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(54) Title: IMPLANTS USING ULTRASONIC BACKSCATTER FOR SENSING ELECTRICAL IMPEDANCE OF TISSUE
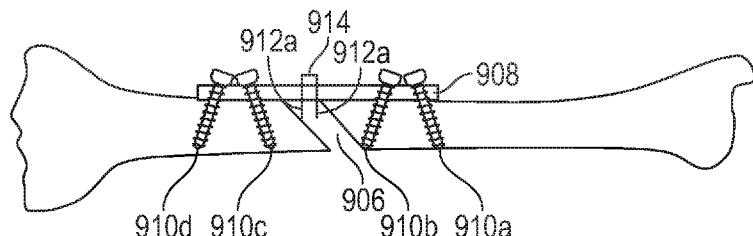
FIG. 9B

(57) Abstract: Described herein is an implantable device configured to detect impedance characteristic of a tissue. In certain exemplary devices, the implantable device comprises (a) an ultrasonic transducer configured to emit an ultrasonic backscatter encoding information relating to an impedance characteristic of a tissue based on a modulated current flowing through the ultrasonic transducer; (b) an integrated circuit comprising (i) a variable frequency power supply electrically connected to a first electrode and a second electrode; (ii) a signal detector configured to detect an impedance, voltage, or current in a circuit comprising the variable frequency power supply, the first electrode, the second electrode, and the tissue; and (iii) a modulation circuit configured to modulate the current flowing through the ultrasonic transducer based on the detected impedance, voltage, or current; and the first electrode and the second electrode configured to be implanted into the tissue in electrical connection with each other through the tissue. Further described are systems including one or more implantable devices and an interrogator for operating the implantable device, methods of measuring impedance characteristic of a tissue in a subject, and methods of monitoring or characterizing a tissue in a subject.

WO 2018/009911 A1

IMPLANTS USING ULTRASONIC BACKSCATTER FOR SENSING ELECTRICAL
IMPEDANCE OF TISSUE

CROSS-REFERENCE TO RELATED APPLICATION

[0001]   This application claims priority to U.S. Provisional Application No. 62/359,672, filed
on July 7, 2016, entitled "NEURAL DUST AND ULTRASONIC BACKSCATER IMPLANTS
AND SYSTEMS, AND APPLICATIONS FOR SUCH SYSTEMS," which is incorporated
herein by reference for all purposes.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002]   This invention was made with government support under Grant Nos. HR0011-15-2-
0006 awarded by the Defense Advanced Research Projects Agency (DARPA), EFRI 1240380
awarded by National Science Foundation (NSF), and IIP-1361975 awarded by Center for
Disruptive Musculoskeletal Innovations (CDMI). The government has certain rights in the
invention.

TECHNICAL FIELD

[0003]   The present invention relates to implantable devices for detecting tissue impedance
and monitoring tissue repair using ultrasonic backscatter.

BACKGROUND

[0004]   A previously known "neural dust" system includes small, implantable devices
(referred to as "neural dust" or "motes"), an implantable ultrasound transceiver that
communicates with each of the motes using ultrasound transmissions and backscatter
transmissions reflected from the motes, and an external transceiver that communicates wirelessly
with the implantable ultrasound transceiver. See Seo et al., *Neural dust: an ultrasonic, low
power solution for chronic brain-machine interfaces*, arXiv: 1307.2196v1 (July 8, 2013); Seo et
al., *Model validation of untethered, ultrasonic neural dust motes for cortical recording*, Journal
of Neuroscience Methods, vol. 224, pp. 114-122, available online Aug. 7, 2014; and Bertrand et
al., *Beamforming approaches for untethered, ultrasonic neural dust motes for cortical recording:
a simulation study*, IEEE EMBC (Aug. 2014). The neural dust system described in these papers

is used for cortical recording (i.e., the recording of brain electrical signals). In that application as shown in the papers, the motes are implanted in the brain tissue (cortex), the ultrasound transceiver (i.e., an "interrogator") is implanted below the dura, on the cortex, and the external transceiver is placed against the head of the patient proximate to where the sub-dural ultrasound transceiver is implanted. This neural dust system is illustrated in FIG. 1.

[0005]   Musculoskeletal diseases are a major cause of pain and reduced quality of life, with one in two adults over the age of 18 reporting suffering from a condition lasting more than 3 months in the past year. In 2004, treatments for musculoskeletal conditions were estimated to total $510 billion. Activities that place stress on bones and joints, as well as sedentary lifestyles can contribute to joint disease. Another area of particular interest is fractures – an estimated 15 million fracture injuries occur each year in the United States alone, with up to 20% of patients experiencing some degree of impaired healing. Within this fracture population, 10% will fail to heal appropriately and result in delayed or non-union, and incidence of non-union rises to 46% when the fractures occur in conjunction with vascular injury. Treatment of fractures costs the U.S. healthcare system $45 billion per year. In particular, multiple reoperations are often necessary to treat non-unions, and 51% of fracture patients do not return to work in 6 months. This causes substantial disability to patients and represents a significant burden on the healthcare system.

[0006]   Determining when a fracture is healed is crucial to making correct clinical decisions for patients, but there are currently no standardized methods of assessing fracture union. Current available tools for assessing fracture healing include radiographic methods, serologic markers, and clinical evaluation. However, poor accuracy, unreliability, need for high doses of radiation, large expense, and/or subjectivity limit their clinical utility. X-ray is one of the most common methods of tracking the progression of disease, but relies on mineralized tissue and thus is unable to discern soft tissue. Other imaging modalities such as CT can overcome this hurdle, but are not always practical due to high radiation doses and expense.

[0007]   Clinically, fractures heal primarily through endochondral ossification, in which bone forms indirectly from a cartilage template. Healing occurs through four overlapping phases of repair, beginning with an inflammatory phase, followed by chondrogenesis of mesenchymal progenitors to form the early cartilage callus that matures into a hard callus of cancellous bone, and finally remodeling into healthy cortical bone. These clearly defined stages of healing can be

well characterized histologically, but they are not detectable by standard radiographic techniques.

[0008] Plain X-ray radiographs are most commonly used to evaluate fractures, however studies have shown that these correlate poorly with bone strength, do not define union with enough accuracy, and are unreliable for determining the stage of fracture healing. X-ray computed tomography (CT), especially quantitative computed tomography (qCT), has great accuracy in determining bone mineral density (BMD); however the cost and high radiation doses required of CT preclude it from being utilized clinically. Dual energy X-ray absorptiometry (DEXA) is often used to diagnosis osteoporosis due to its ability to measure BMD, but it has decreased accuracy when imaging fractures treated with implants so it is not widely used clinically. Ultrasound carries a number of advantages over other techniques, as it is less expensive, does not require exposure to ionizing radiation, and is noninvasive. While it is unable to penetrate cortical bone, there is evidence that it can detect callus formation before radiographic changes are evident. However, interpretation of findings is highly dependent on operator expertise and thick layers of soft tissue can obscure view of bones. There have been multiple studies correlating mechanical properties to bone strength, but soft tissue artifacts often limit the reliability of conclusions. Additional tests exist that require patients to be weight-bearing, so they have limited utility in understanding the early stages of healing. Using serologic biomarkers as early predictors of fracture healing is gaining popularity, but there is still a lot of work to be done. Research is focused on identifying sensitive and specific markers of delayed or failed repair, but multiple patient factors like smoking status, age, gender, etc. make it difficult to present clinical recommendations. In the clinical setting, physical examination by a physician is still the most relied upon technique to determine fracture union. Patients are examined for local signs of infection, ability to weight-bear, and extent of pain. However, relying on patient-reported questionnaires is very qualitative, and physician assessment is subjective and depends on experience.

[0009] Determining when a fracture is healed is useful for making correct clinical decisions for patients, but there are currently no standardized methods of assessing fracture union. This is especially important for early diagnosis and treatment of non-unions. A survey of over 400 orthopaedic surgeons revealed that there is a lack of consensus in defining both clinical and radiographic criteria for delayed union and non-union in tibial fractures. Current available tools

for assessing fracture healing include radiographic methods, mechanical assessment, serologic markers, and clinical evaluation. Devices and methods for quantitative, reliable monitoring of fracture healing, and particularly distinguishing between the early stages of healing, continue to be needed for monitoring bone health.

SUMMARY OF THE INVENTION

[0010]   Described herein are implantable devices useful for determining impedance characteristic of a tissue, systems including such implantable devices and an interrogator for operating the implantable device, and methods of using such implantable devices and systems. Also described herein are methods of determining impedance of a tissue, and methods of monitoring or characterizing a tissue during a healing process.

[0011]   In some embodiments, an implantable device comprises a body about 5 mm or less in length in the longest dimension, comprising (a) an ultrasonic transducer configured to emit an ultrasonic backscatter encoding information relating to an impedance characteristic of a tissue based on a modulated current flowing through the ultrasonic transducer; (b) an integrated circuit comprising (i) a variable frequency power supply electrically connected to a first electrode and a second electrode; (ii) a signal detector configured to detect an impedance, voltage, or current in a circuit comprising the variable frequency power supply, the first electrode, the second electrode, and the tissue; and (iii) a modulation circuit configured to modulate the current flowing through the ultrasonic transducer based on the detected impedance, voltage, or current; and the first electrode and the second electrode configured to be implanted into the tissue in electrical connection with each other through the tissue. In some embodiments, the signal detector is electrically connected to the first electrode and the second electrode. In some embodiments, the signal detector is electrically connected to a third electrode and a fourth electrode configured to be implanted into the tissue in electrical connection through the tissue.

[0012]   In some embodiments, the signal detector is configured to detect an impedance magnitude or an impedance phase angle. In some embodiments, the signal detector is configured to detect an impedance magnitude and an impedance phase angle. In some embodiments, the signal detector is configured to detect a voltage magnitude or a voltage phase. In some embodiments, the signal detector is configured to detect a voltage magnitude and a voltage phase. In some embodiments, the signal detector is configured to detect a current magnitude or a

current phase. In some embodiments, the signal detector is configured to detect a current magnitude and a current phase.

[0013]   In some embodiments, the integrated circuit comprises a digital circuit. In some embodiments, the digital circuit is configured to operate the modulation circuit. In some embodiments, the digital circuit is configured to transmit a digitized signal to the modulation circuit, wherein the digitized signal is based on the detected impedance, current, or voltage. In some embodiments, the digital circuit comprises a processor and a non-transitory computer-readable storage medium storing one or more programs configured to be executed by the one or more processors, the one or more programs comprising instructions for determining the impedance characteristic of the tissue based on the detected current or voltage. In some embodiments, the digital circuit comprises a processor and a non-transitory computer-readable storage medium storing one or more programs configured to be executed by the one or more processors, the one or more programs comprising instructions for determining an impedance magnitude or an impedance phase angle. In some embodiments, the integrated circuit comprises a power circuit. In some embodiments, the integrated circuit comprises an analog-to-digital converter (ADC).

[0014]   In some embodiments, the ultrasonic backscatter encodes an impedance magnitude. In some embodiments, the ultrasonic backscatter encodes an impedance phase angle. In some embodiments, the ultrasonic backscatter encodes an impedance magnitude spectrum comprising a plurality of impedance magnitude measurements taken at different current frequencies. In some embodiments, the ultrasonic backscatter encodes an impedance phase angle spectrum comprising a plurality of impedance phase angle measurements taken at different current frequencies.

[0015]   In some embodiments, the variable frequency power supply is configured to supply a current at a plurality of different frequencies at about 10 Hz or more.

[0016]   In some embodiments, the body of the implantable device has a volume of about 5 mm^3 or less.

[0017]   In some embodiments, the ultrasonic transducer is configured to receive ultrasonic waves that power the implantable device. In some embodiments, the ultrasonic transducer is configured to receive ultrasonic waves that encode instructions for selecting a current frequency. In some embodiments, the ultrasonic transducer is configured to receive ultrasonic waves from

an interrogator comprising one or more ultrasonic transducers. In some embodiments, the ultrasonic transducer is a bulk piezoelectric transducer, a piezoelectric micro-machined ultrasonic transducer (PMUT), or a capacitive micro-machined ultrasonic transducer (CMUT).

[0018]   In some embodiments, the implantable device is implanted in a subject. In some embodiments, the subject is a human. In some embodiments, the implantable device is implanted in the tissue. In some embodiments, the first electrode and the second electrode are implanted in the tissue, and the body is attached to an implantable tissue support structure. In some embodiments, the tissue is a bone, a bone fracture site, an injured soft tissue, or an infected tissue.

[0019]   In some embodiments, the implanted device is at least partially encapsulated by a biocompatible material. In some embodiments, at least a portion of the first electrode and the second electrode are not encapsulated by the biocompatible material.

[0020]   In some embodiments, the implantable device further comprises a non-responsive reflector.

[0021]   Also provided herein is a system comprising one or more implantable devices and an interrogator comprising one or more ultrasonic transducers configured to transmit ultrasonic waves to the one or more implantable devices or receive ultrasonic backscatter from the one or more implantable devices. In some embodiments, the system comprises a plurality of implantable devices. In some embodiments, the interrogator is configured to beam steer transmitted ultrasonic waves to alternatively focus the transmitted ultrasonic waves on a first portion of the plurality of implantable devices or focus the transmitted ultrasonic waves on a second portion of the plurality of implantable devices. In some embodiments, the interrogator is configured to simultaneously receive ultrasonic backscatter from at least two implantable devices. In some embodiments, the interrogator is configured to transit ultrasonic waves to the plurality of implantable devices or receive ultrasonic backscatter from the plurality of implantable devices using time division multiplexing, spatial multiplexing, or frequency multiplexing. In some embodiments, the interrogator is configured to be wearable by a subject.

[0022]   In some embodiments, a method of measuring impedance characteristic of a tissue in a subject comprises receiving ultrasonic waves that power one or more implantable devices comprising an ultrasonic transducer; an integrated circuit comprising a power supply and a signal detector configured to detect an impedance, voltage, or current; and a first electrode and a second

electrode in electrical connection with each other through the tissue; converting energy from the ultrasonic waves into a first electrical current; transmitting the first electrical current to the integrated circuit; applying a second electrical current through the tissue; detecting an impedance, voltage, or current of a circuit formed by the power supply, the first electrode, the second electrode, and the tissue; modulating the first electrical current based on the detected impedance, voltage, or current; transducing the modulated first electrical current into an ultrasonic backscatter that encodes information related to impedance characteristic of the tissue; and emitting the ultrasonic backscatter to an interrogator comprising one or more transducer configured to receive the ultrasonic backscatter. In some embodiments, the method comprises applying the second electrical current through the tissue at a plurality of different current frequencies; and detecting the current impedance, voltage, or current at the plurality of different current frequencies.

[0023]   In some embodiments, a method of monitoring or characterizing a tissue a subject comprises transmitting ultrasonic waves from an interrogator comprising one or more ultrasonic transducers to one or more implantable devices comprising an ultrasonic transducer, an integrated circuit comprising a variable frequency power supply and a signal detector configured to detect an impedance, voltage, or current; and a first electrode and a second electrode in electrical connection with each other through the tissue; receiving from the one or more implantable devices ultrasonic backscatter that encodes information related to impedance characteristic of the tissue at a plurality of different current frequencies.

[0024]   In some embodiment, the information related to impedance comprises information related to impedance at a plurality of different frequencies

[0025]   In some embodiment, the signal detector is electrically connected to the first electrode and the second electrode. In some embodiment, the signal detector is electrically connected to a third electrode and a fourth electrode configured to detect the impedance, voltage, or current.

[0026]   In some embodiment, the power supply is a variable frequency power supply.

[0027]   In some embodiment, the method comprises determining the impedance based on the determined current or voltage. In some embodiment, the method comprises determining an impedance magnitude and an impedance phase angle.

[0028]   In some embodiments, the ultrasonic backscatter encodes the determined impedance magnitude and impedance phase angle. In some embodiments, the ultrasonic backscatter encodes the determined voltage or the determined current.

[0029]   In some embodiments, the method comprises monitoring or characterizing the tissue during a healing process. In some embodiments, the method comprises comparing the information related to impedance characteristic of the tissue at the plurality of different current frequencies to a reference to characterize a tissue disease, an infection in the tissue, or a tissue injury. In some embodiments, the method comprises receiving the ultrasonic backscatter that encodes information related to impedance caused by the tissue at the plurality of different current frequencies at a first time point; receiving the ultrasonic backscatter that encodes information related to impedance caused by the tissue at the plurality of different current frequencies at a second time point; and comparing the information related to impedance caused by the tissue at the plurality of different current frequencies at the first time point and at the second time point to monitor a tissue disease, an infection in the tissue, or a tissue injury. In some embodiments, the method comprises monitoring or characterizing a bone fracture, a bone disease, scar tissue, or an ulcer. In some embodiments, the method comprises monitoring or characterizing a bone disease that causes pathological fracturing. In some embodiments, the method comprises monitoring or characterizing a tissue subject to compartment syndrome. In some embodiments, the method comprises monitoring or characterizing the tissue after a surgery. In some embodiments, the method comprises monitoring or characterizing a bone graft implant or spinal fusion.

[0030]   In some embodiments of the above methods, the tissue is bone, a bone fracture, or a soft tissue.

[0031]   In some embodiments, the method comprises implanting the one or more implantable devices in the subject. In some embodiments, the subject is a human.

[0032]   In some embodiments, the method comprises determining a location or movement of the one or more implantable devices.

[0033]   In some embodiments, the ultrasonic backscatter comprises a digitized signal.

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BRIEF DESCRIPTION OF THE FIGURES

[0034]   FIG. 1 is a schematic of a neural dust system, including an external transceiver, a sub-dural interrogator, and a neural dust mote, as described in Seo et al., *Neural dust: an ultrasonic, low power solution for chronic brain-machine interfaces*, arXiv: 1307.2196v1 (July 8, 2013).

[0035]   FIG. 2A is a block diagram of an exemplary interrogator for a system described herein. The illustrated interrogator includes an ultrasonic transducer array comprising a plurality of ultrasonic transducers. Each of the ultrasonic transducers in the array is operated by a channel, which includes a switch to alternatively configure the transducer to receive or transmit ultrasonic waves. FIG. 2B is a schematic of another exemplary interrogator for a system described herein. The illustrated interrogator includes two ultrasonic transducer arrays, with each ultrasonic transducer array including a plurality of ultrasonic transducers. The interrogator also includes an integrated circuit (which can include a digital circuit, which can include a processor). The integrated circuit is connected to a user interface (which can include a display, keyboard, buttons, etc.), a storage medium (i.e., a non-transitory memory), an input/output (which may be wireless, such as a Bluetooth), and a power supply (such as a battery).

