Reson. Imag.* 2008; 27(2):376–390.
22. Chung AH, Jolesz FA, Hynynen K. Thermal dosimetry of a focused ultrasound beam in vivo by magnetic resonance imaging. *Med. Phys.* 1999; 26(9):2017–2026. [PubMed: 10505893]
23. Tempany CMC, Stewart EA, McDannold N, Quade BJ, Jolesz FA, Hynynen K. MR Imaging–guided Focused Ultrasound Surgery of Uterine Leiomyomas: A Feasibility Study 1. *Radiology.* 2003; 226(3):897–905. [PubMed: 12616023]
24. Hynynen K, Pomeroy O, Smith DN, Huber PE, McDannold NJ, Kettenbach J, Baum J, Singer S, Jolesz FA. MR Imaging–guided Focused Ultrasound Surgery of Fibroadenomas in the Breast: A Feasibility Study 1. *Radiology.* 2001; 219(1):176–185. [PubMed: 11274554]
25. Liberman B, Gianfelice D, Inbar Y, Beck A, Rabin T, Shabshin N, Chander G, Hengst S, Pfeffer R, Chechick A, Hanannel A, Dogadkin O, Catane R. Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. *Ann. Surg. Oncol.* 2009; 16(1): 140–146. [PubMed: 19002530]
26. Furusawa H, Namba K, Thomsen S, Akiyama F, Bendet A, Tanaka C, Yasuda Y, Nakahara H. Magnetic resonance–guided focused ultrasound surgery of breast cancer: reliability and effectiveness. *J. Am. Coll. Surgeons.* 2006; 203(1):54–63.
27. Huber PE, Jenne JW, Rastert R, Simiantonakis I, Sinn H-P, Strittmatter H-J, von Fournier D, Wannenmacher MF, Debus J. A new noninvasive approach in breast cancer therapy using magnetic resonance imaging–guided focused ultrasound surgery. *Cancer Res.* 2001; 61(23):8441–8447. [PubMed: 11731425]
28. Liu H-L, Hua M-Y, Yang H-W, Huang C-Y, Chu P-C, Wu J-S, Tseng I-C, Wang J-J, Yen T-C, Chen P-Y, Wei K-C. Magnetic resonance monitoring of focused ultrasound/magnetic nanoparticle targeting delivery of therapeutic agents to the brain. *Proc. Natl. Acad. Sci.* 2010; 107(34):15205–15210. [PubMed: 20696897]
29. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA. MRgFUS Study Group. Pregnancy outcome after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. *Fertil. Steril.* 2010; 93(1):199–209. [PubMed: 19013566]
30. de Smet M, Heijman E, Langereis S, Hijnen NM, Grüll H. Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: an in vivo proof-of-concept study. *J. Control. Release.* 2011; 150(1):102–110. [PubMed: 21059375]
31. Lafon C, Chapelon JY, Prat F, Gorry F, Margonari J, Theillere Y, Cathignol D. Design and preliminary results of an ultrasound applicator for interstitial thermal coagulation. *Ultrasound in medicine & biology.* 1998; 24(1):113–122. [PubMed: 9483778]
32. Martin RW, Vaezy S, Proctor A, Myntti T, Lee JB, Crum L. Water-cooled, high-intensity ultrasound surgical applicators with frequency tracking. *IEEE Trans. Ultrason., Ferroelect., Freq. Control.* 2003; 50(10):1305–1317.
33. Wu F, Wang Z-B, Chen W-Z, Bai J, Zhu H, Qiao T-Y. Preliminary experience using high intensity focused ultrasound for the treatment of patients with advanced stage renal malignancy. *The Journal of urology.* 2003; 170(6):2237–2240. [PubMed: 14634387]
34. Li J-J, Xu G-L, Gu M-F, Luo G-Y, Rong Z, Wu P-H, Xia J-C. Complications of high intensity focused ultrasound in patients with recurrent and metastatic abdominal tumors. *World J. Gastroenterol.* 2007; 13(19):2747–2751. [PubMed: 17569147]
35. Zhao Z, Wu F. Minimally-invasive thermal ablation of early-stage breast cancer: a systemic review. *Eur. J. Surg. Oncol.* 2010; 36(12):1149–1155. [PubMed: 20889281]
36. Zhang L, Zhu H, Jin C, Zhou K, Li K, Su H, Chen W, Bai J, Wang Z. High-intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins. *Eur. Radiol.* 2009; 19(2):437–445. [PubMed: 18795303]
37. Ergun AS, Huang Y, Zhuang X, Oralkan Ö, Yarahoglu GG, Khuri-Yakub BT. Capacitive micromachined ultrasonic transducers: fabrication technology. *IEEE Trans. Ultrason., Ferroelect., Freq. Control.* 2005; 52(12):2242–2258.

