Interdigitated Annular CMUT Arrays for Ultrasound Assisted Delivery of Fluorescent Contrast Agents

P. Cristman[1], O. Oralkan[1], M. Mandella[2], O. Solgaard[1], C. Contag[2], and B. T. Khuri-Yakub[1]
[1] E. L. Ginzton Laboratory [2] Department of Pediatrics
Stanford University, Stanford CA

***Abstract*—Detection of early stage cancer is critical to successful treatment. Molecular imaging contrast agents offer great promise for early stage cancer detection. For improved image quality and diagnostics there is a need to improve the delivery, activation, and uptake of molecular imaging contrast agents. Low intensity focused ultrasound is one option to improve the delivery of molecular imaging agents. Here we investigate a circularly symmetric interdigitated capacitive micromachined ultrasonic transducer for improved delivery of fluorescent contrast agents to be imaged by a miniature dual axis confocal microscope. In order to apply ultrasound energy in the field of view of the optical microscope interface waves must be exploited. The device clearly focuses the ultrasound energy on the surface and at the center of the device. Overlapping the field of view of the optical microscope is required for improved *in vivo* imaging. Reasonable intensities of about 145 mW/cm^2 have been demonstrated for enhanced delivery of the contrast agents.**

***Index Terms*—CMUT, DAC, Low intensity focused ultrasound, Drug delivery**

I. Introduction

Early stage cancer detection is critical for successful treatment. For this reason there has been a continued effort to detect early stage cancers. One promising advance has been the creation of molecular contrast agents [1-2]. There is a need to improve the delivery, activation, and uptake of these contrast agents. One option is to apply low intensity focused ultrasound directly to the region to be imaged.

Ultrasound has been widely used in medical applications for both diagnostic and therapeutic purposes. Diagnostic imaging is probably the most common application of ultrasound in medicine. The exposure intensity levels for diagnostic ultrasound are below 0.5 W/cm^2. At the other end of the spectrum, high-intensity focused ultrasound (>1000 W/cm^2) is used to destroy tissue to treat cancers and other abnormalities such as arrhythmias in the heart. Ultrasound intensities in the mid-range (e.g., 0.5-3 W/cm^2) are used for other therapeutic applications such as in physical therapy or to enhance drug delivery [3-5].

In vivo microscopic detection and analyses of disease states has tremendous potential for improved screening and management of disease. One device under development at Stanford University is a miniature dual axis confocal (DAC) fluorescent microscope for endoscopic applications [6-7]. The DAC microscope is used to image fluorescent contrast agents that bind specifically to cancer cells. The field of view of the DAC microscope is limited to a depth of 300 μm making the application of ultrasound energy difficult. In order to overlap the acoustic pressure field with the optical field and not interfere with the lens optics, laterally propagating interface waves must be exploited.

A well-known phenomenon in capacitive micromachined ultrasonic transducer (CMUT) imaging arrays is cell-to-cell or element-to-element crosstalk. Crosstalk is in large part due to strong interface waves propagating in the transducer [8]. These interface waves in CMUT technology have been used in conjunction with an interdigitated configuration for sensing fluid properties [9]. Here a circularly symmetric interdigitated CMUT array is being combined with a miniature DAC fluorescence microscope. Using a circular geometry to focus ultrasound energy has been used previously for drop ejection applications [10]. CMUT technology is advantageous for this application because it is easy to fabricate a circular geometry and to integrate with electronics [11]. The central portion of the interdigitated transducer can also be removed conveniently using deep reactive ion etching, a standard process in silicon device fabrication. Section II will discuss the design and fabrication of the device while Section III will address the characterization results.

II. Design

For this application a circularly symmetric interdigitated CMUT is used to focus the surface waves into the field of view of a dual-axis confocal microscope. The circular CMUT transducer has the center removed creating a ring shape allowing a clear path for the optics. Ultimately, the CMUT will be packaged at the end of the miniature DAC microscope to fit inside a 6-mm instrument channel of a commercial endoscope.