[0036]   FIG. 3A shows a block diagram of an exemplary interrogator that can be worn by a subject. The interrogator includes a wireless communication system (a Bluetooth radio, in the illustration), which can be used to communicate with a computer system. FIG. 3B shows an exploded view of a wearable interrogator. The interrogator includes a battery, a wireless communication system, and a transducer array. FIG. 3C shows the wearable interrogator shown in FIG. 3B fully assembled with a harness for attachment to a subject. FIG. 3D illustrates the wearable interrogator attached a subject, namely a rodent (although could be any other animal, such as a human, dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat or mouse). The interrogator includes a transducer array, which is fixed to the body of the subject by an adhesive. FIG. 3E illustrates a cross-section of the transducer array of the interrogator shown in FIGS. 3A-D.

[0037]   FIG. 4 provides a schematic showing the communication between a transducer from an interrogator and an implantable device having a miniaturized ultrasonic transducer. The interrogator transmits ultrasonic waves to the implantable device, and the miniaturized ultrasonic transducer emits ultrasonic backscatter modulated by the sensor. The backscatter is then received by the interrogator.

[0038]   FIG. 5A shows a series of cycles of ultrasonic wave pulses emitted by an interrogator. Upon receiving a trigger from the interrogator (e.g., an FPGA), the transceiver board of the interrogator generates a series of transmit pulses. At the end of the transmit cycle, the switch on the ASIC disconnects the transmit module and connects the receive module. The cycles have a frequency of every 100 microseconds. FIG. 5B shows a zoomed-in view of the transmit pulse sequence (i.e., one cycle) shown in FIG. 5A, with the cycle having six pulses of ultrasonic waves at 1.85 MHz, the pulses recurring every 540 nanoseconds. FIG. 5C shows ultrasonic backscatter emitted by an implantable device. The ultrasonic backscatter reaches the transducer of the interrogator approximately $2t_{Rayleigh}$. FIG. 5D shows a zoomed-in view of the ultrasonic backscatter, which can be analyzed. Analysis of the ultrasonic backscatter can include filtering, rectifying and integrating the ultrasonic backscatter waves. FIG. 5E shows a zoomed in view of the filtered ultrasonic backscatter waves. The backscatter wave includes responsive regions, which are responsive to changes in impedance to the miniaturized ultrasonic transducer, and non-responsive regions that are not responsive to changes in impedance to the miniaturized ultrasonic transducer.

[0039]   FIG. 6 illustrates one embodiment of an ASIC attached to a miniaturized ultrasonic transducer for an implantable device.

[0040]   FIG. 7A illustrates a schematic of an implantable device with a miniaturized ultrasonic transducer, an integrated circuit comprising a variable frequency power supply and an signal detector, and first electrode and a second electrode configured to be in electrical connection with each other through the tissue and to receive a source signal from the variable frequency power supply. The integrated circuit further includes a digital circuit, a modulation circuit, and a power circuit. The implantable device shown in FIG. 7A is configured to detect impedance in a two-terminal impedance detection configuration.

[0041]   FIG. 7B illustrates a schematic of an implantable device configured to detect impedance in a four-terminal impedance detection configuration.

[0042]   FIG. 8A illustrates a schematic of an exemplary implantable device including a miniaturized ultrasonic transducer and an ASIC on a printed circuit board (PCB). FIG. 8B illustrates a schematic of another exemplary implantable device including a miniaturized ultrasonic transducer and an ASIC on a printed circuit board (PCB).

[0043]   FIG. 9A illustrates an implantable device implanted in a bone fracture. FIG. 9B illustrates an implantable device attached to a bone plate with electrodes implanted into a bone fracture. The bone plate is supporting the bone with the bone fracture.

[0044]   FIG. 10A shows impedance magnitude spectra at a plurality of frequencies detected for a plurality of different tissue types representing different phases of bone fracture healing. FIG. 10B shows phase shift spectra at a plurality of frequencies detected for a plurality of different tissue types representing different phases of bone fracture healing.

[0045]   FIG. 11 illustrates a method of manufacturing an implantable device described herein.

[0046]   FIG. 12 is a flowchart for a method of encapsulating an implantable device with amorphous silicon carbide.

[0047]   FIG. 13A shows different geometries of vias used to connect components of the implantable device. FIG. 13B shows a serpentine trace configuration for deformable interconnects.

[0048]   FIG. 14 shows the relationship between time and temperature for curing silver epoxy, an exemplary material for attaching wirebonds during the manufacture of the implantable device.

[0049]   FIG. 15 illustrates a schematic for encapsulating an implantable device in silicon carbide.

[0050]   FIG. 16 shows an assembly prototype schematic and PCB.

[0051]   FIG. 17A-E show processing steps to ensure that the desired miniaturized ultrasonic transducer (PZT) dimension is assembled on the PCB. At FIG. 17A, epoxy solder paste is dispensed onto the board. At FIG. 17B, a piezoelectric material is attached to the PCB. At FIG. 17C, the piezoelectric material is diced to form a bulk piezoelectric ultrasonic transducer of the desired size. At FIG. 17D, the ultrasonic transducer is wirebonded to the PCB. At FIG. 17E, the PCB and ultrasonic transducer is encapsulated in PDMS.

[0052]   FIG. 18 shows a schematic for measuring electrical impedance with a vector network analyzer (VNA),

[0053]   FIG. 19A shows that the measured power transfer efficiency at various bulk piezoelectric ultrasonic transducer sizes matches simulated behavior. FIG. 19B shows that the measured impedance spectroscopy of a PZT crystal matches a simulation. FIG. 19C shows that the frequency response of harvested power of the miniaturized ultrasonic transducer is approximately 6.1 MHz.

[0054] FIG. 20 is a schematic of an exemplary ultrasonic transducer that can be used as part of an interrogator.

[0055] FIG. 21 is a schematic of a setup for acoustic characterization with a calibrated ultrasonic transducer for power delivery verification. The ultrasonic wave receiver is separate from the ultrasonic wave transmitter.

[0056] FIG. 22A shows the output power of a 5 MHz transducer as the hydrophone is moved away from the transducer's surface. FIG. 22B shows that the de-rated peak is shifted to the left in relation to the water peak.

[0057] FIG. 23A shows the XZ cross-section of the transducer output, illustrating a Rayleigh distance and a clear transition from the near-field to far-field propagation. FIG. 23B shows the XY beam cross-section showing a 6 dB bandwidth of the beam at 2.2 mm.

[0058] FIG. 24A shows a focused 2D beam pattern from a transducer array in the XY plane. The measured beam approximates the simulated beam in both the X and Y dimensions. FIG. 24B shows the delay time applied to each transducer element in the ultrasonic transducer array. FIG. 24C shows a simulated 2D XZ cross-sectional beam pattern.

[0059] FIG. 25A shows beam steering of an ultrasonic wave beam transmitted from a transducer array. Underneath each beam pattern is the delay for each transducer in the array to obtain the measured beam pattern, as shown in FIG. 25B. FIG. 25C shows the 1D beam pattern in the X-axis for each beam pattern shown in FIG. 25A. The measured beam pattern closely approximates the simulated beam pattern.

[0060] FIG. 26 shows a simulated scaling of miniaturized ultrasonic transducer link efficiency and received power at 5 mm in tissue.

[0061] FIG. 27A shows de-rated, normalized peak pressure as a function of distance from the surface of an exemplary transducer (of an interrogator) has a de-rated focus at about 8.9 mm at 1.85MHz. FIG. 27B shows the XY cross-sectional beam patterns and the corresponding 1D voltage plot at y=0 at near-field, Rayleigh distance, and far-field showed beam focusing at the Rayleigh distance. FIG. 27C shows that the transducer's output pressure was a linear function of input voltage (up to 32 V peak-to-peak).

[0062] FIG. 28A (duplicate of FIG. 5E shown in different context) shows exemplary backscatter waveform showing different regions of backscatter. The backscatter waveform is found flanked (in time) by regions which correspond to reflections arising from non-responsive

regions; these correspond to reflected pulses from other implantable device components. The measurement from the non-responsive regions (which do not encode biological data) can be used as a reference. As a result of taking this differential measurement, any movements of the entire structure relative to the external transducer during the experiment can be subtracted out. FIG. 28B is a calibration curve obtained in the custom water tank setup, which show the noise floor of 0.18 mV_{rms}. FIG. 28C shows the effect of noise floor as a function of lateral misalignment followed the beam pattern power fall-off. FIG. 28D shows a 1-D plot of the transducer's off-axis voltage and power drop off at y = 0 at Rayleigh distance. FIG. 28E shows a plot of drop in the effective noise floor as a function of angular misalignment. Angular misalignment results in a skewed beam pattern: ellipsoidal as opposed to circular. This increases the radius of focal spot (spreading energy out over a larger area); the distortion of the focal spot relaxes the constraint on misalignment.

[0063]   FIG. 29A shows ultrasonic backscatter from an implantable device, with the implantable device implanted inn ultrasound coupling gel used to mimic tissue. The backscatter includes a transmit feedthrough and ring-down centered at 26 microseconds, and the miniaturized ultrasonic transducer backscatter centered around 47 microseconds. FIG. 29B shows a close-up on the backscatter region from the miniaturized ultrasonic transducer (the responsive region), which shows amplitude modulation as a result of a signal input to the implantable device.

[0064]   FIG. 30 shows digital data corresponding to ASCII characters '*hello world*' wirelessly ready from the implantable device through pulse amplitude backscatter modulation with unipolar encoding.

DETAILED DESCRIPTION OF THE INVENTION

[0065]   An implantable impedance measurement tool on the front end of a small CMOS circuit can be used with an ultrasound interrogator to power and communicate with the implantable device. This system allows the placement of very small sensors (sub-mm) at various locations on the body such as in a fracture gap to monitor healing, by the hip bones to monitor osteoporosis, between spinal segments to monitor fusions, etc. This data can help determine risk for injury, as well as direct physician treatment and potentially allow patients to modify their

rehabilitation programs (i.e. when to begin weight-bearing and how much) according to quantitative data about their bone health.

[0066]   Electrical impedance spectroscopy (EIS) measures the dielectric properties of tissue as a function of frequency, and has been used for decades to characterize biological tissues such as bone. See, for example, International Patent Publication No. WO 2017/030900 A1. As described herein, ultrasonic power delivery and backscatter communication can be used to monitor fracture healing by integrating impedance spectroscopy with the front end of a small CMOS chip to be passively powered and probed by an ultrasound interrogator, which can optionally receive its power from a transceiver via RF power transfer. The implantable devices can be fully implanted in the subject, thereby allowing extended implantation time and obviates the need for external wiring physically connecting the electrodes to an external device.

[0067]   In some embodiments, the implantable bone sensor utilizes impedance spectroscopy to understand bone tissue health and to distinguish between different tissue types present in fracture healing. In some embodiments, the system includes multiple implantable devices that measure and report local physiological data. The CMOS front end can include electrodes and the ability to measure impedance at a range of frequencies. The chip is placed such that the electrodes contact the tissue of interest, such as in a fracture gap, and is passively powered by an ultrasound interrogator. The interrogator can be secured in close proximity such as against the bone or on a tissue support structure (such as a bone plate, nail, rod, or other implant), and establishes power and communication links with the sensor nodes. The interrogator can then powered by an external transceiver via RF power transfer. The interrogator can couple ultrasound energy into the tissue and establish both spatial and frequency differences with sufficient bandwidth to interrogate each sensing node. The sensor nodes can either be active, recovering power at the node to activate CMOS electronics for pre-processing and transmitting data, or passive, maximizing reflectivity of the implantable device a function of measured potential. In either scenario, the implantable devices communicate recorded data to the interrogator by modulating amplitude, frequency, and/or phase of the incoming ultrasound wave. All of these components can include custom hardware as well as custom code.

[0068]   The implantable device described herein includes a miniaturized ultrasonic transducer (such as a miniaturized piezoelectric transducer). The miniaturized ultrasonic transducer receives ultrasonic energy from an interrogator (which may be external or implanted), which

powers the implantable device. The interrogator includes a transmitter and a receiver (which may be integrated into a combined transceiver), and the transmitter and the receiver may be on the same component or different components. Mechanical energy from the ultrasonic waves transmitted by the interrogator vibrates the miniaturized ultrasonic transducer on the implantable device, which generates an electrical current. The current flowing through the miniaturized ultrasonic transducer is modulated by the electrical circuitry in the implantable device based information related to impedance characteristic of the tissue (e.g., a detected magnitude and/or phase of an impedance, voltage or current), and the modulated current flows through the miniaturized ultrasonic transducer. The miniaturized ultrasonic transducer emits an ultrasonic backscatter communicating information related to the impedance, which is detected by the receiver components of the interrogator.

[0069]   A significant advantage of the implantable device is the ability to detect impedance in deep tissue while being wirelessly powered, wirelessly transmit information relating the detected impedance to an interrogator, which can be external or relay the information to an external component. The detected impedance is related to the tissue state, and can be informative for monitoring tissue repair. Thus, the implantable devices can remain in a subject for an extended period of time without needing to charge a battery or retrieve information stored on the device. These advantages, in turn, allow the device to be smaller and less expensive to manufacture. In another advantage, use of ultrasound allows for the relative time for data communication to be related to distance, which can aid in determining location or movement of the implantable device in real time.

[0070]   Electromagnetic (EM) power transfer is not practical for powering small implantable devices due to power attenuation through tissue and the relatively large apertures (e.g. antennas or coils) required to capture such energy. See, for example, Seo et al., *Neural dust: an ultrasonic, low power solution for chronic brain-machine interfaces*, arXiv: 1307.2196v1 (July 2013). Use of EM to supply sufficient power to an implanted device would either require a shallow depth of the implant or would require excessive heating of the tissue to pass the EM waves through the tissue to reach the implantable device. In contrast to EM, ultrasonic power transfer provides low power attenuation in tissue due to the relatively low absorption of ultrasonic energy by tissue and the shorter wavelength of the ultrasonic waves (as compared to

electromagnetic waves). Further, the shorter wavelengths provided by the ultrasonic waves provides high spatial resolution at lower frequencies compared to radio waves.

[0071]   Ultrasonic transducers have found application in various disciplines including imaging, high intensity focused ultrasound (HIFU), nondestructive testing of materials, communication and power delivery through steel walls, underwater communications, transcutaneous power delivery, and energy harvesting. See, e.g., Ishida et al., *Insole Pedometer with Piezoelectric Energy Harvester and 2 V Organic Circuits*, IEEE J. Solid-State Circuits, vol. 48, no. 1, pp. 255-264 (2013); Wong et al., *Advantages of Capacitive Micromachined Ultrasonics Transducers (CMUTs) for High Intensity Focused Ultrasound (HIFU)*, IEEE Ultrasonics Symposium, pp. 1313-1316 (2007); Ozeri et al., *Ultrasonic Transcutaneous Energy Transfer for Powering Implanted Devices*, Ultrasonics, vol. 50, no. 6, pp. 556-566 (2010); and Richards et al., *Efficiency of Energy Conversion for Devices Containing a Piezoelectric Component*, J. Micromech. Microeng., vol. 14, pp. 717-721 (2004). Unlike electromagnetics, using ultrasound as an energy transmission modality never entered into widespread consumer application and was often overlooked because the efficiency of electromagnetics for short distances and large apertures is superior. However, at the scale of the implantable devices discussed herein and in tissue, the low acoustic velocity allows operation at dramatically lower frequencies, and the acoustic loss in tissue is generally substantially smaller than the attenuation of electromagnetics in tissue.

[0072]   The relatively low acoustic velocity of ultrasound results in substantially reduced wavelength compared to EM. Thus, for the same transmission distance, ultrasonic systems are much more likely to operate in the far-field, and hence obtain larger spatial coverage than an EM transmitter. Further, the acoustic loss in tissue is fundamentally smaller than the attenuation of electromagnetics in tissue because acoustic transmission relies on compression and rarefaction of the tissue rather than time-varying electric/magnetic fields that generate displacement currents on the surface of the tissue.

[0073]   In terms of possible applications for the implantable ultrasonic bone sensor, the sensor could be used to track fracture healing, monitor spine fusions, assess bone quality, monitor osteoporosis, as well as in a number of other ways to understand or diagnose general skeletal health. For example, the implantable devices could be implanted in the fracture gap of a broken bone anywhere in the body at the time of surgical intervention, and then interrogated in

the weeks and months after the injury to track the progression of healing. Spine fusions are another application where the implantable devices can be implanted intraoperatively and pinged at later time points to quantify the fusion rate. Bone quality in general could be garnered by this invention, with implantable devices scattered in a region of interest. In addition, some sort of minimally invasive injection of these particles into high-risk areas such as the hip would be very helpful for monitoring osteoporosis. In some embodiments, the implantable device is used to monitor or characterize a tissue ulcer.

[0074]   Implantable devices can be placed at or near a fracture injury to gather as much information as possible about the tissues in the fracture gap. Multiple CMOS implantable devices can be placed at the area of interest to both spatially and temporally resolve the healing process. When used in vivo, impedance spectroscopy may detect subtle changes in the tissue, enabling objective assessment and providing a unique insight into the condition of an injury.

[0075]   In some embodiments, such as for certain clinical application, these impedance sensors can be integrated intra-operatively as part of a surgery to fix or stabilize fractures. Fractures stabilized with a bone plate, screws, intramedullary nail, etc. would allow the interrogator to be easily secured to the implant. Otherwise, the interrogator could also be secured to the bone nearby the area of interest. Depending on the location of interest, it is possible to inject the particles into the body without major surgery.

[0076]   The ultrasonic implantable bone sensor combines some of the benefits of ultrasound with impedance spectroscopy measurements that can be taken right at the area of interest. In some embodiments, the CMOS chips are sub-mm in size, making them very small relative to the area of interest. The implantable device can be placed in a variety of areas around the body without the need for a large implant exactly in or at the area of interest. For example, the implantable devices could be sprinkled in the gap of a fracture injury or within the graft tissue of a spinal fusion. This small profile offers the advantage of being minimally intrusive to the natural healing process of the body.

[0077]   This technology has the potential to fit a wide range of applications. Impedance spectroscopy can be applied widely to monitoring surface injuries as well as internal injuries. This technology is well suited for internal use to monitor bone health in a number of ways, especially in areas that take advantage of the sub-mm size of the sensor nodes.

[0078]   In some embodiments, the implantable devices are used to monitor bone fracture healing. When fractures are treated surgically, surgeons can have the option of also implanting very small CMOS implantable devices in the fracture site along with securing an ultrasound interrogator to a nearby implant or bone. This would enable the physician to collect quantitative information about the state of healing during follow-up visits.

[0079]   In some embodiments, the implantable devices are used to monitor spinal fusions. In surgeries to fuse the spine or other areas of the body, the small front end motes can be implanted with the graft tissue and thus enable the physician to quantitatively track the progression of healing post-surgery.

[0080]   In some embodiments, the implantable devices are used to monitor osteoporosis. Osteoporosis is a major concern for patients, particularly older women. The implantable devices described herein can play a role in measuring risk and performing early detection of issues. Especially if we can deliver these small motes in a minimally invasive way, impedance at each area of interest could be measured regularly to look for irregularities that can indicate osteoporotic bone.

