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CIS II Critical Review of Selected Papers

The selected papers for this critical review are “Miniature ultrasound ring array transducers for transcranial ultrasound neuromodulation of freely-moving small animals,” (Kim H, Kim S, Sim N, et al.) and “Advances in Capacitive Micromachined Ultrasonic Transducers” (Brenner K, Ergun A, Firouzi K, et al), which is a review paper. These papers were chosen because of the relevance with my project, an implantable ultrasound device for neurosurgical monitoring. To achieve our maximum deliverable, we hope to take advantage of the CMUT (Capacitive Micromachined Ultrasonic Transducer) array that enables us to miniaturize the ultrasound portion of our device. Although our mentors are looking to out-source this component of the project due to the lack of microfabrication capabilities at JHU, this is still an important component to understand. In particular, the first paper was selected for its similarity in geometry to our desired CMUT chip while the second paper was selected for its ability to extensively describe the physics behind the CMUT array, elaborate on the microfabrication process, and its breadth in analyzing the advantages and disadvantages of using the CMUT array for medical imaging purposes.

A CMUT array is consisted of several CMUT elements, which are each made up of parallel connected cells (Brenner). Each cell has a flexible membrane and a fixed bottom plate which are conductive and forms a capacitor. The CMUT interacts with air or water to radiate and sense ultrasound. To receive, an ultrasonic wave causes the flexible membrane to vibrate, allowing the change of capacitance to be detected. To transmit, an alternating voltage is applied that causes the flexible membrane to vibrate and send out ultrasound. CMUTs are advantageous for medical imaging purposes because of its ability to be customized with electronics, small size, and low cost, allowing this to be mass produced and easily accessible.

Kim’s group uses this CMUT array technology to fabricate a miniature ultrasound transducer for stimulating the motor cortex of mice. In the past, due to the bulkiness of standard transducers (due to hand ergonomics and the size of the traditional piezoelectric crystals), small animals have been limited to stimulation under anesthesia and fixed

stereotactically. No neuromodulation experiments have been done for awake and head-fixed animals (Kim). The main result of this study was the demonstration of neuromodulation using a lightweight CMUT array for both asleep (due to anesthesia) and awake mice, allowing them to study the effects of neuromodulation of freely-moving mice as well.

Kim's CMUT array was designed with an outer diameter of 8.1mm and an inner diameter of 5.2mm. This geometry was chosen due to its ability to naturally focus at the center, the large aperture, minimal skull heating, and for the space at the center for integration with other electronics. This is particularly important to my project because it falls under our space constraint of 14mm (the size of a standard drilled hole for every neurosurgery). These advantages of a ring-like structure also coincide with our goals because we want to be able to focus on a specific area of the brain (e.g. location of a removed tumor), minimize any overheating and be able to combine the CMUT array with wireless technology, power, and possibly beam-forming circuitry.

To test the success of their fabricated new array, they performed several tests before the in vivo experiments with mice. First, they tested the beam profile of the CMUT array by performing a volumetric scan (5mm wide by 10mm long) from the center of the ring. They found that the focus length (2.3mm) and maximum intensity ($50\text{mW}/\text{cm}^2$) were comparable to a simulated beam profile. Furthermore, they proved that the device does not cause significant overheating (an increase of 0.1°C after 240s of continuous activity) for their experiment (0.2 continuous seconds of activity). Another important aspect to consider is the MR compatibility. For this experiment, it was important for them to consider this because of the possible combination of neuromodulation with fMRI. They found that the CMUT array alone does not cause measurable effects on the images, however, they did find that a connector they used to apply voltage caused noticeable distortions in the magnetic field of the MRI scanner. This is a significant discovery for my project because although it proves that the CMUT array is MRI compatible and has no effect on the images, the electronics used to integrate with the CMUT array need to be chosen carefully to avoid MR incompatibility.