The first generation of devices was fabricated in two sizes; one for testing and characterization with bench top setups and the other for potential integration in the 6 mm package. The larger devices for bench top testing have an inner diameter of 2 mm and an outer diameter of 4.5 mm. The new miniature DAC microscope package uses a 1 mm diameter gradient index lens to relay the image location outside of the device. The final ultrasound device would be centered around this 1 mm lens. Therefore the devices for potential integration have a 1.2 mm inner diameter and a 2.6 mm outer diameter. The outer diameter is currently limited by wiring constraints. In future generations the outer diameter will be increased to better utilize the available space and reduced for packaging in smaller catheter based applications.

The CMUT devices were fabricated using the standard wafer bonding process [12]. The final step using deep reactive ion etching to open the center region and singulate the devices was not performed for initial testing. With over 200 devices per 4 inch wafer a wide variety of designs were produced. The optimal frequency for sonoporation is not well known and requires exploring a wide parameter space using the specific contrast agents. The plate thickness of the CMUTs was 1 μm. Each device had a uniform cell geometry varying from device to device. Both circular and 2:1 aspect ratio rectangular geometries were fabricated. The width or diameter of the cells ranged from 20 μm to 60 μm. The ring spacing was constant for any one device but did vary from 10 μm to 30 μm in different designs. Finally the number of finger pairs ranged form 3 to 5 for the small devices and 5 to 10 for the larger devices. The vacuum gap height of the devices was 500 nm.

By varying the size and shape of the CMUT cell used to create the finger pairs of the interdigitated transducer a wide range of operating frequencies from below 1 MHz to 20 MHz were fabricated. The majority of designs are in the 1 MHz to 5 MHz range most common for ultrasound mediated drug delivery. The broad frequency range available will allow for testing to find an optimal frequency for the tissues found in the gastrointestinal track. An optical picture of a fabricated small device with 60 μm circular cells is shown in Figure 1. The device was sectioned into four quadrants so a possible defect in one quadrant could be isolated and the whole device was not lost. The four quadrant design enables a few other tests that would not be possible with continuous rings such as time of flight measurements to non-excited cells to measure the speed of the surface waves. The interdigitated CMUT fundamentally only requires two signal connections and one ground connection.

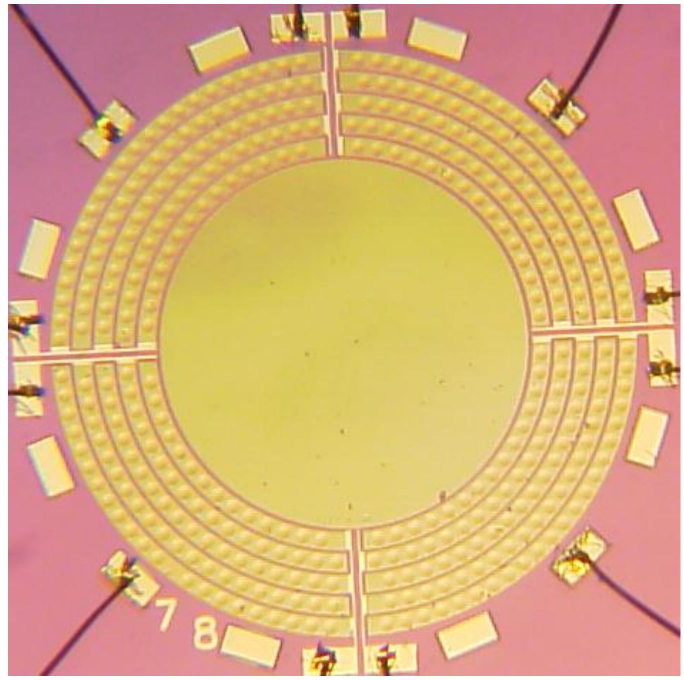

Fig. 1. Fabricated interdigitated CMUT wire bonded to test board. Device is a small device with 60 μm circular cells.