[0081]   In some embodiments, the implantable devices are used to monitor bone quality. The integration of this on a small CMOS chip can allow it to be deployed nearly anywhere of interest in the body and powered passively via external RF.

[0082]   In some embodiments, the implantable devices are used to detect compartment syndrome. Compartment syndrome occurs as a result of increased pressure within a compartment of tissue that leads to insufficient blood supply to the muscles and nerves in the area. This can be detected by impedance, so integrating sensors around the area that has suffered from a traumatic injury would enable objective data collection about the tissue health and reflect pressure in the area. In addition, the impedance spectroscopy system may include two or more electrodes which may be arrayed in an appropriate manner given the particular application, and may include a microcontroller to control, for example, the obtaining of samples indicative of bone health.

[0083]   In addition, the frequency of measurements may be determined by the use case. In some cases, a physician may want nearly continuous data collection to achieve high temporal resolution as bone tissue undergoes changes (for example, if an area has undergone trauma and it is highly likely that vascularization is rapidly decreasing in an emergency room setting). In other

cases, a measurement may only be necessary once as a diagnostic measure to understand the quality of the tissue at a specific time. Likely, most use cases will fall somewhere in the middle, where measurements are taken on a daily, weekly, or monthly basis to understand slow changes that bones may be going through.

[0084] The implantable devices described herein can be implanted in or used in a subject (e.g., a vertebrate animal). In some embodiments, the subject is a mammal. Exemplary subjects include a rodent (such as a mouse, rat, or guinea pig), cat, dog, chicken, pig, cow, horse, sheep, rabbit, etc. In some embodiments, the subject is a human.

Definitions

[0085] As used herein, the singular forms "a," "an," and "the" include the plural reference unless the context clearly dictates otherwise.

[0086] Reference to "about" a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[0087] The term "miniaturized" refers to any material or component about 5 millimeters or less (such as about 4 mm or less, about 3 mm or less, about 2 mm or less, about 1 mm or less, or about 0.5 mm or less) in length in the longest dimension. In certain embodiments, a "miniaturized" material or component has a longest dimension of about 0.1 mm to about 5 mm (such as about 0.2 mm to about 5 mm, about 0.5 mm to about 5 mm, about 1 mm to about 5 mm, about 2 mm to about 5 mm, about 3 mm to about 5 mm, or about 4 mm to about 5 mm) in length. "Miniaturized" can also refer to any material or component with a volume of about 5 mm^3 or less (such as about 4 mm^3 or less, 3 mm^3 or less, 2 mm^3 or less, or 1 mm^3 or less). In certain embodiments, a "miniaturized" material or component has a volume of about 0.5 mm^3 to about 5 mm^3, about 1 mm^3 to about 5 mm^3, about 2 mm^3 to about 5 mm^3, about 3 mm^3 to about 5 mm^3, or about 4 mm^3 to about 5 mm^3.

[0088] A "piezoelectric transducer" is a type of ultrasonic transceiver comprising piezoelectric material. The piezoelectric material may be a crystal, a ceramic, a polymer, or any other natural or synthetic piezoelectric material.

[0089] A "non-responsive" ultrasonic wave is an ultrasonic wave with a reflectivity independent of a detected signal. A "non-responsive reflector" is a component of an implantable

device that reflects ultrasonic waves such that the reflected waveform is independent of the detected signal.

[0090]   The term "subject" refers to an animal.

[0091]   It is understood that aspects and variations of the invention described herein include "consisting" and/or "consisting essentially of" aspects and variations.

[0092]   Where a range of values is provided, it is to be understood that each intervening value between the upper and lower limit of that range, and any other stated or intervening value in that stated range, is encompassed within the scope of the present disclosure. Where the stated range includes upper or lower limits, ranges excluding either of those included limits are also included in the present disclosure.

[0093]   It is to be understood that one, some or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0094]   Features and preferences described above in relation to "embodiments" are distinct preferences and are not limited only to that particular embodiment; they may be freely combined with features from other embodiments, where technically feasible, and may form preferred combinations of features.

[0095]   The description is presented to enable one of ordinary skill in the art to make and use the invention and is provided in the context of a patent application and its requirements. Various modifications to the described embodiments will be readily apparent to those persons skilled in the art and the generic principles herein may be applied to other embodiments. Thus, the present invention is not intended to be limited to the embodiment shown but is to be accorded the widest scope consistent with the principles and features described herein. Further, sectional headings are provide for organizational purposes and are not to be considered limiting. Finally, the entire disclosure of the patents and publications referred in this application are hereby incorporated herein by reference for all purposes.

Interrogator

[0096]   The interrogator can wirelessly communicate with one or more implantable devices using ultrasonic waves, which are used to power and/or operate the implantable device. The

interrogator can further receive ultrasonic backscatter from the implantable device, which encodes information indicative of detected impedance. The interrogator includes one or more ultrasonic transducers, which can operate as an ultrasonic transmitter and/or an ultrasonic receiver (or as a transceiver, which can be configured to alternatively transmit or receive the ultrasonic waves). The one or more transducers can be arranged as a transducer array, and the interrogator can optionally include one or more transducer arrays. In some embodiments, the ultrasound transmitting function is separated from the ultrasound receiving function on separate devices. That is, optionally, the interrogator comprises a first device that transmits ultrasonic waves to the implantable device, and a second device that receives ultrasonic backscatter from the implantable device. In some embodiments, the transducers in the array can have regular spacing, irregular spacing, or be sparsely placed. In some embodiments the array is flexible. In some embodiments the array is planar, and in some embodiments the array is non-planar.

[0097]   An exemplary interrogator is shown in FIG. 2A. The illustrated interrogator shows a transducer array with a plurality of ultrasonic transducers. In some embodiments, the transducer array includes 1 or more, 2 or more, 3 or more, 5 or more, 7 or more, 10 or more, 15 or more, 20 or more, 25 or more, 50 or more, 100 or more 250 or more, 500 or more, 1000 or more, 2500 or more, 5000 or more, or 10,000 or more transducers. In some embodiments, the transducer array includes 100,000 or fewer, 50,000 or fewer, 25,000 or fewer, 10,000 or fewer, 5000 or fewer, 2500 or fewer, 1000 or fewer, 500 or fewer, 200 or fewer, 150 or fewer, 100 or fewer, 90 or fewer, 80 or fewer, 70 or fewer, 60 or fewer, 50 or fewer, 40 or fewer, 30 or fewer, 25 or fewer, 20 or fewer, 15 or fewer, 10 or fewer, 7 or fewer or 5 or fewer transducers. The transducer array can be, for example a chip comprising 50 or more ultrasonic transducer pixels. The interrogator shown in FIG. 2A illustrates a single transducer array; however the interrogator can include 1 or more, 2 or more, or 3 or more separate arrays. In some embodiments, the interrogator includes 10 or fewer transducer arrays (such as 9, 8, 7, 6, 5, 4, 3, 2, or 1 transducer arrays). The separate arrays, for example, can be placed at different points of a subject, and can communicate to the same or different implantable devices. In some embodiments, the arrays are located on opposite sides of an implantable device. The interrogator can include an ASIC, which includes a channel for each transducer in the transducer array. In some embodiments, the channel includes a switch (indicated in FIG. 2A by "T/Rx"). The switch can alternatively configure the transducer connected to the channel to transmit ultrasonic waves or receive ultrasonic waves. The switch

can isolate the ultrasound receiving circuit from the higher voltage ultrasound transmitting circuit. In some embodiments, the transducer connected to the channel is configured only to receive or only to transmit ultrasonic waves, and the switch is optionally omitted from the channel. The channel can include a delay control, which operates to control the transmitted ultrasonic waves. The delay control can control, for example, the phase shift, time delay, pulse frequency and/or wave shape (including amplitude and wavelength). The delay control can be connected to a level shifter, which shifts input pulses from the delay control to a higher voltage used by the transducer to transmit the ultrasonic waves. In some embodiments, the data representing the wave shape and frequency for each channel can be stored in a 'wave table'. This allows the transmit waveform on each channel to be different. Then, delay control and level shifters can be used to 'stream' out this data to the actual transmit signals to the transducer array. In some embodiments, the transmit waveform for each channel can be produced directly by a high-speed serial output of a microcontroller or other digital system and sent to the transducer element through a level shifter or high-voltage amplifier. In some embodiments, the ASIC includes a charge pump (illustrated in FIG. 2A) to convert a first voltage supplied to the ASIC to a higher second voltage, which is applied to the channel. The channels can be controlled by a controller, such as a digital controller, which operates the delay control. In the ultrasound receiving circuit, the received ultrasonic waves are converted to current by the transducers (set in a receiving mode), which is transmitted to a data capture circuit. In some embodiments, an amplifier, an analog-to-digital converter (ADC), a variable-gain-amplifier or a time-gain-controlled variable-gain-amplifier (which can compensate for tissue loss), and/or a band pass filter is included in the receiving circuit. The ASIC can draw power from a power supply, such as a battery (which is preferred for a wearable embodiment of the interrogator). In the embodiment illustrated in FIG. 2A, a 1.8V supply is provided to the ASIC, which is increased by the charge pump to 32V, although any suitable voltage can be used. In some embodiments, the interrogator includes a processor and or a non-transitory computer readable memory. In some embodiments, the channel described above does not include a T/Rx switch but instead contains independent Tx (transmit) and Rx (receive) with a high-voltage Rx (receiver circuit) in the form of a low noise amplifier with good saturation recovery. In some embodiments, the T/Rx circuit includes a circulator. In some embodiments, the transducer array contains more transducer elements than processing channels in the interrogator transmit /receive circuitry, with a

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multiplexer choosing different sets of transmitting elements for each pulse. For example, 64 transmit receive channels connected via a 3:1 multiplexer to 192 physical transducer elements – with only 64 transducer elements active on a given pulse.

[0098] FIG. 2B illustrates another embodiment of interrogator. As shown in FIG. 2B, the interrogator includes one or more transducers 202. Each transducer 202 is connected to a transmitter/receiver switch 204, which can alternatively configure the transducer to transmit or receive ultrasonic waves. The transmitter/receiver switch is connected to a processor 206 (such as a central processing unit (CPU), a custom dedicated processor ASIC, a field programmable gate array (FPGA), microcontroller unit (MCU), or a graphics processing unit (GPU)). In some embodiments, the interrogator further includes an analog-digital converter (ADC) or digital-to-analog converter (DAC). The interrogator can also include a user interface (such as a display, one or more buttons to control the interrogator, etc.), a memory, a power supply (such as a battery), and/or an input/output port (which may be wired or wireless).

[0099] In some embodiments, the interrogator is implantable. An implanted interrogator may be preferred when the implantable devices are implanted in a region blocked by a barrier that does not easily transmit ultrasonic waves. For example, the interrogator can be implanted subcranially, either subdurally or supradurally. A subcranial interrogator can communicate with implantable devices that are implanted in the brain. Since ultrasonic waves are impeded by the skull, the implanted subcranial interrogator allows for communication with the implantable devices implanted in the brain. In another example, an implantable interrogator can be implanted as part of, behind or within another implanted device, such as a bone plate. In some embodiments, the interrogator is implanted on or next to a nail, rod, or other implant used to secure bone or other tissue. In some embodiments, the implanted interrogator can communicate with and/or is powered by an external device, for example by EM or RF signals.

[0100] In some embodiments, the interrogator is external (i.e., not implanted). By way of example, the external interrogator can be a wearable, which may be fixed to the body by a strap or adhesive. In another example, the external interrogator can be a wand, which may be held by a user (such as a healthcare professional). In some embodiments, the interrogator can be held to the body via suture, simple surface tension, a clothing-based fixation device such as a cloth wrap, a sleeve, an elastic band, or by sub-cutaneous fixation. The transducer or transducer array of the interrogator may be positioned separately from the rest of the transducer. For example, the

transducer array can be fixed to the skin of a subject at a first location (such as proximal to one or more implanted devices), and the rest of the interrogator may be located at a second location, with a wire tethering the transducer or transducer array to the rest of the interrogator. FIG. 3A-E shows an example of a wearable external interrogator. FIG. 3A shows a block diagram of the interrogator, which includes a transducer array comprising a plurality of transducers, an ASIC comprising a channel for each transducer in the transducer array, a battery (lithium polymer (LiPo) battery, in the illustrated example), and a wireless communication system (such as a Bluetooth system). FIG. 3B illustrates an exploded view of a wearable interrogator, including a printed circuit board (PCB) 302, which includes the ASIC, a wireless communication system 304, a battery 306, an ultrasonic transducer array 308, and a wire 310 tethering the ultrasonic transducer array 308 to the ASIC. FIG. 3C shows the wearable interrogator 312 shown in FIG. 3B with a harness 314, which can be used to attach the interrogator to a subject. FIG. 3D shows the assembled interrogator 316 attached to a subject, with the transducer array 308 attached at a first location, and the rest of the interrogator attached to a second location. FIG. 3E shows a cross-section schematic of an exemplary ultrasonic transducer array 308, which includes a circuit board 318, vias 320 attaching each transducer 322 to the circuit board 318, a metalized polyester film 324, and an absorptive backing layer 326. The metalized polyester film 324 can provide a common ground and acoustic matching for the transducers, while the absorptive backing layer 326 (such as tungsten powder filled polyurethane) can reduce ringing of the individual transducers.

[0101]   The specific design of the transducer array depends on the desired penetration depth, aperture size, and the size of the transducers within the array. The Rayleigh distance, R, of the transducer array is computed as:

$$R = \frac{D^2 - \lambda^2}{4\lambda} \approx \frac{D^2}{4\lambda}, D^2 \gg \lambda^2$$

where D is the size of the aperture and λ is the wavelength of ultrasound in the propagation medium (i.e., the tissue). As understood in the art, the Rayleigh distance is the distance at which the beam radiated by the array is fully formed. That is, the pressure filed converges to a natural focus at the Rayleigh distance in order to maximize the received power. Therefore, in some

embodiments, the implantable device is approximately the same distance from the transducer array as the Rayleigh distance.

[0102]   The individual transducers in a transducer array can be modulated to control the Raleigh distance and the position of the beam of ultrasonic waves emitted by the transducer array through a process of beamforming or beam steering. Techniques such as linearly constrained minimum variance (LCMV) beamforming can be used to communicate a plurality of implantable devices with an external ultrasonic transceiver. See, for example, Bertrand et al., *Beamforming Approaches for Untethered, Ultrasonic Neural Dust Motes for Cortical Recording: a Simulation Study*, IEEE EMBC (Aug. 2014). In some embodiments, beam steering is performed by adjusting the power or phase of the ultrasonic waves emitted by the transducers in an array.

[0103]   In some embodiments, the interrogator includes one or more of instructions for beam steering ultrasonic waves using one or more transducers, instructions for determining the relative location of one or more implantable devices, instructions for monitoring the relative movement of one or more implantable devices, instructions for recording the relative movement of one or more implantable devices, and instructions for deconvoluting backscatter from a plurality of implantable devices.

Communication Between an Implantable Device and an Interrogator

[0104]   The implantable device and the interrogator wirelessly communicate with each other using ultrasonic waves. The implantable device receives ultrasonic waves from the interrogator through a miniaturized ultrasonic transducer on the implantable device. Vibrations of the miniaturized ultrasonic transducer on the implantable device generate a voltage across the electric terminals of the transducer, and current flows through the device, including, if present, the ASIC. Current also flows through tissue, and the impedance of the tissue on that current is detected. Current passing through the transducer (which is converted to the ultrasonic backscatter and emitted from the implantable device) is modulated based on the detected impedance. If the detected impedance changes, the current transmitted to the transducer changes, resulting in changes in backscatter. The backscatter is then received by an external ultrasonic transceiver (which may be the same or different from the external ultrasonic transceiver that transmitted the initial ultrasonic waves). The information from the detected

impedance can thus be encoded by changes in amplitude, frequency, or phase of the backscattered ultrasound waves.

[0105] FIG. 4 illustrates an interrogator in communication with an implantable device. The external ultrasonic transceiver emits ultrasonic waves ("carrier waves"), which can pass through tissue. The carrier waves cause mechanical vibrations on the miniaturized ultrasonic transducer (e.g., a miniaturized bulk piezoelectric transducer, a PUMT, or a CMUT). A voltage across the miniaturized ultrasonic transducer is generated, which imparts a current flowing through an integrated circuit on the implantable device. In some embodiments, the implantable device includes an ASIC, and current flows from the miniaturized ultrasonic transducer, through the ASIC, and the signal detector. The current flowing through the miniaturized ultrasonic transducer causes the transducer on the implantable device to emit backscatter ultrasonic waves. The current flowing back to the miniaturized ultrasonic transducer changes the amplitude, frequency, and/or phase of the backscatter ultrasonic wave emitted or reflected from the ultrasonic transducer. Since the impedance affects the current returning to the ASIC and/or the miniaturized ultrasonic transducer, the backscatter waves encode information relating to the detected impedance. The backscatter waves can be detected by the interrogator, and can be deciphered to quantify the impedance detected by the implantable device.

[0106] Communication between the interrogator and the implantable device can use a pulse-echo method of transmitting and receiving ultrasonic waves. In the pulse-echo method, the interrogator transmits a series of interrogation pulses at a predetermined frequency, and then receives backscatter echoes from the implanted device. In some embodiments, the pulses are about 200 nanoseconds (ns) to about 1000 ns in length (such as about 300 ns to about 800 ns in length, about 400 ns to about 600 ns in length, or about 540 ns in length). In some embodiments, the pulses are about 100 ns or more in length (such as about 150 ns or more, 200 ns or more, 300 ns or more, 400 ns or more, 500 ns or more, 540 ns or more, 600 ns or more, 700 ns or more, 800 ns or more, 900 ns or more, 1000 ns or more, 1200 ns or more, or 1500 ns or more in length). In some embodiments, the pulses are about 2000 ns or less in length (such as about 1500 ns or less, 1200 ns or less, 1000 ns or less, 900 ns or less, 800 ns or less, 700 ns or less, 600 ns or less, 500 ns or less, 400 ns or less, 300 ns or less, 200 ns or less, or 150 ns or less in length). In some embodiments, the pulses are separated by a dwell time. In some embodiments, the dwell time is about 100 ns or more in length (such as about 150 ns or more, 200 ns or more, 300 ns or more,

400 ns or more, 500 ns or more, 540 ns or more, 600 ns or more, 700 ns or more, 800 ns or more, 900 ns or more, 1000 ns or more, 1200 ns or more, or 1500 ns or more in length). In some embodiments, the dwell time is about 2000 ns or less in length (such as about 1500 ns or less, 1200 ns or less, 1000 ns or less, 900 ns or less, 800 ns or less, 700 ns or less, 600 ns or less, 500 ns or less, 400 ns or less, 300 ns or less, 200 ns or less, or 150 ns or less in length). In some embodiments, the pulses are square, rectangular, triangular, sawtooth, or sinusoidal. In some embodiments, the pulses output can be two-level (GND and POS), three-level (GND, NEG, POS), 5-level, or any other multiple-level (for example, if using 24-bit DAC). In some embodiments, the pulses are continuously transmitted by the interrogator during operation. In some embodiments, when the pulses are continuously transmitted by the interrogator a portion of the transducers on the interrogator are configured to receive ultrasonic waves and a portion of the transducers on the interrogator are configured to transmit ultrasonic waves. Transducers configured to receive ultrasonic waves and transducers configured to transmit ultrasonic waves can be on the same transducer array or on different transducer arrays of the interrogator. In some embodiments, a transducer on the interrogator can be configured to alternatively transmit or receive the ultrasonic waves. For example, a transducer can cycle between transmitting one or more pulses and a pause period. The transducer is configured to transmit the ultrasonic waves when transmitting the one or more pulses, and can then switch to a receiving mode during the pause period. In some embodiments, the one or more pulses in the cycle includes about 1 to about 10 pulses (such as about 2 to about 8, or about 4 to about 7, or about 6) pulses of ultrasonic waves in any given cycle. In some embodiments, the one or more pulses in the cycle includes about 1 or more, 2 or more, 4 or more, 6 or more, 8 or more, or 10 or more pulses of ultrasonic waves in any given cycle. In some embodiments, the one or more pulses in the cycle includes about 20 or fewer, about 15 or fewer, about 10 or fewer, about 8 or fewer, or about 6 or fewer pulses in the cycle. The pulse cycle can be regularly repeated, for example every about 50 microseconds (μs) to about 300 μs (such as about every 75 μs to about 200 μs, or every about 100 μs) during operation. In some embodiments, the cycle is reaped every 50 μs or longer, every 100 μs or longer, every 150 μs or longer, every 200 μs or longer, every 250 μs or longer, or every 300 μs or longer. In some embodiments, the cycle is repeated every 300 μs or sooner, every 250 μs or sooner, every 200 μs or sooner, every 150 μs or sooner, or every 100 μs or sooner. The cycle frequency can set, for example, based on the distance between the interrogator

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and the implantable device and/or the speed at which the transducer can toggle between the transmitting and receiving modes.