38. Yoon, H-S.; Ho, M-C.; Apte, N.; Cristman, P.; Vaithilingam, S.; Kupnik, M.; Pauly, KB.; Khuri-Yakub, BT. Fabrication of CMUT Cells with Gold Center Mass for Higher Output Pressure. AIP Conf. Proc; Tokyo, Japan. 2010.
39. Oralkan Ö, Ergun AS, Cheng CH, Johnson JA, Karaman M, Lee TH, Khuri-Yakub BT. Volumetric ultrasound imaging using 2-D CMUT arrays. IEEE Trans. Ultrason., Ferroelect., Freq. Control. 2003; 50(11):1581–1594.
40. Choe JW, Oralkan Ö, Nikoozadeh A, Gencel M, Stephens DN, O'Donnell M, Sahn DJ, Khuri-Yakub BT. Volumetric Real-Time Imaging Using a CMUT Ring Array. IEEE Trans. Ultrason., Ferroelect., Freq. Control. 2012; 59(6):1201–1211.
41. Daft, C.; Calmes, S.; Da Graca, D.; Patel, K.; Wagner, P.; Ladabaum, I. Microfabricated ultrasonic transducers monolithically integrated with high voltage electronics. IEEE Ultrasonics Symp; Montreal, Canada. 2004.
42. Wygant IO, Jamal NS, Lee HJ, Nikoozadeh A, Oralkan Ö, Karaman M, Khuri-Yakub BT. An integrated circuit with transmit beamforming flip-chip bonded to a 2-D CMUT array for 3-D ultrasound imaging. IEEE Trans. Ultrason., Ferroelect., Freq. Control. 2009; 56(10):2145–2156.
43. Ergun, AS.; Barnes, S.; Gardner, E. An assessment of the thermal efficiency of capacitive micromachined ultrasonic transducers. IEEE Ultrasonics Symp; New York, NY, USA. 2007.
44. Chen, Y.; Wen, Y.; Li, P. IEEE Inf. Acquisition. Hefei Shi, China: 2004. Loss mechanisms in piezoelectric transducers and its response to stress.
45. Schenck JF. The role of magnetic susceptibility in magnetic resonance imaging: MRI magnetic compatibility of the first and second kinds. J. Med. Phys. 1996; 23(6):815–850.
46. Khuri-Yakub BT, Oralkan Ö. Capacitive micromachined ultrasonic transducers for medical imaging and therapy. J. Micromech. Microeng. 2011; 21(5):54004–54015. [PubMed: 21860542]
47. Ebbini ES, Yao H, Shrestha A. Dual-mode ultrasound phased arrays for image-guided surgery. Ultrason. Imaging. 2006; 28(2):65–82. [PubMed: 17094688]
48. Bouchoux G, Lafon C, Berriet R, Chapelon JY, Fleury G, Cathignol D. Dual-mode ultrasound transducer for image-guided interstitial thermal therapy. Ultrasound Med. Biol. 2008; 34(4):607–616. [PubMed: 18055099]
49. Wong SH, Watkins RD, Kupnik M, Pauly KB, Khuri-Yakub BT. Feasibility of MR-Temperature Mapping of Ultrasonic Heating from a CMUT. IEEE Trans. Ultrason., Ferroelect., Freq. Control. 2008; 55(4):811–818.
50. Wong SH, Kupnik M, Watkins RD, Pauly KB, Khuri-Yakub BT. Capacitive Micromachined Ultrasonic Transducers for Therapeutic Ultrasound Applications. IEEE Trans. Biomed. Eng. 2010; 57(1):114–123. [PubMed: 19628448]
51. Oralkan Ö, Ergun AS, Johnson JA, Karaman M, Demirci U, Kaviani K, Lee TH, Khuri-Yakub BT. Capacitive micromachined ultrasonic transducers: next-generation arrays for acoustic imaging? IEEE Trans. Ultrason., Ferroelect., Freq. Control. 2002; 49(11):1596–1610.
52. Smith SW, Pavy HG Jr, Von Ramm OT. High-speed ultrasound volumetric imaging system. I. Transducer design and beam steering. IEEE Trans. Ultrason., Ferroelect., Freq. Control. 1991; 38(2):100–108.
53. Turnbull DH, Foster FS. Beam steering with pulsed two-dimensional transducer arrays. IEEE Trans. Ultrason., Ferroelect., Freq. Control. 1991; 38(4):320–333.
54. Cheng, CH.; Ergun, AS.; Khuri-Yakub, BT. Electrical through wafer interconnects with 0.05 picofarad parasitic capacitance on 400 μ m thick silicon substrate. Solid-State Sensor, Actuator, and Microsystems Workshop; Hilton Head Island, SC, USA. 2002.
55. Zhuang, X.; Wygant, IO.; Lin, D-S.; Kupnik, M.; Oralkan, Ö.; Khuri-Yakub, BT. Trench-isolated CMUT arrays with a supporting frame: Characterization and imaging results. IEEE Ultrason. Symp; New York, NY, USA. 2007.
56. Bhuyan A, Choe JW, Lee BC, Wygant IO, Nikoozadeh A, Oralkan Ö, Khuri-Yakub BT. Integrated Circuits for Volumetric Ultrasound Imaging With 2-D CMUT Arrays. IEEE Trans. Biomed. Circuits Syst. 2013; 7(6):796–804. [PubMed: 24473544]
57. Nelson TR, Pretorius DH. Three-dimensional ultrasound imaging. Ultrasound Med. Biol. 1998; 24(9):1243–1270. [PubMed: 10385948]