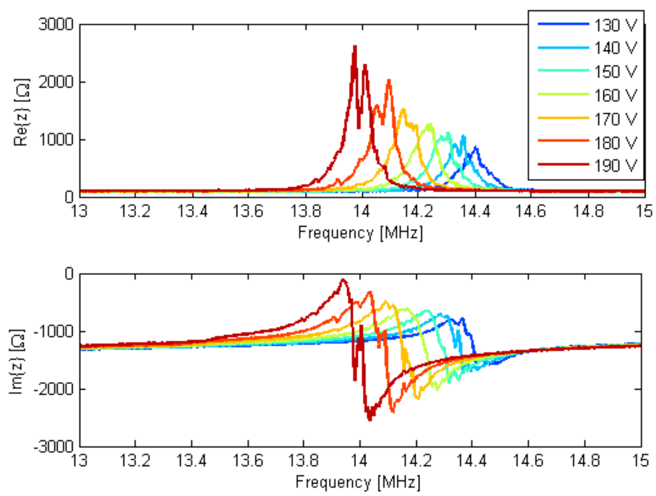

Fig. 2. Input impedance in air of 30 μm circular cells.

III. Characterization Results

After fabrication to confirm the device functionality the input impedance measurements were taken (Agilent Technologies, Model 4294A, Palo Alto, CA). A sample input impedance measurement as a function of the DC bias voltage is shown in Figure 2. After probing a device for functionality it was then wire bonded to a printed circuit board to connect the quadrants and bias for differential excitation. In order to excite adjacent rings out of phase for efficient generation of interface waves a balanced to unbalanced transformer (Mini-Circuits, ADT1-6T+, Brooklyn, NY) was used. By creating the phase shift in the AC excitation the same DC supply voltage can be used for all the CMUT cells. This means that any initial charging or charging drift will be the as similar as possible for all CMUT cells. A circuit diagram including the balanced to unbalanced transformer, coupling capacitors, current limiting resistors is show in Figure 3.

After wire bonding to the PCB the devices were measured using Laser Doppler Vibrometry (LDV) to confirm the correct motion of the cells. The out of phase motion of the cells was confirmed using a single point system (Polytec GmbH. OFV 2100, Berlin Germany) for the majority of the devices. A few devices were measured using a scanning system the MSA-500 at Polytec's North American headquarters in Irvine CA. Figure

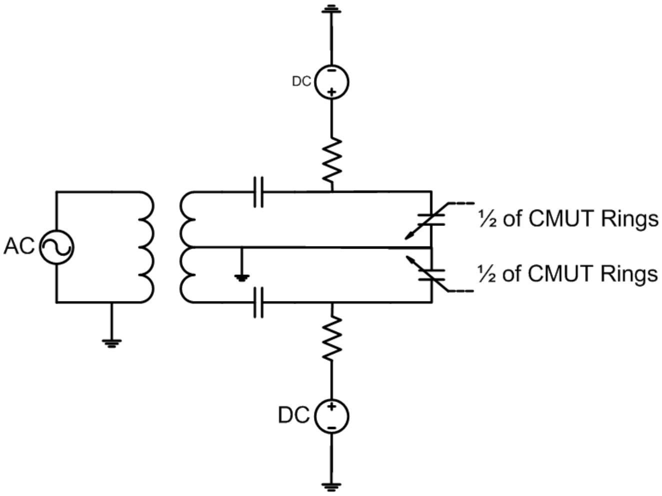

Fig. 3. Biasing circuit for interdigitated excitation including balanced to unbalanced transformer, coupling capacitors, and current limiting resistors.

4 shows one example of this motion taken with the MSA-500. The optical picture under the LDV data shows the rectangular cells measured as reference. The red color represents upward deflection of the cell and the green downward deflection. The cells showed peak to peak deflections greater than 100 nm in air.

The devices were placed in vegetable oil and again LDV measurements were taken. In immersion the cells still showed peak to peak displacements over 100 nm. Using the LDV to measure the center silicon displacement the self focusing was clearly observed. Figure 5 shows one measurement for a device operating at 1.2 MHz in immersion excited by a small AC excitation of only 10 V peak to peak. A different device operating at 6 MHz was excited with a large AC signal of 53 V peak to peak showed peak to peak displacements over 6 nm on the silicon surface.

To confirm the self focusing nature of the circular geometry measurements were taken using a calibrated hydrophone (Onda Corporation, HNP-0400, Sunnyvale). Measuring the same 1.2 MHz device a peak pressure of 66 kPa was measured on focus. This represents an average intensity of 145 mW/cm^2. The 3-dB focal spot size of the pressure field was 400 μm by 400 μm at 1.5 mm distance. Figure 6 shows the hydrophone measurement. The hydrophone measurement of the device at 6 MHz showed a smaller 200 μm by 200 μm 3-dB focal spot.