[0107]   FIG. 5 illustrates cycled pulse-echo ultrasonic communication between the interrogator and the implantable device. FIG. 5A shows a series of pulse cycles with a frequency of every 100 microseconds. During the transmission of the pulses, the transducers in the array are configured to transmit the ultrasonic waves. After the pulses are transmitted, the transducers are configured to receive backscattered ultrasonic waves. FIG. 5B shows a zoom-in view of a cycle, which shows six pulses of ultrasonic waves, with a frequency of every 540 nanoseconds. Backscattered ultrasonic waves detected by the interrogator are shown in FIG. 5C, with a zoom-in view of a single pulse shown in FIG. 5D. As shown in FIG. 5D, the ultrasonic backscatter received from the implantable device can be analyzed, which may include filtering (for example, to remove the wave decay) the backscattered waves, rectifying the backscattered waves, and integrating the waves to determine the data encoded by the waves. In some embodiments, the backscatter waves are analyzed using a machine learning algorithm. FIG. 5E shows a zoomed in version of the filtered backscattered waves. The backscatter wave shown in FIG. 5E includes four distinct regions corresponding to reflections arising from mechanical boundaries: (1) reflection from the biocompatible material that encapsulates the implantable device; (2) reflection from the top surface of the miniaturized ultrasonic transducer; (3) reflection from the boundary between the printed circuit board and the miniaturized ultrasonic transducer; and (4) reflection from the back of the printed circuit board. The amplitude of the backscatter waves reflected from the surface of the miniaturized transducer changed as a function of changes in impedance of the current flowing through the miniaturized ultrasonic transducer, and can be referred to as the "responsive backscatter" since this region of the backscatter can encode information relating to the detected impedance. The other regions of the ultrasonic backscatter can be referred to as "non-responsive backscatter," and are useful in determining the position of the implantable device, movement of the implantable device, and/or temperature changes proximal to the implantable device, as explained below. In some embodiments, the device further comprises a non-responsive reflector. In some embodiments, the non-responsive reflector is a cube. In some embodiments, the non-responsive reflector comprises silicon. In some embodiments, the non-responsive reflector is a surface of rigid material. The non-responsive reflector is attached to the implantable device but electrically isolated, and can reflect

ultrasonic waves that are not responsive to changes in current impedance, for example due to detected impedance.

[0108]   The frequency of the ultrasonic waves transmitted by the transducer can be set depending on the drive frequency or resonant frequency of the miniaturized ultrasonic transducer on the implantable device. In some embodiments, the miniaturized ultrasonic transducers are broad-band devices. In some embodiments, the miniaturized ultrasonic transducers are narrow-band. For example, in some embodiments the frequency of the pulses is within about 20% or less, within about 15% or less, within about 10% or less, within about 5% or less of the resonant frequency of the miniaturized ultrasonic transducer. In some embodiments, the pulses are set to a frequency about the resonant frequency of the miniaturized ultrasonic transducer. In some embodiments, the frequency of the ultrasonic waves is between about 100 kHz and about 100 MHz (such as between about 100 kHz and about 200 kHz, between about 200 kHz and about 500 kHz, between about 500 kHz and about 1 MHz, between about 1 MHz and about 5 MHz, between about 5 MHz and about 10 MHz, between about 10 MHz and about 25 MHz, between about 25 MHz and about 50 MHz, or between about 50 MHz and about 100 MHz). In some embodiments, the frequency of the ultrasonic waves is about 100 kHz or higher, about 200 kHz or higher, about 500 kHz or higher, about 1 MHz or higher, about 5 MHz or higher, about 10 MHz or higher, about 25 MHz or higher, or about 50 MHz or higher. In some embodiments, the frequency of the ultrasonic waves is about 100 MHz or lower, about 50 MHz or lower, about 25 MHz or lower, about 10 MHz or lower, about 5 MHz or lower, about 1 MHz or lower, about 500 kHz or lower, or about 200 kHz or lower. Higher frequency allows for a smaller miniaturized ultrasonic transducer on the implantable device. However, higher frequency also limits the depth of communication between the ultrasonic transducer and the implantable device. In some embodiments, the implantable device and the ultrasonic transducer are separated by about 0.1 cm to about 15 cm (such as about 0.5 cm to about 10 cm, or about 1 cm to about 5 cm). In some embodiments, the implantable device and the ultrasonic transducer are separated by about 0.1 cm or more, about 0.2 cm or more, about 0.5 cm or more, about 1 cm or more, about 2.5 cm or more, about 5 cm or more, about 10 cm or more, or about 15 cm or more. In some embodiments, the implantable device and the ultrasonic transducer are separated by about 20 cm or less, about 15 cm or less, about 10 cm or less, about 5 cm or less, about 2.5 cm or less, about 1 cm or less, or about 0.5 cm or less.

[0109] In some embodiments, the backscattered ultrasound is digitized by the implantable device. For example, the implantable device can include an oscilloscope or analog-to-digital converter (ADC) and/or a memory, which can digitally encode information in current (or impedance) fluctuations. The digitized current fluctuations, which reflect data sensed by the signal detector, are received by the ultrasonic transducer, which then transmits digitized acoustic waves. The digitized data can compress the analog data, for example by using singular value decomposition (SVD) and least squares-based compression. In some embodiments, the compression is performed by a correlator or pattern detection algorithm. The backscatter signal may go through a series of non-linear transformation, such as 4th order Butterworth bandpass filter rectification integration of backscatter regions to generate a reconstruction data point at a single time instance. Such transformations can be done either in hardware (i.e., hard-coded) or in software.

[0110] In some embodiments, an interrogator communicates with a plurality of implantable devices. This can be performed, for example, using multiple-input, multiple output (MIMO) system theory. For example, communication between the interrogator and the plurality of implantable devices using time division multiplexing, spatial multiplexing, or frequency multiplexing. In some embodiments, two or more (such as 3, 4, 5, 6, 7, 8, 9, 10 or more, 12 or more, about 15 or more, about 20 or more, about 25 or more, about 50 or more, or about 100 or more) implantable devices communicate with the interrogator. In some embodiments, about 200 or fewer implantable devices (such as about 150 or fewer, about 100 or fewer, about 50 or fewer, about 25 or fewer, about 20 or fewer, about 15 or fewer, about 12 or fewer, or about 10 or fewer implantable devices) are in communication with the interrogator. The interrogator can receive a combined backscatter from the plurality of the implantable devices, which can be deconvoluted, thereby extracting information from each implantable device. In some embodiments, interrogator focuses the ultrasonic waves transmitted from a transducer array to a particular implantable device through beam steering. The interrogator focuses the transmitted ultrasonic waves to a first implantable device, receives backscatter from the first implantable device, focuses transmitted ultrasonic waves to a second implantable device, and receives backscatter from the second implantable device. In some embodiments, the interrogator transmits ultrasonic waves to a plurality of implantable devices, and then receives ultrasonic waves from the plurality of implantable devices.

[0111]   In some embodiments, the interrogator is used to determine the location or velocity of the implantable device. Velocity can be determined, for example, by determining the position or movement of a device over a period of time. The location of the implantable device can be a relative location, such as the location relative on the transducers on the interrogator. Knowledge of the location or movement of the implantable device allows for knowledge of the precise location of impedance measured in the tissue. For example, if a plurality of implantable devices are implanted in the tissue, healing throughout the tissue may not be uniform. By determining the location of the implantable device and associating the location with the detected impedance, it is possible to characterize or monitor the tissue at a more localized point. A plurality of transducers on the interrogator, which may be disposed on the same transducer array or two or more different transducer arrays, can collect backscatter ultrasonic waves from an implantable device. Based on the differences between the backscatter waveform arising from the same implantable device and the known location of each transducer, the position of the implantable device can be determined. This can be done, for example by triangulation, or by clustering and maximum likelihood. The differences in the backscatter may be based on responsive backscatter waves, non-responsive backscatter waves, or a combination thereof.

[0112]   In some embodiments, the interrogator is used to track movement of the implantable device. Movement of the implantable device that can be tracked by the interrogator includes lateral and angular movement. Such movement may arise, for example, due to shifting of one or more organs such as the liver, stomach, small or large intestine, kidney, pancreas, gallbladder, bladder, ovaries, uterus, or spleen (which may be the result, for example, of respiration or movement of the subject), or variations in blood flow (such as due to a pulse). Thus, in some embodiments, the implantable device is useful for tracking movement of an organ or a pulse rate. Movement of the implantable device can be tracked, for example, by monitoring changes in the non-responsive backscatter waves. In some embodiments, movement of the implantable device is determined my comparing the relative location of the implantable device at a first time point to the relative location of the implantable device at a second time point. For example, as described above, the location of an implantable device can be determined using a plurality of transducers on the interrogator (which may be on a single array or on two or more arrays). A first location of the implantable device can be determined at a first time point, and a second location of the implantable device can be determined at a second time point, and a movement vector can be

determined based on the first location at the first time point and the second location at the second time point.

Implantable Device

[0113]   The implantable device includes a miniaturized ultrasonic transducer (such as a miniaturized piezoelectric transducer, a capacitive micro-machined ultrasonic transducer (CMUT), or a piezoelectric micro-machined ultrasonic transducer (PMUT)), an application specific integrated circuit (ASIC) comprising a variable frequency power supply and a signal detector, and first electrode and a second electrode configured to be in electrical connection with each other through the tissue and to receive a source signal from the variable frequency power supply. The signal detector is configured to detect current (either or both of a current magnitude and/or current phase), a voltage (either or both of a voltage magnitude and/or voltage phase), and/or impedance (either or both of an impedance magnitude and/or impedance phase angle) in a circuit formed by the variable frequency power supply, the first electrode, the tissue, and the second electrode. In some embodiments, the signal detector is configured to determine the impedance based on the detected current and/or voltage. The integrated circuit modulates current flowing within the miniaturized ultrasonic transducer based on the phase-sensitive current and voltage detected by the signal detector. The modulated current impacts the ultrasonic backscatter emitted by the ultrasonic transducer.

[0114]   In some embodiments, the signal detector is electrically connected to the first electrode and the second electrode. In some embodiments, the signal detector is directly connected to the first electrode and the second electrode. For example, the signal detector can be configured for two-terminal impedance detection.

[0115]   In some embodiments, the signal detector is electrically connected to a third electrode and fourth electrode configured to be implanted into the tissue in electrical connection through the tissue. For example, the implantable device can be configured to detect impedance using four-terminal sensing. The variable frequency power supply can apply a current or voltage through the tissue using the first electrode and the second electrode. The third electrode and the fourth electrode are preferably disposed in the tissue between the first electrode and the second electrode, and the signal detector can detect the impedance, voltage, or current of the circuit formed by the first electrode, second electrode, variable power supply, and the tissue.

[0116]   The variable frequency power supply is configured to apply current to the electrodes at a selected frequency. The frequency may be selected by the digital circuit (for example, the digital circuit may include a processor or microcontroller and a computer-readable non-transitory memory comprising one or more programs configured to be executed by the processor or microcontroller , the one or more programs comprising instructions for selecting the frequency). In some embodiments, the frequency is selected by transmitting a signal encoded in ultrasonic waves from the interrogator to the implantable device, which causes the frequency to be selected. In some embodiments, the selected frequency is about 1 kHz or more, about 10 kHz or more, about 100 kHz or more, about 500 kHz or more, or about 1 MHz or more. In some embodiments, the selected frequency is about 2 MHz or less, about 1 MHz or less, about 500 kHz or less, about 100 kHz or less, or about 10 kHz or less. The signal detector can detect the current, impedance and/or voltage at one or more different frequencies. In some embodiments, the signal detector detects the current, impedance and/or voltage at 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, 15 or more, 20 or more, or 25 or more different frequencies. In some embodiments, the signal detector detects the current, impedance and/or voltage at 30 or fewer, 25 or fewer, 20 or fewer, 15 or fewer, or 10 or fewer different frequencies. By determining the current, impedance and/or voltage at a plurality of different frequencies, an impedance spectrum (i.e., a spectrum of impedance magnitude and/or impedance phase angle at a plurality of different frequencies) can be determined. As explained herein and in International Patent Publication No. WO 2017/030900, changes in the impedance spectrum can be indicative of a changing tissue status. See also Swisher et al., *Impedance sensing device enables early detection of pressure ulcers* in vivo, Nature Communications, vol. 6, no. 6575 (2015).

[0117]   In some embodiments, the integrated circuit includes one or more analog circuits, which can utilize electrical power provided by the transducer to power one or more analog amplifiers, which can increase the modulation depth of the signal modulated on the backscatter impedance.

[0118]   In some embodiments the integrated circuit includes one or more digital circuits, which can include a memory and one or more circuit blocks or systems for operating the implantable device. These systems can include, for example an onboard microcontroller or processor, a finite state machine implementation or digital circuits capable of executing one or more programs stored on the implant or provided via ultrasonic communication between

interrogator and implant. In some embodiments, the digital circuit includes an analog-to-digital converter (ADC), which can convert analog signal from the signal detector into a digital signal. In some embodiments, the digital circuit includes a digital-to-analog converter (DAC), which converts a digital signal into an analog signal prior to directing the signal to a modulator. In some embodiments, the digital circuit operates the variable frequency power supply and/or receives a signal from the signal detector encoding the voltage, current, or impedance. In some embodiments, the digital circuit operates a modulation circuit (which can also be referred to as a "backscatter circuit"). In some embodiments, the digital circuit transmits a signal to the modulation circuit encoding the detected voltage, impedance, or current. In some embodiments, the digital circuit determines a complex impedance of the tissue based on the detected voltage or current, and the digital circuit transmits a signal to the modulation circuit encoding the determined complex impedance.

[0119]   In some embodiments, the digital circuit can operate a modulation circuit (which can also be referred to as the "backscatter circuit"), which connects to the miniaturized ultrasonic transducer. The modulation circuit includes a switch, such as an on/off switch or a field-effect transistor (FET). An exemplary FET that can be used with some embodiments of the implantable device is a metal-oxide-semiconductor field-effect transistor (MOSFET). The modulation circuit can alter the impedance presented to the miniaturized ultrasonic transducer, and the variation in current passing through the transducer encodes signals transmitted by the digital circuit. The digital circuit can also operate one or more amplifiers, which amplifies the current directed to the switch.

[0120]   In some embodiments, the integrated circuit includes a power circuit, which is configured to power components of the implanted device. The power circuit can include, for example, a rectifier, a charge pump, and/or an energy storage capacitor. In some embodiments, the energy storage capacitor is included as a separate component. Ultrasonic waves that induce a voltage differential in the miniaturized ultrasonic transducer provide power for the implantable device, which can be managed by the power circuit.

[0121]   In some embodiments, the integrated circuit comprises one or more analog circuits which utilize the electrical power provided by the transducer to power one or more analog amplifiers, increasing the modulation depth of the signal modulated onto the backscatter impedance.

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[0122]   FIG. 8A includes one embodiment of a miniaturized ultrasonic transducer (identified as the "piezo") connected to an ASIC. The ASIC includes a power circuit, a modulation circuit (or "backscatter circuit"), and a variable frequency power supply (the "stimulation circuit"). The power circuit includes an energy storage capacitor ("cap"). The electrodes can be implanted in tissue.

[0123]   FIG. 7A illustrates a schematic of the implantable device with a miniaturized ultrasonic transducer 702, an integrated circuit 704, and a first electrode 706 and a second electrode 708 implanted in tissue 710. The first electrode 706 and the second electrode 708 are in electrical connection with each other through the tissue 710, as current applied to the first electrode 706 by the variable frequency power supply 712 passes through the tissue 710 to reach the second electrode 708. A signal detector 714 is electrically connected between the first electrode 706 and the second electrode 708. A digital circuit 716 is configured to operate the variable frequency power supply 712 and receive a signal encoding the voltage, current, or impedance detected by the signal detector 714. The digital circuit 716 is also configured to operate a modulation circuit 718. The digital circuit 716 can transmit a signal (which may be analog or digitized) encoding information relating to the detected impedance (e.g., the impedance, the voltage, the current, or any spectrum for multiple frequencies of the impedance, voltage, or current, which may include magnitude and phase) to the modulation circuit 718, which modulates current flowing to the miniaturized ultrasonic transducer 702. The embodiment illustrated in FIG. 7A further includes a power circuit 720, which is configured to receive and store energy from the current generated by the miniaturized ultrasonic transducer 702. The power circuit 720 can also provide to one or more additional components of the integrated circuit 704, such as the digital circuit 716, the variable frequency power supply 712, and/or the signal detector 714.