To start their in vivo experiments, Kim performed an in vivo acute (under anesthesia) experiment without craniotomy (healthy mice). Each stimulation trial uses 40 4.5-ms pulses. The success of the motor response was measured by increasing intensity (caused by adjusting the AC voltage). Per intensity, 25 stimulation trials were conducted and the success/failure rates were measured using a threshold. For the tested 4 mice, there was an increase in the success rate as the intensity increased, which corresponds to previously published studies using the bulky ultrasound transducers. They also performed several control experiments to prove that the motor responses were not caused by an electrical leakage or a buzzing sound that was present throughout the experiment. For the in vivo neuromodulation of awake mice, they found a success rate of 100% over 10 trials and showed that the device did not impede on walking, feeding or grooming. At the end of their experiment, they were able to conclude that not only was the CMUT array able to be easily reused and replaced, but they were also able to show that CMUT arrays are just as safe as the bulky transducers, with no significant tissue damage to the motor cortex.

This publication is important in the research community because it shows that CMUT arrays are a promising piece of technology for neuromodulation specifically due to its small size. Specifically, for my project, this publication is important because, not only do they provide a very detailed supplementary methods of the fabrication of this device, the CMUT array is exactly what we envision for our device. Furthermore, the authors also mention the possibilities of their technology that they haven't yet explored. Specifically, they mention that combining this chip with a beam-forming circuit can allow them to dynamically focus and target different locations of the brain without moving the device. The shape of the ringed array also allows them to narrowly focus on their target. This is significant because we want our ultimate device to be able to target and move to the desired imaging plane as it is being implanted, and instead of just sending our ultrasound to stimulate neurons, we want to beamform the received data to form a medical image. On the other hand, in this study, their device is not entirely MR compatible. This is an important point for us to consider because our device must be MR compatible and invisible. Brain surgery patients routinely get MRI scans every 3 months so our implanted device must not affect the MRI scanner or the scan itself. Although they were able to

show that the CMUT array itself has no affect on the scanner or image, the connector they used did. This means that when we design the integration of the CMUT array with a beam-forming circuit, wireless communication and the battery, we need to be aware that each component must be MR compatible and conduct experiments to prove this critical component of our medical device.

As mentioned before, the second review paper was chosen for its breadth in analyzing different applications for CMUT arrays, specifically CMUT for medical imaging. With CMUTs and post processing methods, it is possible to make a single chip ultrasound imaging system. Although possible, Brenner acknowledges that although signal integrity may be retained due to high transmit voltages, signal quality may be compromised due to low receive voltages. However, there already exists several processes that overcomes this problem (e.g integration with different kinds of circuitry), allowing ultrasound imaging on a chip to be a strong and viable option towards a low cost and truly portable imaging system. In addition, Brenner even mentions that combining this technology with wireless communication and novel battery technologies can turn these systems into a flexible, wearable and even ingestible imaging system. They have already developed an ingestible capsule that can provide images of the gastrointestinal tract by wirelessly transmitting to a computer. While the research community is finding novel ways to use CMUT arrays, industry companies are also beginning to see the advantages of using CMUT arrays for their transducers, rather than using the piezoelectric crystals (Brenner). For example, Butterfly iQ Network has released their first probe that uses a 9000 element CMUT array that can be plugged into a smartphone and produce equal quality ultrasound images compared to a piezoelectric transducer.

The applications discussed in this review paper are significant to the research community because it represents what researchers are using CMUT arrays for and demonstrates the breadth of possible applications. Particularly, the medical imaging applications discussed in this paper are most relevant to my project. Aside from the clear advantages of using CMUT arrays for ultrasound imaging, it is also clear that the disadvantages are mitigated through the integration of other electronics, thus supporting our decision to turn to CMUT arrays for miniaturizing the ultrasound imaging system aspect of our device.

Furthermore, the demonstration from multiple publications that CMUT arrays have the capability to reproduce medical grade images is another major advantage because it shows that miniaturizing does not sacrifice image quality.

In conclusion, the papers that I have selected show that CMUT arrays are a promising solution to miniaturizing ultrasound systems, a crucial aspect of my project's maximum deliverable. The fact that several publications have proven the safety and MR compatibility of this technology as well as the uncompromised medical grade image is hugely significant to our design of the implantable ultrasound device. Although our plan is not to fabricate this ourselves, understanding the CMUT array and the different possible customizable geometries, allow us to better design this novel ultrasound device.