58. Jensen JA, Svendsen NB. Calculation of pressure fields from arbitrarily shaped, apodized, and excited ultrasound transducers. *IEEE Trans. Ultrason., Ferroelect., Freq. Control.* 1992; 39:262–267.
59. Jensen JA. Field: A program for simulating ultrasound systems. *Med. Biol. Eng. Comput.* 1996; 34(1-1):351–353. [PubMed: 8945858]
60. Soneson, JE. A User-Friendly Software Package for HIFU Simulation; AIP Conf. Proc; 2009.
61. Rozanova-Pierrat A. Mathematical analysis of Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation. HAL. 2006
62. Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm. *J. Appl. Physiol.* 1948; 1(2):93–122. [PubMed: 18887578]
63. Nyborg WL. Solutions of the bio-heat transfer equation. *Phys. Med. Biol.* 1988; 33(7):785–792. [PubMed: 3212041]
64. Wu J, Du G. Temperature elevation generated by a focused Gaussian beam of ultrasound. *Ultrasound Med. Biol.* 1990; 16(5):489–498. [PubMed: 2238255]
65. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int. J. Radiat. Oncol.* 1984; 10(6):787–800.
66. Yarmolenko PS, Moon EJ, Landon C, Manzoor A, Hochman DW, Viglianti BL, Dewhirst MW. Thresholds for thermal damage to normal tissues: An update. *Int. J. Hyperther.* 2011; 27(4):320–343.
67. Yoon, H-S.; Firouzi, K.; Bhuyan, A.; Jang, J.; Choe, JW.; Nikoozadeh, A.; Chang, C.; Watkins, RD.; Stephens, D.; Butts-Pauly, K.; Khuri-Yakub, P. A Dual-Mode Integrated 2-D CMUT array for Real-time Volumetric imaging and HIFU. AIP Conf. Proc; Utrecht, Netherlands. 2015.
68. Ebbini, ES.; Bischof, JC.; Coad, JE. Lesion formation and visualization using dual-mode ultrasound phased arrays. *IEEE Ultrasonics Symp*; Atlanta, GA, USA. 2001.
69. Jang, JH.; Rasmussen, MF.; Bhuyan, A.; Yoon, H-S.; Moini, A.; Chang, C.; Watkins, RD.; Choe, JW.; Nikoozadeh, A.; Stephens, D.; Oralkan, Ö.; Pauly, KB.; Khuri-Yakub, B. Dual-mode integrated circuit for imaging and HIFU with 2-D CMUT arrays. *IEEE Ultrasonics Symp*; Taipei, Taiwan. 2015.

Fig. 1.

Optical pictures of (a) front side of a CMUT array, (b) backside of a CMUT array, (c) top-view of an ASIC, (d) a CMUT array and an ASIC integrated in a PGA.

Fig. 2.

(a) Sorted phase delay of 1024 elements with indication of the channel assignment, (b) array element location for an 8-mm focal depth, viewing from the top.

Fig. 3. Simulated peak pressure of a focused array comparing the 8-group phase delay with the exact phase delay. (a) Radial direction at the focus, (b) axial direction at the center of the array

Fig. 4.