[0124]   FIG. 7B illustrates a schematic of the implantable device configured to detect impedance in a four-terminal impedance sensing configuration. The implantable device includes a miniaturized ultrasonic transducer 722, an integrated circuit 724, and a first electrode 726 and a second electrode 728 implanted in tissue 730. The first electrode 726 and the second electrode 728 are in electrical connection with each other through the tissue 720, as current applied to the first electrode 726 by the variable frequency power supply 732 passes through the tissue 730 to the second electrode 728. A signal detector 734 is electrically connected to a third electrode 736

and a fourth electrode 738, which are implanted in the tissue 730. The third electrode 736 and the fourth electrode 738 are disposed between (i.e., "nested") the first electrode 726 and the second electrode 728. A digital circuit 746 is configured to operate the variable frequency power supply 742 and receive a signal encoding the voltage, current, or impedance detected by the signal detector 734. The digital circuit 736 is also configured to operate a modulation circuit 738. The digital circuit 736 can transmit a signal (which may be analog or digitized) encoding information relating to the detected impedance (e.g., the impedance, the voltage, the current, or any spectrum for multiple frequencies of the impedance, voltage, or current, which may include magnitude and phase) to the modulation circuit 738, which modulates current flowing through the miniaturized ultrasonic transducer 722. The embodiment illustrated in FIG. 7B further includes a power circuit 740, which is configured to receive and store energy from the current generated by the miniaturized ultrasonic transducer 722. The power circuit 740 can also provide to one or more additional components of the integrated circuit 724, such as the digital circuit 736, the variable frequency power supply 732, and/or the signal detector 734.

[0125] The implantable devices are miniaturized, which allows for comfortable and long-term implantation while limiting tissue inflammation that is often associated with implantable devices. The body forms the core of the miniaturized implantable device (e.g., the ultrasonic transducer and the integrated circuit), and the electrodes branch from the body and implant in the tissue to measure impedance. In some embodiments, the longest dimension of the implantable device or the body of the implantable device is about 5 mm or less, about 4 mm or less, about 3 mm or less, about 2 mm or less, about 1 mm or less, about 0.5 mm or less, or about 0.3 mm or less in length. In some embodiments, the longest dimension of the implantable device or body of the implantable device is about 0.2 mm or longer, about 0.5 mm or longer, about 1 mm or longer, about 2 mm or longer, or about 3 mm or longer in the longest dimension of the device. In some embodiments, the longest dimension of the implantable device or the body of the implantable device is about 0.2 mm to about 5 mm in length, about 0.3 mm to about 4 mm in length, about 0.5 mm to about 3 mm in length, about 1 mm to about 3 mm in length, or about 2 mm in length.

[0126] In some embodiments, one or more of the electrodes are on the body of the device, for example a pad on the body of the device. In some embodiments, one or more of the electrodes extend from the body of the implantable device at any desired length, and can be implanted at any depth within the tissue. In some embodiments, an electrode is about 0.1 mm in

length or longer, such as about 0.2 mm or longer, about 0.5 mm or longer, about 1 mm in length
or longer, about 5 mm in length or longer, or about 10 mm in length or longer. In some
embodiments, the electrodes are about 15 mm or less in length, such as about 10 mm or less,
about 5 mm or less, about 1 mm or less, or about 0.5 mm or less in length. In some
embodiments, the first electrode is disposed on the body of the implantable device and the
second electrode extends from the body of the implantable device.

[0127]   In some embodiments, the implantable device has a volume of about 5 mm^3 or less
(such as about 4 mm^3 or less, 3 mm^3 or less, 2 mm^3 or less, or 1 mm^3 or less). In certain
embodiments, the implantable device has a volume of about 0.5 mm^3 to about 5 mm^3, about 1
mm^3 to about 5 mm^3, about 2 mm^3 to about 5 mm^3, about 3 mm^3 to about 5 mm^3, or about 4 mm^3
to about 5 mm^3. The small size of the implantable device allows for implantation of the device
using a biopsy needle.

[0128]   In some embodiments, the implantable device is implanted in a subject. The subject
can be for example, a vertebrate animal, such as a mammal. In some embodiments, the subject is
a human, dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, or mouse.

[0129]   In some embodiments, the implantable device or a portion of the implantable device
(such as the miniaturized ultrasonic transducer and the integrated circuit) is encapsulated by a
biocompatible material (such as a biocompatible polymer), for example a copolymer of N-vinyl-
2-pyrrolidinone (NVP) and n-butylmethacrylate (BMA), polydimethylsiloxane (PDMS),
parylene, polyimide, silicon nitride, silicon dioxide, silicon carbide, alumina, niobium, or
hydroxyapatite. The silicon carbide can be amorphous silicon carbide or crystalline silicon
carbide. The biocompatible material is preferably impermeable to water to avoid damage or
interference to electronic circuitry within the device. In some embodiments, the implantable
device or portion of the implantable device is encapsulated by a ceramic (for example, alumina
or titania) or a metal (for example, steel or titanium). In some embodiments, the electrodes or a
portion of the electrodes are not encapsulated by the biocompatible material.

[0130]   In some embodiments, the miniaturized ultrasonic transducer and the ASIC are
disposed on a printed circuit board (PCB). The electrodes can optionally be disposed on the
PCB, or can otherwise be connected to the integrated circuit. FIGS. 8A and 8B illustrate
exemplary configurations of the implantable device including a PCB. FIG. 8A shows the
piezoelectric transducer 802 and an ASIC 804 disposed on a first side 806 of the PCB 808. A

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first electrode 810 and a second electrode 812 are disposed on a second side 814 of the PCB 808. FIG. 8B sows the piezoelectric transducer 814 on a first side 816 of the PCB 818, and the ASIC 820 on the second side 822 of the PCB 818. A first electrode 824 initiates on the first side 816 of the PCB, and a second electrode 826 is initiates on the second side 822 of the PCB 818. The first electrode 824 and the second electrode 826 can extend from the PCB 818 to be configured to be in electrical connection with each other through the tissue.

[0131] The miniaturized ultrasonic transducer of the implantable device can be a micro-machined ultrasonic transducer, such as a capacitive micro-machined ultrasonic transducer (CMUT) or a piezoelectric micro-machined ultrasonic transducer (PMUT), or can be a bulk piezoelectric transducer. Bulk piezoelectric transducers can be any natural or synthetic material, such as a crystal, ceramic, or polymer. Exemplary bulk piezoelectric transducer materials include barium titanate ($BaTiO_3$), lead zirconate titanate (PZT), zinc oxide (ZO), aluminum nitride (AlN), quartz, berlinite ($AlPO_4$), topaz, langasite ($La_3Ga_5SiO_{14}$), gallium orthophosphate ($GaPO_4$), lithium niobate ($LiNbO_3$), lithium tantalite ($LiTaO_3$), potassium niobate ($KNbO_3$), sodium tungstate (Na_2WO_3), bismuth ferrite ($BiFeO_3$), polyvinylidene (di)fluoride (PVDF), and lead magnesium niobate-lead titanate (PMN-PT).

[0132] In some embodiments, the miniaturized bulk piezoelectric transducer is approximately cubic (i.e., an aspect ratio of about 1:1:1 (length:width:height). In some embodiments, the piezoelectric transducer is plate-like, with an aspect ratio of about 5:5:1 or greater in either the length or width aspect, such as about 7:5:1 or greater, or about 10:10:1 or greater. In some embodiments, the miniaturized bulk piezoelectric transducer is long and narrow, with an aspect ratio of about 3:1:1 or greater, and where the longest dimension is aligned to the direction of propagation of the carrier ultrasound wave. In some embodiments, one dimension of the bulk piezoelectric transducer is equal to one half of the wavelength (λ) corresponding to the drive frequency or resonant frequency of the transducer. At the resonant frequency, the ultrasound wave impinging on either the face of the transducer will undergo a 180° phase shift to reach the opposite phase, causing the largest displacement between the two faces. In some embodiments, the height of the piezoelectric transducer is about 10 μm to about 1000 μm (such as about 40 μm to about 400 μm, about 100 μm to about 250 μm, about 250 μm to about 500 μm, or about 500 μm to about 1000 μm). In some embodiments, the height of the piezoelectric transducer is about 5 mm or less (such as about 4 mm or less, about 3 mm or less,

about 2 mm or less, about 1 mm or less, about 500 μm or less, about 400 μm or less, 250 μm or less, about 100 μm or less, or about 40 μm or less). In some embodiments, the height of the piezoelectric transducer is about 20 μm or more (such as about 40 μm or more, about 100 μm or more, about 250 μm or more, about 400 μm or more, about 500 μm or more, about 1 mm or more, about 2 mm or more, about 3 mm or more, or about 4 mm or more) in length.

[0133]   In some embodiments, the ultrasonic transducer has a length of about 5 mm or less such as about 4 mm or less, about 3 mm or less, about 2 mm or less, about 1 mm or less, about 500 μm or less, about 400 μm or less, 250 μm or less, about 100 μm or less, or about 40 μm or less) in the longest dimension. In some embodiments, the ultrasonic transducer has a length of about 20 μm or more (such as about 40 μm or more, about 100 μm or more, about 250 μm or more, about 400 μm or more, about 500 μm or more, about 1 mm or more, about 2 mm or more, about 3 mm or more, or about 4 mm or more) in the longest dimension.

[0134]   The miniaturized ultrasonic transducer is connected two electrodes; the first electrode is attached to a first face of the transducer and the second electrode is attached to a second face of the transducer, wherein the first face and the second face are opposite sides of the transducer along one dimension. In some embodiments, the electrodes comprise silver, gold, platinum, platinum-black, poly(3,4-ethylenedioxythiophene (PEDOT), a conductive polymer (such as conductive PDMS or polyimide), or nickel. In some embodiments, the transducer is operated in shear-mode where the axis between the metallized faces (i.e., electrodes) of the transducer are orthogonal to the motion of the transducer.

[0135]   In some embodiments, the implantable device is implanted in tissue. The tissue can be, for example, a bone, a bone fracture, a bone graft, or a tissue that suffered a traumatic injury. In some embodiments, the tissue is a marrow canal or a cortical bone of a bone fracture. In some embodiments, the implantable device is implanted in a subject, and the electrodes of the implantable device are implanted in a different location than the implantable device. FIG. 9A shows an implantable device 902 implanted in a bone fracture 904. In some embodiments, the electrodes are implanted in a target tissue, and the remainder of the device attached to another tissue or structure. For example, the electrodes can be implanted in a target tissue and the rest of the implantable device can be attached to a bone plate; screw, staple, or other fastener; rod; or other implantable device. FIG. 9B shows a bone fracture 906 supported by a bone plate 908. The bone plate 908 is held to the bone by screws 910a, 910b, 910c, and 910d. Electrodes 912a

and 912d of an implantable device are implanted in the bone fracture 906, and the body 914 of the implantable device is attached to the bone plate 908.

[0136]   During healing of damaged tissue, impedance of a current flowing through the tissue changes. Although impedance at a single frequency changes during the healing process, the change is more apparent in view of an impedance spectrum (impedance magnitude spectrum, phase shift spectrum, or complex impedance spectrum) across a plurality of current frequencies. Thus, changes in impedance or one or more impedance spectra can be monitored during the healing process. For example, bone fracture healing can be monitored by observing changes in impedance or one or more impedance spectra during any one of the bone fracture healing phases or a transition from a first bone fracture healing phase to a second bone fracture healing phase. Bone fracture healing phases can include: (1) an inflammatory phase, (2) an early cartilage callus (i.e., soft callus) formation phase, (3) a cancellous bone (i.e., hard callus) formation phase, and (4) a cortical bone formation (i.e., remodeling) phase. These phases of bone fracture healing are descriptive of general bone healing, although a person of skill in the art would recognize that bone fracture healing can be described in other phase characterizations. For example, bone healing can be described to include three bone healing phases: (1) a reactive phase, (2) a reparative phase, and (3) a remodeling phase. Bone healing can also be described to include five bone healing phases: (1) an inflammatory phase, (2) a granulation tissue formation phase, (3) a cartilage callus formation phase, (4) a lamellar bone deposition phase, and (5) a remodeling phase.

[0137]   The implantable device is configured to detect an impedance (which may include an impedance magnitude and/or phase angle), or a voltage or current from which the impedance can be detected. In some embodiments, the digital circuit determines the impedance based on the voltage or current. In some embodiments, impedance is determined using a separate device (i.e., a separate computer system). The complex impedance includes an impedance magnitude, $|Z|$, and a phase-shift between the current and voltage (i.e, the phase angle), θ. The phase-sensitive current and the phase-sensitive voltage can be measured at a plurality of frequencies, to determine a complex impedance spectrum, a impedance magnitude spectrum (see FIG. 10A), or a phase-shift spectrum (see FIG. 10B). FIGS. 10A and 10B are reproduced from WO 2017/030900, and show impedance magnitude spectra and phase angle spectra for several different tissue types (blood, coagulated blood, cartilage, cancellous bone, and cortical bone),

which correspond to phases of healing of a bone fracture. As a bone-fracture passes through the different phases of healing, the complex impedance spectrum, impedance magnitude spectrum, and phase-shift spectrum shifts.

[0138] In some embodiments, the implantable device is used to monitor healing following a bone fusion (such as a spinal fusion), which may follow a surgery. This can include monitoring, for example, bone healing after implantation of a bone graft.

[0139] In some embodiments, the implantable device is used to monitor bone quality, which may be separate from monitoring fracture healing. For example, bone quality may be measured for monitoring the progression of certain bone diseases, which can cause weakened bones that are more prone to fracture (i.e., a pathologic fracture). Exemplary bone diseases include osteoporosis, bone cancer (such as metastatic bone disease), brittle bone disease (i.e., osteogenesis imperfecta), osteomalacia, Paget's disease, osteitis, and bone cysts.

[0140] In some embodiments, the implantable device is used to monitor soft tissue healing. For example, the implantable device can be implanted in tissue that suffered a traumatic injury to monitor the tissue compartment syndrome or healing of scar tissue. In some embodiments, the implantable device is used to monitor a site of infection. In some embodiments, the implantable device is used to monitor an ulcer.

Manufacture of an Implantable Device

[0141] The implantable devices can be manufactured by attaching a miniaturized ultrasonic transducer (such as a bulk piezoelectric transducer, a CMUT, or a PMUT) to a first electrode on a first face of the transducer, and a second electrode to a second face of the transducer, wherein the first face and the second face are on opposite sides of the transducer. The first electrode and the second electrode can be attached to an integrated circuit, which may be disposed on a printed circuit board (PCB). The integrated circuit can include a variable frequency power supply and a signal detector. Two or more electrodes are also attached to the integrated circuit, and are configured to be in electrical connection with each other through the tissue and to receive a source signal from the variable frequency power supply. Attachment of the components to the PCB can include, for example, wirebonding, soldering, flip-chip bonding, or gold bump bonding.

[0142] Certain piezoelectric materials can be commercially obtained, such as metalized PZT sheets of varying thickness (for example, PSI-5A4E, Piezo Systems, Woburn, MA, or PZT 841,

APC Internationals, Mackeyville, PA). In some embodiments, a piezoelectric material sheet is diced into a desired size, and the diced piezoelectric material is attached to the electrodes. In some embodiments, the electrodes are attached to the piezoelectric material sheet, and the piezoelectric material sheet is diced to the desired size with the electrodes attached to the piezoelectric material. The piezoelectric material can be diced using a dicing saw with a ceramic blade to cut sheets of the piezoelectric material into individualized piezoelectric transducer. In some embodiments, a laser cutter is used to dice or singulate the piezoelectric material. In some embodiments, patterned etching is used to dice or singulate the piezoelectric material.

[0143] The miniaturized ultrasonic transducer is connected two electrodes; the first electrode is attached to a first face of the transducer and the second electrode is attached to a second face of the transducer, wherein the first face and the second face are opposite sides of the transducer along one dimension. In some embodiments, the electrodes comprise silver, gold, platinum, platinum-black, poly(3,4-ethylenedioxythiophene (PEDOT), a conductive polymer (such as conductive PDMS or polyimide), or nickel. In some embodiments, the transducer is operated in shear-mode where the axis between the metallized faces (i.e., electrodes) of the transducer is orthogonal to the motion of the transducer.

[0144] In some embodiments, the electrode is attached to the piezoelectric transducer by electroplating or vacuum depositing the electrode material onto the face of the piezoelectric transducer. In some embodiments, the electrodes are soldered onto the piezoelectric transducer using an appropriate solder and flux. In some embodiments, the electrodes are attached to the piezoelectric transducer using an epoxy (such as a silver epoxy) or low-temperature soldering (such as by use of a solder paste).

[0145] In an exemplary embodiment, solder paste is applied to a pad on a printed circuit board (PCB), either before or after the integrated circuit is attached to the PCB. The size of the pad on the circuit board can depend on the desired size of the piezoelectric transducer. Solely by way of example, if the desired size of piezoelectric transducer is about 100 μm x 100 μm x 100 μm, the pad can be about 100 μm x 100 μm. The pad functions as the first electrode for the implantable device. A piezoelectric material (which may be larger than the pad) is placed on the pad, and is held to the pad by the applied solder paste, resulting in a piezoelectric-PCB assembly. The piezoelectric-PCB assembly is heated to cure the solder paste, thereby bonding the piezoelectric transducer to the PCB. If the piezoelectric material is larger than the pad, the

piezoelectric material is cut to the desired size, for example using a wafer dicing saw or a laser cutter. Non-bonded portions of the piezoelectric material (for example, the portions of the piezoelectric material that did not overlay the pad) are removed. A second electrode is attached to the piezoelectric transducer and the PCB, for example by forming a wirebond between the top of the piezoelectric transducer and the PCB, which completes the circuit. The wirebond is made using a wire made from any conductive material, such as aluminum, copper, silver, or gold.

[0146] The integrated circuit and the miniaturized ultrasonic transducer can be attached on the same side of the PCB or on opposite sides of the PCB. In some embodiments, the PCB is a flexible PCB, the integrated circuit and the miniaturized ultrasonic transducer are attached to the same side of the PCB, and the PCB is folded, resulting in an implantable device in which the integrated circuit and the miniaturized ultrasonic transducer are on opposite sides of the PCB.

[0147] Optionally, the device or a portion of the device is encapsulated in or a portion of the device is encapsulated in a biocompatible material (such as a biocompatible polymer), for example a copolymer of N-vinyl-2-pyrrolidinone (NVP) and n-butylmethacrylate (BMA), polydimethylsiloxane (PDMS, e.g., Sylgard 184, Dow Corning, Midland, MI), parylene, polyimide, silicon nitride, silicon dioxide, alumina, niobium, hydroxyapatite, or silicon carbide. The silicon carbide can be amorphous silicon carbide or crystalline silicon carbide. In some embodiments, the biocompatible material (such as amorphous silicon carbide) is applied to the device by plasma enhanced chemical vapor deposition (PECVD) or sputtering. PECVD may use precursors such as SiH_4 and CH_4 to generate the silicon carbide. In some embodiments, the implantable device or portion of the implantable device is encased in a ceramic (for example, alumina or titania) or a metal (for example, steel or titanium) suitable for medical implantation.