IV. Conclusion

Here a circularly symmetric interdigitated CMUT array was proposed for low intensity focused ultrasound contrast agent delivery. The device was fabricated and initial electrical and acoustic testing was preformed. Self focusing was clearly demonstrated by LDV measurements on the silicon surface and calibrated hydrophone measurements at a distance. The exact pressures produced at the surface are difficult to measure without potentially damaging the device or the hydrophone. The measurements at a distance suggest the devices are capable of producing the intensities necessary for sonoporation.

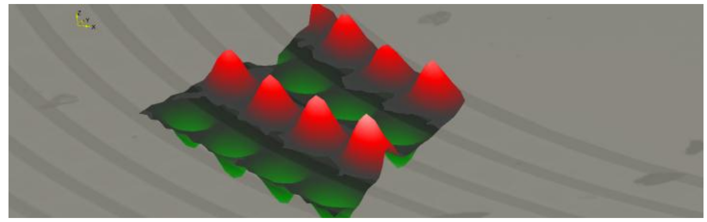

Fig. 4. Differential motion of interdigitated CMUT cells measured on Polytec MSA-500 scanning laser vibrometer. Optical picture frames the vibrometer data showing the rings, cells, and center region of the devices. The red color represents motion out of the plane and the green color represents motion into the plane.

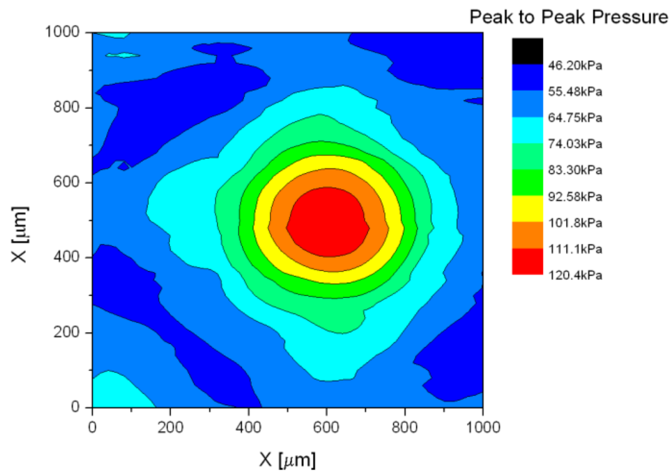

Fig. 6. Calibrated hydrophone measurement of center focusing showing an average intensity of 145 mW/cm^2.

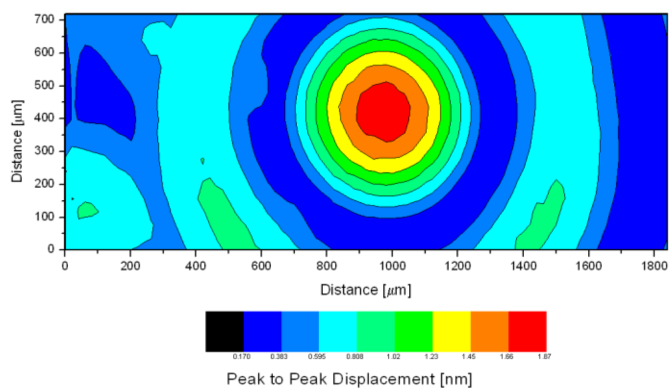

Fig. 5. LDV measurement of center silicon displacement at low biasing conditions.

Testing the effectiveness of sonoporation near the surface in phantoms will begin soon. For this device there is no substitute for *in vivo* testing because sonoporation results from both thermal and non-thermal ultrasound effects.

The device has promise as a photo-acoustic receiver as well. Since the device is already packaged with a scanning laser the interdigitated CMUT can act as a large highly sensitive single element receiver. The position of the laser can be used to map the generation location of the photo-acoustic signal giving optical resolution to the photo-acoustic image. Previous work has shown the low noise high sensitivity of CMUTs as photo-acoustic receivers. Some additional circuitry would be needed to switch between driving and receiving modes of the device.

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