Simulated focusing gain of a focused array with increasing number of phase groups. The dotted line indicates the simulated focusing gain of the ideally focused array with the exact 1024-channel phase delays.

(a)

(b)

Fig. 5.

(a) System block diagram, (b) optical picture of the experimental setup.

(a)

(b)

Fig. 6.

(a) Illustration of the experimental setup, (b) an optical picture of a tissue holder with an acoustic window in the center.

Fig. 7.

Temperature simulation results. (a) Peak temperature change at the focus, (b) 2-D temperature profile near focus, the contours are the temperature at the end of the sonication, colored area is the tissue region that exceeded the thermal dose of $240 CEM_{43}$.

Fig. 8. Measured peak-to-peak pressure at the surface of the transducer. (a) Measured pressure with increasing DC bias (b) Long-time measurement at DC 40 V and peak-to-peak AC 60 V input

Fig. 9.
Measured peak-to-peak pressure at the focus.

Fig. 10.

Ex-vivo tissue experiments with a bovine muscle tissue (a) placed with a thermocouple (b) after 1-min sonication (c) after 2-min sonication.

Fig. 11.

Ex-vivo tissue experiments (a) bovine muscle tissue, with 12 of 1-min sonication (b) bovine liver tissue, with 12 of 1-min sonication.

Fig. 12.

Initial temperature change. Temperature measured before starting every 1-min sonication. The dotted line indicates 37 °C body temperature.

Fig. 13.

Temperature change when medium is water. During 1-min sonication the temperature at the surface of the transducer increased by 3 °C only.

TABLE I

CMUT Array Specifications

Parameter	Value
Number of elements	1024
Center frequency (MHz)	5
CMUT cells per element	24
Element width (μm)	250
Element height (μm)	250

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TABLE II

CMUT Cell Specifications

Parameter	Value
Radius of total area (μm)	21
Radius of plate (μm)	19
Thickness of plate (μm)	0.7
Radius of top electrode (μm)	12.5
Gap height (μm)	0.2
Thickness of insulation layer (μm)	0.146

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TABLE III

Field Simulation Parameters

Parameter	Value
Center frequency (MHz)	5
Focal depth (mm)	8.0
Number of elements in x-direction	32
Number of elements in y-direction	32
Element pitch in x-direction (mm)	0.25
Element pitch in y-direction (mm)	0.25
Speed of sound (m/s)	1540
Peak surface pressure (MPa)	1
Simulation frequency (MHz)	100

TABLE IV**Pressure Simulation Parameters**

	Parameter	Value
Medium 1 (Water)	Speed of sound (m/s)	1500
	Density (kg/m ³)	1000
	Absorption (dB/m/MHz)	0.217
	Exponent of absorption	2
	Nonlinear parameter	3.5
Medium 2 (Tissue)	Speed of sound (m/s)	1629
	Density (kg/m ³)	1000
	Absorption (dB/m/MHz)	58
	Exponent of absorption	1
	Nonlinear parameter	4.5
	Medium transition distance (mm)	2
Transducer	Radius (mm)	4
	Focal depth (mm)	8
	Frequency (MHz)	5
	Peak surface pressure (MPa) *	0.5

* Peak surface pressure was chosen to match the experimental peak-to-peak pressure of 8.5 MPa measured at the focus with vegetable oil medium.

TABLE V

Temperature Simulation Parameters

Parameter		Value
Medium 1 (Water)	Heat capacity (J/kg/K)	4180
	Thermal conductivity (W/m/K)	0.6
	Perfusion rate (kg/m ³ /s)	0
Medium 2 (Tissue)	Heat capacity (J/kg/K)	4180
	Thermal conductivity (W/m/K)	0.6
	Perfusion rate (kg/m ³ /s)	20
Sonication sequence	Number of pulse	1
	Sonication duration (s)	60
	Cool-off duration (s)	5

TABLE VI

Experimental Parameters

	Parameter	Value
	DC bias (V)	40
CMUT array settings	Peak-to-peak AC input (V)	60
	Measured peak-to-peak pressure at the focus (MPa)	8.5
Trial 1-1	Sonication duration (s)	30
Trial 1-2	Sonication duration (s)	60
Trial 1-3	Sonication duration (s)	120
Trial 2-1	Number of sonication	12
	Sonication duration (s)	60
Trial 2-2	Number of sonication	12
	Sonication duration (s)	60