[0148] FIG. 11 illustrates an exemplary method of producing the implantable device described herein. At step 1102, an application specific integrated circuit (ASIC) is attached to a PCB. The PCB can include two or more electrodes for detecting impedance in tissue. A solder (such as a silver epoxy) can be applied to the PCB (for example, at a first pad disposed on the PCB), and the ASIC can be placed on the solder. The solder can be cured, for example by heating the PCB with the ASIC. In some embodiments, the PCB with the ASIC is heated to about 50 °C to about 200 °C, such as about 80 °C to about 170 °C, or about 150 °C. In some embodiments, the PCB with the ASIC is heated for about 5 minutes to about 600 minutes, such as about 10 minutes to about 300 minutes, about 10 minutes to about 100 minutes, about 10

minutes to about 60 minutes, about 10 minutes to about 30 minutes, or about 15 minutes. Optionally, the ASIC is coated with additional solder. At step 1104, a piezoelectric transducer (the "piezo" in FIG. 11) is attached to the PCB. A solder (such as a silver epoxy) can be applied to the PCB (for example, at a second pad disposed on the PCB), and a piezoelectric material can be placed on the solder. The piezoelectric material can be a fully formed (i.e., "diced") piezoelectric transducer, or can be a piezoelectric material sheet that is cut to form the piezoelectric transducer once attached to the PCB. The solder can be cured, for example by heating the PCB with the piezoelectric material. In some embodiments, the PCB with the piezoelectric material is heated to about 50 °C to about 200 °C, such as about 80 °C to about 170 °C, or about 150 °C. In some embodiments, the PCB with the piezoelectric material is heated for about 5 minutes to about 600 minutes, such as about 10 minutes to about 300 minutes, about 10 minutes to about 100 minutes, about 10 minutes to about 60 minutes, about 10 minutes to about 30 minutes, or about 15 minutes. The piezoelectric material can be cut using a saw or laser cutter to the desired dimensions. In some embodiments, the piezoelectric material is a solgel (such as a PZT solgel) and the transducer material can be shaped with deep reactive ion etching (DRIE). Although FIG. 11 illustrates attachment of the ASIC to the PCB at step 1102 prior to attachment of the piezoelectric material to the PCB at step 1104, a person of skill in the art will appreciate that the ASIC and the piezoelectric material can be attached in any order. At step 1106, the ASIC and the piezoelectric transducer are wirebonded to the PCB. Although the method illustrated in FIG. 11 shows the ASIC and the piezoelectric transducer to the PCB after the ASIC and the piezoelectric transducer are attached to the PCB, a person of skill in the art will appreciate that the ASIC can be wirebonded to the PCB after the ASIC is attached to the PCB, and can be wirebonded either before or after attachment of the piezoelectric transducer. Similarly, the piezoelectric transducer may be wirebonded to the PCB either before or after attachment or wirebonding of the ASIC to the PCB. At step 1108, at least a portion of the device is coated with a biocompatible material. Preferably, at least the piezoelectric transducer and the ASIC are coated with the biocompatible material. In some embodiments, the sensor is not or at least a portion of the sensor is not coated with the biocompatible material. For example, in some embodiments, the implantable device comprises a pair of electrodes which are not coated with the biocompatible material, which allows the electrodes to detect changes in tissue impedance.

In some embodiments, the biocompatible material is cured, for example by exposure to UV light or by heating.

[0149]   In some embodiments, the implantable device or a portion of the implantable device is encapsulated in an amorphous silicon carbide (a-SiC) film. FIG. 12 illustrates a method of manufacturing an implantable device encapsulated in an a-SiC film. At step 1202, a polyimide layer is applied to a smooth surface. At step 1204, an a-SiC layer is applied to the polyimide layer. This can be done, for example, using plasma enhanced chemical vapor deposition (PECVD), using SiH_4 and CH_4 as precursors. At step 1206, one or more ports are etched into the a-SiC layer. In some embodiments, ports are also etched into the polyimide layer. The ports provide access for portions of the implantable device that are not encapsulated by the a-SiC, such as portions of a sensor or an electrode that will contact the tissue after implant. In some embodiments, etching comprises reactive-ion etching. At step 1208, the implantable device is attached to the a-SiC layer. The implantable device may be pre-assembled before being attached to the a-SiC layer, or may be built on the a-SiC. In some embodiments, a printed circuit board (PCB), miniaturized ultrasonic transducer, and sensor are attached to the a-SiC layer. The miniaturized ultrasonic transducer and the sensor need not come in direct contact with the a-SiC layer, as they may be attached to the PCB. Attachment of miniaturized ultrasonic transducer or sensor to the PCB may occur before or after attachment of the PCB to the a-SiC layer. In some embodiments, attachment of miniaturized ultrasonic transducer or sensor to the PCB comprises wirebonding the miniaturized ultrasonic transducer or sensor to the PCB. In some embodiments, the sensor includes a portion that interfaces with the ports etched into the a-SiC layer. In some embodiments, an ASIC is attached to the PCB, which may occur before or after attachment of the PCB to the a-SiC layer. At step 1210, an exposed portion of the implantable device is coated with an a-SiC layer. In some embodiments, the exposed portion of the implantable device is coated with an a-SiC layer using PECVD. At step 1212, the encapsulated implantable device is embossed, thereby releasing the implantable device from the SiC layer.

EXEMPLARY EMBODIMENTS

[0150]   Embodiment 1. An implantable device, comprising:

a body about 5 mm or less in length in the longest dimension, comprising:

(a) an ultrasonic transducer configured to emit an ultrasonic backscatter encoding information relating to an impedance characteristic of a tissue based on a modulated current flowing through the ultrasonic transducer;

(b) an integrated circuit comprising:

(i) a variable frequency power supply electrically connected to a first electrode and a second electrode;

(ii) a signal detector configured to detect an impedance, voltage, or current in a circuit comprising the variable frequency power supply, the first electrode, the second electrode, and the tissue; and

(iii) a modulation circuit configured to modulate the current flowing through the ultrasonic transducer based on the detected impedance, voltage, or current; and

the first electrode and the second electrode configured to be implanted into the tissue in electrical connection with each other through the tissue.

[0151]   Embodiment 2. The implantable device of embodiment 1, wherein the signal detector is electrically connected to the first electrode and the second electrode.

[0152]   Embodiment 3. The implantable device of embodiment 1, wherein the signal detector is electrically connected to a third electrode and a fourth electrode configured to be implanted into the tissue in electrical connection through the tissue.

[0153]   Embodiment 4. The implantable device of any one of embodiments 1-3, wherein the signal detector is configured to detect an impedance magnitude or an impedance phase angle.

[0154]   Embodiment 5. The implantable device of any one of embodiments 1-4, wherein the signal detector is configured to detect an impedance magnitude and an impedance phase angle.

[0155]   Embodiment 6. The implantable device of any one of embodiments 1-5, wherein the signal detector is configured to detect a voltage magnitude or a voltage phase.

[0156]   Embodiment 7. The implantable device of any one of embodiments 1- 6, wherein the signal detector is configured to detect a voltage magnitude and a voltage phase.

[0157]   Embodiment 8. The implantable device of any one of embodiments 1-7, wherein the signal detector is configured to detect a current magnitude or a current phase.

[0158]   Embodiment 9. The implantable device of any one of embodiments 1-8, wherein the signal detector is configured to detect a current magnitude and a current phase.

[0159]   Embodiment 10. The implantable device of any one of embodiments 1-10, wherein the integrated circuit comprises a digital circuit.

[0160]   Embodiment 11. The implantable device of embodiment 10, wherein the digital circuit is configured to operate the modulation circuit.

[0161]   Embodiment 12. The implantable device of embodiment 10 or 11, wherein the digital circuit is configured to transmit a digitized signal to the modulation circuit, wherein the digitized signal is based on the detected impedance, current, or voltage.

[0162]   Embodiment 13. The implantable device of any one of embodiments 10-12, wherein the digital circuit comprises a processor and a non-transitory computer-readable storage medium storing one or more programs configured to be executed by the one or more processors, the one or more programs comprising instructions for determining the impedance characteristic of the tissue based on the detected current or voltage.

[0163]   Embodiment 14. The implantable device of any one of embodiments 10-13, wherein the digital circuit comprises a processor and a non-transitory computer-readable storage medium storing one or more programs configured to be executed by the one or more processors, the one or more programs comprising instructions for determining an impedance magnitude or an impedance phase angle.

[0164]   Embodiment 15. The implantable device of any one of embodiments 1-14, wherein the ultrasonic backscatter encodes an impedance magnitude.

[0165]   Embodiment 16. The implantable device of any one of embodiments 1-15, wherein the ultrasonic backscatter encodes an impedance phase angle.

[0166]   Embodiment 17. The implantable device of any one of embodiments 1-16, wherein the ultrasonic backscatter encodes an impedance magnitude spectrum comprising a plurality of impedance magnitude measurements taken at different current frequencies.

[0167]   Embodiment 18. The implantable device of any one of embodiments 1-17, wherein the ultrasonic backscatter encodes an impedance phase angle spectrum comprising a plurality of impedance phase angle measurements taken at different current frequencies.

[0168]   Embodiment 19. The implantable device of any one of embodiments 1-18, wherein the integrated circuit comprises a power circuit.

[0169]   Embodiment 20. The implantable device of any one of embodiments 1-19, wherein the modulation circuit comprising a switch.

[0170]　　　Embodiment 21. The implantable device of embodiment 20, wherein the switch comprises a field effect transistor (FET).

[0171]　　　Embodiment 22. The implantable device of any one of embodiments 1-21, wherein the integrated circuit comprises an analog-to-digital converter (ADC).

[0172]　　　Embodiment 23. The implantable device of any one of embodiments 1-22, wherein the variable frequency power supply is configured to supply a current at a plurality of different frequencies at about 10 Hz or more.

[0173]　　　Embodiment 24. The implantable device of any one of embodiments 1-23, wherein the body has a volume of about 5 mm3 or less.

[0174]　　　Embodiment 25. The implantable device of any one of embodiments 1-24, wherein the body has a volume of about 1 mm3 or less.

[0175]　　　Embodiment 26. The implantable device of any one of embodiments 1-25, wherein the ultrasonic transducer is configured to receive ultrasonic waves that power the implantable device.

[0176]　　　Embodiment 27. The implantable device of any one of embodiments 1-26, wherein the ultrasonic transducer is configured to receive ultrasonic waves that encode instructions for selecting a current frequency.

[0177]　　　Embodiment 28. The implantable device of any one of embodiments 1-27, wherein the ultrasonic transducer is configured to receive ultrasonic waves from an interrogator comprising one or more ultrasonic transducers.

[0178]　　　Embodiment 29. The implantable device of any one of embodiments 1-28, wherein the ultrasonic transducer is a bulk piezoelectric transducer.

[0179]　　　Embodiment 30. The implantable device of embodiment 29, wherein the bulk ultrasonic transducer is approximately cubic.

[0180]　　　Embodiment 31. The implantable device of any one of embodiments 1-28, wherein the ultrasonic transducer is a piezoelectric micro-machined ultrasonic transducer (PMUT) or a capacitive micro-machined ultrasonic transducer (CMUT).

[0181]　　　Embodiment 32. The implantable device of any one of embodiments 1-31, wherein the implantable device is implanted in a subject.

[0182]　　　Embodiment 33. The implantable device of embodiment 32, wherein the subject is a human.

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[0183] Embodiment 34. The implantable device of any one of embodiments 1-33, wherein the implantable device is implanted in the tissue.

[0184] Embodiment 35. The implantable device of any one of embodiments 1-33, wherein the first electrode and the second electrode are implanted in the tissue, and the body is attached to an implantable tissue support structure.

[0185] Embodiment 36. The implantable device of embodiment 35, wherein the implantable tissue support structure is a bone plate, a rod, or a fastener.

[0186] Embodiment 37. The implantable device of any one of embodiments 1-36, wherein the tissue is a bone or a bone fracture site.

[0187] Embodiment 38. The implantable device of any one of embodiments 1-36, wherein the tissue is a soft tissue subjected to an infection or an injury.

[0188] Embodiment 39. The implantable device of any one of embodiments 1-38, wherein the implanted device is at least partially encapsulated by a biocompatible material.

[0189] Embodiment 40. The implantable device of embodiment 39, wherein at least a portion of the first electrode and the second electrode are not encapsulated by the biocompatible material.

[0190] Embodiment 41. The implantable device of embodiment 39 or 40, wherein the biocompatible material is a copolymer of N-vinyl-2-pyrrolidinone (NVP) and n-butylmethacrylate (BMA), polydimethylsiloxane (PDMS), parylene, polyimide, silicon nitride, silicon dioxide, alumina, niobium, hydroxyapatite, silicon carbide, titania, steel, or titanium.

[0191] Embodiment 42. The implantable device of embodiment 39 or 40, wherein the biocompatible material is a ceramic or a metal.

[0192] Embodiment 43. The implantable device of any one of embodiments 1-42, wherein the implantable device further comprises a non-responsive reflector.

[0193] Embodiment 44. A system comprising one or more implantable devices according to any one of embodiments 1-43 and an interrogator comprising one or more ultrasonic transducers configured to transmit ultrasonic waves to the one or more implantable devices or receive ultrasonic backscatter from the one or more implantable devices.

[0194] Embodiment 45. The system of embodiment 44, wherein the interrogator comprises a first ultrasonic transducer configured to transmit ultrasonic waves and a second ultrasonic

transducer configured to receive ultrasonic backscatter from the one or more implantable devices.

[0195]   Embodiment 46. The system of embodiment 44 or 45, wherein the interrogator comprises two or more separate interrogator devices, wherein a first interrogator device is configured to transmit ultrasonic waves to the one or more implantable devices and a second interrogator device is configured to receive ultrasonic backscatter from the one or more implantable devices.

[0196]   Embodiment 47. The system of any one of embodiments 44-46, wherein the interrogator comprises two or more ultrasonic transducer arrays, wherein each transducer array comprises two or more ultrasonic transducers.

[0197]   Embodiment 48. The system of any one of embodiments 44-47, wherein at least one of the one or more ultrasonic transducers is configured to alternatively transmit ultrasonic waves to the one or more implantable devices or receive ultrasonic backscatter from the one or more implantable devices, wherein the configuration of the transducer is controlled by a switch on the interrogator.

[0198]   Embodiment 49. The system of any one of embodiments 44-48, wherein the system comprises a plurality of implantable devices.

[0199]   Embodiment 50. The system of embodiment 49, wherein the interrogator is configured to beam steer transmitted ultrasonic waves to alternatively focus the transmitted ultrasonic waves on a first portion of the plurality of implantable devices or focus the transmitted ultrasonic waves on a second portion of the plurality of implantable devices.

[0200]   Embodiment 51. The system of embodiment 49, wherein the interrogator is configured to simultaneously receive ultrasonic backscatter from at least two implantable devices.

[0201]   Embodiment 52. The system of embodiment 49, wherein the interrogator is configured to transit ultrasonic waves to the plurality of implantable devices or receive ultrasonic backscatter from the plurality of implantable devices using time division multiplexing.

[0202]   Embodiment 53. The system of embodiment 49, wherein the interrogator is configured to transit ultrasonic waves to the plurality of implantable devices or receive ultrasonic backscatter from the plurality of implantable devices using spatial multiplexing.

[0203]   Embodiment 54. The system of embodiment 49, wherein the interrogator is configured to transit ultrasonic waves to the plurality of implantable devices or receive ultrasonic backscatter from the plurality of implantable devices using frequency multiplexing.

[0204]   Embodiment 55. The system according to any one of embodiments 44-54, wherein the interrogator is configured to be wearable by a subject.

[0205]   Embodiment 56. A method of measuring impedance characteristic of a tissue in a subject, comprising:

receiving ultrasonic waves that power one or more implantable devices comprising an ultrasonic transducer; an integrated circuit comprising a power supply and a signal detector configured to detect an impedance, voltage, or current; and a first electrode and a second electrode in electrical connection with each other through the tissue;

converting energy from the ultrasonic waves into a first electrical current;

transmitting the first electrical current to the integrated circuit;

applying a second electrical current through the tissue;

detecting an impedance, voltage, or current of a circuit formed by the power supply, the first electrode, the second electrode, and the tissue;

modulating the first electrical current based on the detected impedance, voltage, or current;

transducing the modulated first electrical current into an ultrasonic backscatter that encodes information related to impedance characteristic of the tissue; and

emitting the ultrasonic backscatter to an interrogator comprising one or more transducer configured to receive the ultrasonic backscatter.

[0206]   Embodiment 57. The method embodiment 56, comprising:

applying the second electrical current through the tissue at a plurality of different current frequencies; and

detecting the current impedance, voltage, or current at the plurality of different current frequencies.

[0207]   Embodiment 58. A method of monitoring or characterizing a tissue a subject, comprising:

transmitting ultrasonic waves from an interrogator comprising one or more ultrasonic transducers to one or more implantable devices comprising an ultrasonic transducer, an

integrated circuit comprising a variable frequency power supply and a signal detector configured to detect an impedance, voltage, or current; and a first electrode and a second electrode in electrical connection with each other through the tissue;

receiving from the one or more implantable devices ultrasonic backscatter that encodes information related to impedance characteristic of the tissue at a plurality of different current frequencies.

[0208]   Embodiment 59. The method of any one of embodiments 56-58, wherein the information related to impedance comprises information related to impedance at a plurality of different frequencies

[0209]   Embodiment 60. The method of any one of embodiments 56-59, wherein the signal detector is electrically connected to the first electrode and the second electrode.

[0210]   Embodiment 61. The method of any one of embodiments 56-59, wherein the signal detector is electrically connected to a third electrode and a fourth electrode configured to detect the impedance, voltage, or current.

[0211]   Embodiment 62. The method of any one of embodiments 56-61, wherein the power supply is a variable frequency power supply.

[0212]   Embodiment 63. The method of any one of embodiments 56-62, comprising determining the impedance based on the determined current or voltage.

[0213]   Embodiment 64. The method of any one of embodiments 56-63, comprising determining an impedance magnitude and an impedance phase angle.

[0214]   Embodiment 65. The method of embodiment 64, wherein the ultrasonic backscatter encodes the determined impedance magnitude and impedance phase angle.

[0215]   Embodiment 66. The method of any one of embodiments 56-65, wherein the ultrasonic backscatter encodes the determined voltage or the determined current.

[0216]   Embodiment 67. The method of any one of embodiments 56-66, comprising monitoring or characterizing the tissue during a healing process.

[0217]   Embodiment 68. The method of any one of embodiments 56-67, comprising comparing the information related to impedance characteristic of the tissue at the plurality of different current frequencies to a reference to characterize a tissue disease, an infection in the tissue, or a tissue injury.

[0218]   Embodiment 69. The method of any one of embodiments 56-67, comprising:

receiving the ultrasonic backscatter that encodes information related to impedance caused by the tissue at the plurality of different current frequencies at a first time point;

receiving the ultrasonic backscatter that encodes information related to impedance caused by the tissue at the plurality of different current frequencies at a second time point; and

comparing the information related to impedance caused by the tissue at the plurality of different current frequencies at the first time point and at the second time point to monitor a tissue disease, an infection in the tissue, or a tissue injury.

[0219]   Embodiment 70. The method of any one of embodiments 56-69, wherein the tissue is bone, a bone fracture, or a soft tissue.

[0220]   Embodiment 71. The method of any one of embodiments 56-70, wherein the method comprises monitoring or characterizing a bone fracture, a bone disease, scar tissue, or an ulcer.

[0221]   Embodiment 72. The method of any one of embodiments 56-71, wherein the method comprises monitoring or characterizing a bone disease that causes pathological fracturing.

[0222]   Embodiment 73. The method of any one of embodiments 56-72, wherein the method comprises monitoring or characterizing bone quality in a subject with osteoporosis, a bone cancer, brittle bone disease, osteomalacia, Paget's disease, osteitis, or a bone cyst.

[0223]   Embodiment 74. The method of any one of embodiments 56-72, wherein the method comprises monitoring or characterizing a bone fracture.

[0224]   Embodiment 75. The method of any one of embodiments 56-70, wherein the method comprises monitoring or characterizing a tissue subject to compartment syndrome.

[0225]   Embodiment 76. The method of any one of embodiments 56-70, wherein the method comprises monitoring or characterizing the tissue after a surgery.

[0226]   Embodiment 77. The method of any one of embodiments 56-70, wherein the method comprises monitoring or characterizing a bone graft implant.

[0227]   Embodiment 78. The method of any one of embodiments 56-70, wherein the method comprises monitoring or characterizing a spinal fusion.

[0228]   Embodiment 79. The method of any one of embodiments 56-70, wherein the method comprises monitoring or characterizing an ulcer.

[0229]   Embodiment 80. The method of any one of embodiments 56-79, comprising implanting the one or more implantable devices in the subject.

[0230]   Embodiment 81. The method of any one of embodiments 56-80, wherein the subject is a human.

[0231]   Embodiment 82. The method of any one of embodiments 56-81, comprising determining a location of the one or more implantable devices.

[0232]   Embodiment 83. The method of any one of embodiments 56-82, comprising detecting angular or lateral movement of the one or more implantable devices.

[0233]   Embodiment 84. The method of any one of embodiments 56-83, wherein the ultrasonic backscatter comprises a digitized signal.

[0234]   Embodiment 85. An internal body condition sensing system, comprising:

an ultrasound transceiver configured to generate ultrasound transmissions and receive ultrasound backscatter produced by generated ultrasound transmissions; and

a body implantable device comprising an impedance spectroscopy system to measure dielectric properties of tissue, and comprising an ultrasound backscatter communication system to modulate in reflected ultrasound backscatter communications information indicative of the measured dielectric properties.

[0235]   Embodiment 86. The internal body condition sensing system of embodiment 85, wherein the impedance spectroscopy system is configured to measure dielectric properties indicative of bone health.

[0236]   Embodiment 87. A method of monitoring bone health, comprising:

implanting at a location at or near bone a body implantable device comprising a sensor to sense a biologic condition indicative of bone health, the body implantable device further comprising an ultrasound backscatter communication system to modulate in reflected ultrasound backscatter communications information indicative of the sensed biologic condition indicative of bone health; and

using an ultrasound transceiver configured to generate ultrasound transmissions and receive ultrasound backscatter produced by generated ultrasound transmissions, to interrogate the body implantable device to obtain information indicative of the sensed biologic condition indicative of bone health.

[0237]   Embodiment 88. The method of embodiment 87, wherein the sensor of the body implantable device is an impedance spectroscopy system to measure dielectric properties of bone tissue.

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[0238] Embodiment 89. The method of embodiment 88, wherein the impedance spectroscopy system is configured to measure dielectric properties indicative of bone health.

[0239] Embodiment 90. The method of any of embodiments 87-89, wherein the body implantable device is positioned in a bone fracture gap.

[0240] Embodiment 91. The method of any of embodiments 87-89, wherein the body implantable device is positioned between spinal vertebrae to monitor fusion between the vertebrae.

[0241] Embodiment 92. The method of any of embodiments 87-89, wherein the body implantable device is positioned proximate to a bone to monitor osteoporosis.

EXAMPLES

Example 1 – Manufacture of an Implantable Device

[0242] In short form, the assembly steps of the implantable device are as follows:

1. Attach ASIC to PCB.

2. Wirebond ASIC ports to PCB

3. Attach piezoelectric element to PCB.

4. Wirebond piezoelectric element ports to PCB.

5. Encapsulate full device except for recording electrodes.

[0243] The ASIC measures 450 μm by 500 μm by 500pm and is fabricated by Taiwan Semiconductor Manufacturing Company's 65 nm process. Each chip contains two transistors with 5 ports each: source, drain, gate, center, and bulk. Each FET uses the same bulk, so either bulk pad can be bonded to, but the transistors differ in that the transistor padded out to the top row does not contain a resistor bias network whereas the transistor padded out in the bottom row does. The chip additionally contains smaller pads for electroplating. The same process can be applied to ASIC's with more complex circuitry and thus more pads. These pads were not used in this example. Three versions of the FET were taped out:

Die 1: Long channel FET with threshold voltage: 500 mV

Die 2: Short channel FET with threshold voltage at 500 mV

Die 3: Native FET with threshold voltage at 0 mV

[0244] Confirmation of electrical characteristics of these FETs were measured using a specially designed CMOS characterization board which contained of a set of pads as

wirebonding targets and a second set of pads in which wires were soldered to. A sourcemeter (2400 Sourcemeter, Keithley Instruments, Cleveland, OH) was used to supply V_{DS} to the FET and measure I_{DS}. An adjustable power supply (E3631A, Agilent, Santa Clara, CA) was used to modulate V_{GS} and the I-V characteristics of the FETs were obtained. Uncharacteristic IV curves for type 2 dies were consistently measured, and upon impedance measurement, found that the short channel of the die 2s would short out the FET.

[0245]   The piezoelectric element is lead-zirconium titanate (PZT). It is purchased as a disc from APC International and diced into.750 μm x 750 μm x 750 μm cubes using a wafer saw (DAD3240, Disco, Santa Clara, CA) with a ceramic blade (PN CX-010-'270-080-H). This mote size was chosen as it maximized power transfer efficiency. For more details, see Seo et al., *Neural dust: an ultrasonic, low power solution for chronic brain-machine interfaces*, arXiv: 1307.2196v1 (July 8, 2013).

[0246]   The implantable device was implanted in the sciatic nerve of a Long-Evans rat. The nerve is a large diameter nerve bundle which innervates the hind limb. The nerve is between 1 and 1.4 mm in diameter, and its size and accessibility make it an ideal candidate for device implantation. While several iterations of the implantable device were made, the following example discusses the development of two versions implanted in rat models.

[0247]   The implantable device substrate integrates the ASIC with the piezoelectric element and recording electrodes. The first version of the implantable device used custom-designed PCBs purchased from The Boardworks (Oakland, CA) as a substrate. The PCBs were made of FR-4 and were 30 mil (approximately 0.762 mm) in thickness. The dimensions of the board were 3 mm x 1 mm. This design was the first attempt an integrated communication and sense platform, so pad size and spacing was chosen to facilitate assembly at the cost of larger size. To conserve PCB real-estate, each face of the PCB included pads for either the piezoelectric element or the ASIC and its respective connections to the PCB. Additionally, two recording pads were placed on the ASIC-face of the board. All exposed electrodes were plated with ENIG by The Boardworks. The pad for the ASIC to sit on was 500 μm by 500 μm, chosen to fit the size of the die. The wirebond target pad size was chosen to be 200 μm by 200 μm and spaced roughly 200μm away from the edge of the die in order to give enough clearance for wirebonding (discussed below). Electrode size and spacing varied and were empirically optimized using four pairs of electrodes spaced 2 mm, 1.5 m, 1 mm, and 0.5 mm away from each other. It was found

that electrodes spacing greater than 1.5 mm were optimal for recording. Minimal signal attenuation was noted between 2 mm and 1.5 mm, and signal strength decreased by about 33% between 1.5 mm and 1 mm.

[0248] In the second iteration of implantable device, three concerns primary concerns were addressed: 1) size, 2) ease of wirebonding, 3) implantation/communication. First, to decrease board thickness the FR-4 substrate was replaced with a 2 mil (about 50.8 μm) thick polyimide flexible PCB (AltaFlex, Santa Clara, CA), as well as thinning the ASIC (Grinding and Dicing Services Inc., San Jose, CA) to 100 μm. To facilitate bonding, the ASIC and PZT coupon were moved to the same side, with only the recording electrodes on the backside of the substrate. While putting the ASIC and PZT coupon on the same side of the board does impose a limit on how much the substrate size can be reduced, spacing between the electrodes restricted the board length of at least 2 mm. To push minimization efforts ASIC bonding pads were reduced to 100 μm by 100 μm, but the 200 μm spacing between bonding pads and the ASIC itself had to be maintained to provide space for wirebonding. The attachment pads for the PZT coupon was also shrunk and placed closer to the edge of the board, with the rationale that the PZT coupon did not have to wholly sit on the board, but could hang off it. Additionally, the location of the pads relative to the ASIC was also modified to facilitate bonding. In the original design, the bond pad layout surrounding the ASIC required two wirebonds to cross. This is not impossible, but very difficult to avoid shorting the pads. Thus, the pad layout was shifted so that the bonds are relatively straight paths. Finally, during animal experiments, it was found that alignment of the implantable device was quite difficult. To combat this, four 1 inch test leads that extended off the board were added, two of which connected directly to the source and drain of the device to harvest power could be measured and to use that as an alignment metric. The other two leads connect to the gate and center ports in order to obtain a ground truth signal. In order to prevent confusion over which lead belonged to which port, the vias were given unique geometries. See FIG. 13A.

[0249] There was some fear that the test leads may be easily broken or would easily displace the mote if force was applied on them. Thus, a version with serpentine traces was designed. Serpentine traces (FIG. 13B) have often been used to enable deformable interconnects, as their structure allows them to "accordion" out. Conceptually, the serpentine trace design can be through of a series of cantilevers in series via connector beams.

[0250]   Along with the presented designs, a miniaturized version of the implantable device using both sides of the substrate was also designed and assembled. In this design, the board measures roughly 1.5 mm by 0.6 mm by 1 mm. Due to the miniaturization of the board, a 5 mil silver wire "tail" was attached to the device for recording. This version was not tested *in vivo*.

[0251]   The ASIC and PZT coupon were attached to the PCB substrate using adhesives. There are three majors concerns to choosing an adhesive: 1) the adhesive needs to fix the ASIC and PZT tightly enough that the ultrasonic power from wirebonding does not shake the components, 2) due to the sub-millimeter scales and pitches of the components/substrate pads, application of the adhesive was done in a relatively precise way, and 3) the adhesive must be electrically conductive.

[0252]   The ASIC and diced PZT were originally attached to the PCB substrate using a low temperature-curing solder paste. Solder paste consists of powder metal solder suspended as spheres in flux. When heat is applied, the solder balls begin to melt and fuse together. However, it was found that the curing of the solder paste would often result in translating or rotating the PZT coupon or mote during reflow. This presented problems for PZT alignment and power harvesting, as well as problems for wirebonding due to the bondpads no longer being appropriately positioned from the chip. However, it was found that a two-part silver epoxy, which simply consists of silver particles suspended in epoxy was capable of curing without repositioning the chip or PZT coupon. Thus, the ASIC and diced PZT were pasted onto the PCB using a two-part conductive silver epoxy (H20E, Epotek, Billerica, MA). The PCBs were then affixed to a glass slide using Kapton tape (Polyimide Film Tape 5413, 3M, St. Paul, MN) and put into a convection oven at 150°C for 15 minutes to cure the epoxy. While higher temperatures could yield faster curing (FIG. 14), care was taken to avoid heating the PZT beyond 160°C, half the Curie temperature of the PZT. Heating the PZT any higher runs the risk of depolarizing the PZT. It was found that the 150°C cure had no effect on the CMOS performance.

[0253]   The connections between the top of the PZT and the PCB as well as the ASIC and the PCB were made by wirebonding 1 mil Al wire using an ultrasonic wedge bonder (740DB, West Bond, Scotts Valley, CA); in this method of bonding, the Al wire is threaded through the wedge of the bondhead and ultrasonic energy "scrubs" the Al wire against the substrate, generating heat through friction.. This heat results in welding the two materials together.

[0254]   Wirebonding to the ASIC was challenging to avoid shorts due to the size of the CMOS pads and the size of the foot of the wirebond. This problem was accentuated due to the positioning of the wirebonding targets in the first version of the implantable device board, which forced the feet of two bonds to be placed across the smaller width of the ASIC pad rather than the length. While thinner gold wire was available to use for bonding, the difficulty of bonding gold thermosonically with a wedge bonder made it impractical to use gold wires for bonding with this equipment. Furthermore, in order to effectively wirebond, it is important to have a flat and fixed substrate; hence, our original design of having the ASIC and PZT on different sides of the board often caused trouble during the wirebonding process in our first version of implantable boards. Thus, the substrate design choices made in the second iteration of the implantable device (moving ASIC and PZT to the same side, repositioning the pads to provide straight paths to wirebond targets) greatly improved wirebonding yield.

[0255]   Finally, because an ultrasonic bonder was used, it was found that bonding to the PZT resulted in a charge build up would damage the chip once the PZT was fully bonded to the substrate. To avoid this, the source and drain test leads of the device were discharged to Earth ground directly prior to wirebonding the PZT.

[0256]   The final step of the implantable device assembly is encapsulation. This step achieves two goals: 1) insulation of the PZT, bondpads, and ASIC from aqueous environments and 2) protection of the wirebonds between the ASIC/PZT coupon and the PCB. At the same time, there must be some method to either remove or prevent the encapsulant from covering the recording electrodes. Additionally, the encapsulant must not impede device implantation. Finally, while it is not crucial, it is of interest to choose an encapsulant that is optically transparent so that the device can be inspected for physical defects if some damage occurred during the encapsulation.

[0257]   The first encapsulant used was Crystalbond (509', SPI Supplies, West Chester, PA). Crystalbond is an adhesive that is solid at room temperature but begins to soften' at 71°C and melts into a viscous liquid at 121°C. Upon removing heat from the Crystalbond, it re-solidifies within minutes, allowing for good control. To encapsulate the implantable device, a small flake of Crystalbond was shaved off with a razor and placed directly over the device. The board was then heated using a hotplate, first bringing the temperature to around 70°C when the flake would begin to deform and then slowly increasing the temperature until the Crystalbond became fully liquid. Once the edge of the liquid Crystalbond drop expanded past the furthest wirebond but not

the recording pad, the hotplate was turned off and the board was quickly moved off the plate onto a cooling chuck where the Crystalbond would re-solidify.

[0258] While Crystal bond was effective, it was found that UV curable epoxide could give us better selectivity and biocompatibility, as well as rapid curing. First, a light-curable acrylic (3526, Loctite, Dusseldorf; Germany) was tested, which cures with exposure to ultraviolet light. A sewing needle was used as an applicator to obtain high precision and the epoxy was cured with a 405 nm laser point for 2 minutes. This epoxy worked well, but was not medical-grade and thus not appropriate for a biological implant. Thus, a medical-grade UV curable epoxy (OG116-31, EPO-TEK, Billercia, MA) was tried. The epoxy was cured in a UV chamber (Flash, Asiga, Anaheim Hills, CA) with 92 mW/cm^2 at 365 nm for 5 minutes. While this epoxy was slightly less viscous than the Loctite epoxy, using a sewing needle again as an applicator allowed for selective encapsulation. As an insulator and protection mechanism for the wirebonds; the epoxy was very effective, but was found to leak during prolonged submersion in water (~1 hour). A second medical grade epoxy which touted stability for up to a year, was considered (301-2, EPO-TEK, Billerica, MA), but was found to be not viscous enough and required oven-baking for curing. Despite the instability of the UV epoxy, the duration of use was suitable for acute *in vivo* experiments.

[0259] To improve encapsulant stability, parylene-C was also considered as an encapsulation material. Parylene-C is an FDA approved biocompatible polymer which is chemically and biologically inert, a good barrier and electrical insulator, and extremely conformal when vapor deposited). Vapor deposition of Parylene-C is achieved by vaporizing powder Parylene-C dimer at temperatures above 150°C. The vapor Parylene-C dimer is then heated at 690 °C in order for pyrolysis to occur, cleaving the Parylene-C dimer into monomers. The monomer then fills the chamber, which is kept at room temperature. The monomer almost instantaneously polymerizes once it comes into contact with any surfaces. For all devices, Paraylene-C was deposited using a parylene deposition system (SCS Labcoter 2 Parylene Deposition System, Specialty Coating Systems, Indianapolis, IN) with the parameters shown in Table 1. Note that the table indicates the chamber gauge temperature as 135 °C. This is distinct from the actual chamber temperature; rather the chamber gauge is simply the vacuum gauge of the process chamber. It is important to keep the temperature to at least 135°C to prevent parylene from depositing onto the gauge. For the first batch of FR-4 boards, parylene was addressed by selectivity by using Kapton tape to

mask off the electrodes. However, it was found that due to the small pitch between the recording electrodes and the ASIC wirebonding targets, there was not enough surface area for the tape to affix well to the board and it often slipped off, resulting in coated electrode pads. In the second iteration of implantable device, a parylene coat was attempted using a strategy in which the entire board was coated, then remove the parylene off the electrodes with a probe tip. In order to assure that parylene was coated onto the entire device, the implantable devices were suspended in air by damping them between two stacks of glass slides.

Table 1: Parylene-C Deposition Parameters

Furnace Temperature	690 deg. C
Chamber Gauge Temperature	135 deg. C
Vaporizer Temperature	175 deg. C
Base Pressure	14 mTorr
Operating Pressure	35 mTorr
Paralyene-C Mass	5 g

[0260]   The following provides additional details for manufacturing the implantable device.

[0261]   Before beginning to work with the PCBs, ASICs, or PZT coupons, prepare two sample holders for the dust boards. To do so, simply take two glass slides (3 mm x 1 mm x 1 mm slides work well) and put a strip of double-sided tape on the slide lengthwise. The tape will be used to fix the dust motes in place so that the rest of the steps can be performed. On one of the slides, also add a piece of Kapton tape (3M) sticky-side up on top of the double-sided tape. This slide will be the slide used for curing as the high temperature of the cure can cause problems with the adhesive on the double-sided tape.

[0262]   Next, mix a small amount of silver paste by weighing out a 1:1 ratio of part A and part B in a weigh boat. A large amount of silver-epoxy is not needed for the assembly process. Shown below is roughly 10 g of epoxy (5g of each part) which is more than enough for three boards, Note that the mixed-silver epoxy has a shelf life of two weeks if placed at 4°C. So leftover epoxy can and should be refrigerated when not in use. Additionally, older epoxies (several days to a week) tend to be slightly more viscous than fresh epoxy which can make application easier,

[0263] The substrates come panelized and will need to be removed. Each board is connected to the panel at several attachment points on the test leads and vias - these attachment points can be cut using a micro-scalpel (Feather Safety Razor Co., Osaka, Japan). Once the PCB has been singulated, using carbon-fiber tipped tweezers .or ESD plastic tweezers, place the singulated PCB onto the high-temperature sample holder.

[0264] The diced/thinned die are shipped on dicing tape, which can make it tricky to remove the die. In order to reduce the adhesion between the die and tape, it can be helpful to deform the tape. Using carbon-tipped or ESD plastic tweezers, gently press the tape and work the tweezers in a circular motion around the die. To check if the die has been freed, gently nudge the chip with the tip of the tweezers. If the die does not come off easily, continue to press into tape surrounding the chip. Once the chip has come off, carefully place the chip onto the high-temperature sample holder next to its board. It is advisable to bring the sample holder to the chip rather than the other way around so that the chip is not in transit, Care must be taken in this step to avoid losing or damaging the die. Never force a die off the tape, as excessive force can cause a chip to fly off the tape.

[0265] Next, attach the die using silver epoxy. Under a microscope, use a pin or something equally fine to apply a small amount silver epoxy to the CMOS pad on the PCB. In this step, it is better to err on the side of too little epoxy than too much epoxy since more silver paste can always be applied, but removing silver paste is non-trivial. Small amounts of uncured epoxy can be scraped away with the same tool used for application, just ensure the epoxy has been wiped off the tool.

[0266] Once the epoxy has been placed on the pad, the ASIC can be placed onto the epoxy. Due to a CAD error, some of the chips have been reflected. It is important to take care that chips which are reflected have been oriented the correct way on the board to ensure no wires need to cross during wirebonding.

[0267] Once the ASICs have been situated on the boards correctly, the silver epoxy can be cured by placing it into an oven at 150 °C for 15 minutes. Note that different temperatures can be used if needed - see FIG. 14 for details. After the silver epoxy has been cured, double-check adhesion by gently pushing on each die, If the die moves; a second coat of silver epoxy will be needed.

[0268]   To prepare for wirebonding, move the devices from the high-temperature sample holder to the regular sample holder. This change is necessary because the adhesion of double-sided tape is stronger than that of the Kapton tape so wirebonding will be made easier. A piece of double-sided tape should be good enough to affix the sample holder to the wirebonder's workholder. It is best to ensure that the workholder has not been previously covered with double-sided tape so that the test leads do not get accidentally stuck to anything. If necessary, clean-room tape can be used to provide additional clamping of the sample holder.

[0269]   Ensure the wirebonder is in good condition by making bonds on the provided test-substrate using default settings. Ensuring that the wirebonder is in condition is important, as a damaged wedge will not bond well and effectively just damage the ASIC pads. Forward bonds (first bond on the die, second bond on the substrate) should be made in the following order: 1. Gate. 2. Bulk. 3. Center. 4. Drain. 5. Source. While it is not critical that the bonds be made in this order, this order minimizes the number of substrate reorientations and prevents accidental damage to the bonds due to the bondhead. Small angle adjustments of the workholder can be made to facilitate bonding; it is imperative that this bond be as straight as possible. In the case that the foot of the second bond lifts from the substrate, changing the number of bonds to one and bonding the foot again may help. If proper adhesion cannot be made, a potential solution is to connect the foot of the bond and the substrate using silver epoxy. Additionally, shorts caused by two bond-feet touching can be resolved by very carefully cutting away the bridging metal using a microscalpel.

[0270]   Known working bonding parameters can be found in Table 2, below. These parameters are simply guidelines and should be modified as necessary. Needing excess power (greater than 490) is typically indicative of a problem: substrate fixing (both PCB to glass slide and CMOS to PCB), wedge condition, and pad condition should all be checked. In the case of pad condition, damaged pads due to previous wirebonding attempts will usually require higher power - in some cases, the devices are salvageable, but failed attempts to bond with power higher than 600 usually results in too much damage to the pads for good bonding.

Table 2: Westbond 7400B A1 Parameters for ASIC

Bond #	Power	Time
1 (ASIC)	420	40 ms
2 (Substrate)	420	40 ms

[0271]   Post-wire bonding, the device should undergo electrical testing to ensure proper bonding. If using a type 1 die, the I-V characteristics should be roughly as shown in Table 3.

Table 3: Typical I-V characteristics for Type 1 Die under $V_{ds} = 0.1$ V

V_{gs}	I_{ds}
0 V	0.5 μA
0.1 V	0.74 μA
0.2 V	10.6 μA
0.3 V	51.4 μA
0.4 V	0.192 mA
0.5 V	0.39 mA
0.6 V	1.14 mA
0.7 V	1.55 mA
0.8 V	1.85 mA

If the I-V characteristics do not seem correct, a valuable troubleshooting method is checking the resistances between the drain and center, source and center, and drain and source. If the die is working properly, one should expect roughly 90 kΩ resistance between the drain and center and source and center, and roughly 180 k Ω between the drain and source.

[0272]   After confirmation that the FET is connected properly, the PZT coupon should be attached. This is done in a similar fashion to attaching the ASIC: place a dab of silver epoxy using a sewing needle on the appropriate pad. It is best to put the epoxy dab on the back edge of the pad (towards the end of the board) since the PZT coupon will not be centered on the pad, but pushed back so that the coupon hangs off the board. Keep in mind that the polarity of the PZT coupon has a small effect on its efficiency. To determine whether or not the coupon is in the correct position, check if the bottom face is larger than the top face. Due to the path of the dicing

saw, the bottom of the coupon, is slightly larger than the top of the coupon. Thus, the edges of the bottom face can be seen from a top down view, then the coupon has been placed in the same orientation as it was when the disk was diced.

[0273]   Wirebonding the PZT is done in a similar manner to the ASIC (forward bonding, the PZT to the PCB). However, one crucial change is that the drain and source vias should be grounded. There is an earth ground port next to Westbond which can be accessed via a banana connector. As a guideline, the parameters shown in Table 4have been known to work.

Table 4: Westbond 7400B A1 Parameters for PZT

Bond #	Power	Time
1 (PZT)	390	40 ms
2 (Substrate)	490	40 ms

[0274]   A successful bond may require several attempts depending on how well the PZT coupon is attached to the substrate. The more attempts that are made, the worse the mechanical structure of the PZT becomes (the silver coating will become damaged) so it is best to try to very quickly optimize the process. Bonds that fail due to foot detachment generally imply not enough power. Bonds that fail due to the wire breaking at the foot generally imply too much power.

[0275]   After a successful bond is made, it is always good to do another electrical test to ensure that bonding the PZT has not damaged the ASIC.

[0276]   As a final step, test wires were soldered to the vias and encapsulate the device, The test wires are 3 mil silver wires. Nate that these wires are insulated: the insulation can be removed by putting the wire close to a flame (not in the flame) and watching the plastic melt and recede.

[0277]   After soldering wires, the device can now be encapsulated. The encapsulant is OG116-31 medical-grade UV curable epoxy and should be dispensed using a sewing needle. An effective method is to put a large drop of epoxy over the PZT coupon and a large drop over the ASIC. Using a clean needle, push the droplet over the board so that the entire topside of the board is coated. The epoxy should wet the board, but not spill over due to its surface tension. Once the main body of the board is coated, the vias should also be coated, as well as the side faces of the piezo. The board can then be cured in a UV chamber for roughly 5 minutes. It has

been found that the test wires can occasionally contact something in the UV chamber and short the ASIC. Thus, prior to putting the board in the chamber, it is good to wrap the wires down or place it on some tape in order to isolate them from any chamber surfaces.

[0278] Following curing, the backside should be coated. In particular the exposed PZT coupon which hangs over the board as well as the backside of the test vias and the two vias on the backside of the board which connect the electrodes to the topside of the board. This part can be a little tricky due to the small space between the backside vias and the electrodes, so it is best to start with a very small amount of epoxy and place it near the edge of the board, then drag the epoxy up towards the vias. The backside of the board should be cured in the same manner as the topside. Once the board is fully encapsulated, a final electrical test should be done, and upon passing, the implantable device is now complete.

Example 2 - Set-up for Testing Implantable Devices

[0279] Testing of implantable has always been tricky due to the thinness of the test leads that extend out from the board. Clipping onto and off of these vias for I-V measurements has often resulted in pulling the leads off the body of the device. Furthermore, due to the test leads, it is difficult to perform water-tank test measurements; as exposed electronics in water would result in shorts. In order to circumvent this issue, a PCB was designed to serve as a testbed for implantable device measurements. The PCB (Bay Area Circuits, Fremont, CA) was made of FR-4 and 60 mil thick; it includes four vias, distributed on the board to match the layout of the version two implantable device boards.

[0280] Gold header pins (Pin Strip Header, 3M, Austin, TX) were soldered into the vias so that they extended from the board on both sides of the board. This enabled us to place our devices onto the test bed, and tap into the implantable by accessing the header pins. Next, to insulate the vias, plastic caps made out of polyethylene terephthalate (PETG) were 3D printed (Flashforge Creator X, FlashForge, Jinhua, China). These caps were printed with a groove so that an O-ring could be placed inside the groove and create a waterproof seal around the header pins. The caps were connected to the board and compression was created by drilling 2 mm holes through the PCB and cap using a micro-mill (47158, Harbor Freight, Camarillo, CA) and screwing the cap and board together. Wires extending from the testbed were soldered to the header pins and the pins were then encapsulated. To measure the effectiveness of the seal, the

boards were submerged in an aqueous 6 M NaCl solution and the resistance between the pins was measured using a Keithley 2400. A MATLAB script was written to automatically record and plot the resistance over time. A drop in the resistance would indicate that the seal was broken. As an additional test, a piece of litmus paper was also put under the plastic cap with the intention that if the cap leaked, the litmus paper would change color. The pins were encapsulated using the same medical grade epoxy used to encapsulate the implantable device boards, and parylene was deposited over the epoxy on the back side of the testboards for a completely waterproof barrier. The resistance between the two neighboring pins of the testbed submerged in salt water solution as a function of time for only epoxy insulation and epoxy plus parylene insulation was measured. Without a parylene barrier, the epoxy began to leak, allowing salt water to short out the pins of the testbed.

Example 3 – Implantable Devices Encapsulated in Silicon Carbide

[0281]   Rather than an epoxy encapsulant, silicon carbide (SiC) may be a more effective material for insulating and protecting the implantable device. SiC is formed by the covalent bonding of Si and C, forming tetrahedrally oriented molecules with short bond length and thus, high bond strength, imparting high chemical and mechanical stability. Amorphous SiC (a-SiC) has been welcomed by the biomedical community as a coating material as it can be deposited at much lower temperatures than ordinarily required by crystalline SiC and is an electrical insulator. Deposition of a-SiC is generally performed via plasma enhanced chemical vapor deposition (PECVD) or sputtering. Ongoing research using sputtered a-SiC has shown that it is difficult to achieve a pinhole free layer of SiC. Rather, PECVD using SiH_4 and CH_4 as precursors is capable of yielding impressive, pinhole free SiC films.

[0282]   Furthermore, implanted a-SiC has shown impressive biocompatibility. Previous studies have shown that a 50 μm iridium shaft coated with a-SiC implanted in the rabbit cortex for ~20 days did not show the usual chronic inflammatory response of macrophage, lymphocyte, monocyte recruited to the insertion site. See Hess et al., *PECVD silicon carbide as a thin film packaging material for microfabricated neural electrodes*, Materials Research Society Symposium Proceedings, vol. 1009, doi: 10.1557/PROC-1009-U04-03 (2007).

[0283]   It is interesting to consider an approach to implantable devices that would involve constructing the devices on silicon with a silicon carbide encapsulant for a truly chronic implant.

A possible process is shown in FIG. 15. One of the largest challenges here is ensuring that the PECVD of SiC dues not depole the piezoelectric material. In order to have contamination-free films, it is important to deposit at a minimum temperature of 200 °C, but below the Curie temperature of the piezoelectric transducer.

Example 4 – Power Transfer to and Backscatter of a Miniaturized Ultrasonic Transducer

[0284]   A set of experiments were carried out with PZT due to the relative ease of obtaining PZT crystals with varying geometry. Metalized PZT sheets of several thicknesses were obtained (PSI-5A4E, Piezo Systems, Woburn, MA and PZT 84, APC Internationals, Mackeyville, PA), with a minimum PZT thickness of 127 μm. The PZT was fully encapsulated in PDMS silicon for biocompatibility.

[0285]   The most commonly used method to dice PZT ceramics is to use a wafer dicing saw with an appropriate ceramic blade to cut PZT sheets into individual PZT crystals. The minimum resolution of the cut is determined by the kerf of the blade and can be as small as 30 μm.

[0286]   Another possible option is to use a laser cutter. Unlike the dicing saw, laser cutting realizes the cuts by focusing a high-power laser beam onto a material, which melts, vaporizes, removes, and scribes the piece. The precision of laser cutting can be down to 10 μm and is limited by the wavelength of the laser. However, for treating sensitive samples such as PZT ceramics, the temperature at the site of cuts can be damaging to the piezoelectric performance of the material. Excimer laser cutting of ceramics uses UV laser to cut with excimer from noble gases, but such laser cutter is extremely expensive and no suitable services are currently available. As a result, a dicing saw was used to perform all the cuts.

[0287]   In order to drive or extract electrical energy from the PZT, an electrical connection is made to both the top and bottom plates. The materials typically used as an electrode for PZT are silver or nickel. Silver is generally used for a wide variety of non-magnetic and AC applications and silver in the form of flakes suspended in a glass frit is usually screened onto the ceramic and fired. For high electric field DC applications, silver is likely to migrate and bridge the two plates. As a result, nickel, which has good corrosion resistance and does not electro-migrate as readily can be electroplated or vacuum deposited as an alternative.

[0288]   Both materials can be soldered onto with the appropriate solder and flux. For instance, silver is soluble in tin, but a silver loaded solder can be used to prevent scavenging of

silver in the electrode. Phosphor content from the nickel plating can make soldering tricky, but the correct flux can remove surface oxidation. However, when soldering, in order to avoid exceeding the Curie point and depoling the PZT sample, the soldering temperature must be between 240 and 300 °C. Even at these temperatures, since the PZT is also pyroelectric, one must be careful not to exceed 2 - 4 seconds of soldering time.

[0289]   Alternatively, an electrical connection can be made using either silver epoxy or low temperature soldering using solder paste. Standard two-part silver epoxy can provide a sufficient electrical conductivity and can be cured even at room temperature overnight. However, the joints tend to be fragile and can easily break during testing. The bond can be reinforced by using a non-conductive epoxy as an encapsulation but this additional layer presents a mechanical load to the PZT and can significantly dampen its quality factor. Low-temperature solder paste on the other hand undergoes a phase change between the temperature of 150 and 180 °C and can provide great electrical connection and a bond strength that is comparable to that achieved with flash soldering. Therefore, the low-temperature soldering approach was used.

[0290]   Wafer dicing is capable of cutting PZTs into small crystals of 10's of μm. However, samples that are smaller than 1 mm in dimension are extremely difficult to handle with tweezers and bond to. In addition, due to the variation in the length of wire used to interface with top and bottom plates of PZT crystals (and therefore parasitic inductance and capacitance introduced by the wire) and the amount of solder paste dispensed across a number of samples, the impedance spectroscope measurements were inconsistent.

[0291]   Therefore, a 31 mil thick two-layer FR-4 PCB where all of the electrical interconnects short and de-embed out the parasitics from the wires and the board was fabricated. The fabricated board, which includes numerous test structures and a module for individually characterizing 127 μm, 200 μm, and 250 μm thick PZT crystals are shown with dimensions in FIG. 16. Each unit cell in the test module contains two pads with specified dimensions on one side of the PCB to interface with the PZT crystals and pads for discrete components for backscattering communication on the opposite side. The pitch between the unit cells is limited by the size of the discrete components and is roughly 2.3 mm x 2 mm.

[0292]   In order to avoid directly handling tiny PZT crystals, FIGS. 17A-E outlines a scalable process flow to bond PZT onto the PCB. As shown in FIG. 17A, the solder paste is dispensed using a pump at a constant pressure and for a controlled amount of time on one of the pads on the

top side. The pads are either 250 μm^2, 200 μm^2, or 127 μm^2 based on the thickness of the PZT used. FIG. 17B shows a PZT piece larger than the pad (that can be easily handled) is placed on top to cover the pads. The board and piezo assembly are baked in an oven to cure the solder paste. Therefore, PZT crystals are now bonded to pre-soldered bumped electrodes. FIG. 17C shows a wafer dicing saw makes a total of four cuts along the edges of the pad with the solder paste using alignment markers on the board, with non-bonded areas dropping off and leaving an array of small PZT crystals bonded to the PCB. FIG. 17D shows single wirebond makes an electrical contact between the top plate of the PZT and an electrode on the PCB, completing the circuit. Finally, FIG. 17E shows the entire assembly is encapsulated in PDMS (Sylgard 184, Dow Corning, Midland, MI) to protect the wirebond and provide insulation.

[0293]   Since piezoelectric material is an electro-mechanical structure, its electrical and mechanical properties were characterized. The following details the test setup and techniques to perform such measurements.

[0294]   Any electrical device can be modeled as a black box using a mathematical construct called two-port network parameters. The properties of the circuits are specified by a matrix of numbers and the response of the device to signals applied to its input can be calculated easily without solving for all the internal voltages and currents in the network. There are several different types of two-port network parameters, such as Z-parameters, Y-parameters, S-parameters, and ABCD-parameters, etc. and the conversion between different parameters can be easily derived. The apparatus that enables us to extract these parameters is called a vector network analyzer (VNA). A VNA incorporates directional couplers to decompose the voltage in each port into incident and reflected waves (based on impedance mismatching), and calculate the ratio between these waves to compute scattering or S-parameters.

[0295]   Before performing measurements using a VNA, one must calibrate the instrument since the internal directional couples are non-ideal. Calibration also allows us to move the reference plane of the measurement to the tips of the cable, i.e., calibrate out parasitics from the cable. There are several calibration standards but the most commonly used is open, short, and load calibration procedures. The measurement schematic is shown in FIG. 18. Alligator clips, which are soldered onto the ends of the coaxial cable, are used to interface with the top/bottom plates. The parasitics from the clips were not significant below 100 MHz.

[0296]   As an example, a VNA (E5071C ENA, Agilent Technologies, Santa Clara, CA) was used to measure the electrical properties of a $(250 \text{ μm})^3$ PZT crystal. It was noted that the measured capacitance of the PZT crystal vastly differs from the capacitance expected from a simple parallel-plate capacitance model due to significant parasitic capacitances from the PCB and the fixture (clip and connector). Since the VNA coefficients from the calibration step previously outlined only moved the measurement plane to the tips of the cable, open/short/load calibration structures fabricated on the same board were used to include the board and fixture parasitics. The measured PZT response matched the expected response after calibration.

[0297]   Using this calibration technique, the impedance of the PZT can be plotted as a function of frequency, as shown in FIG. 19B. From this plot, however, it is extremely difficult to determine whether there is any electro-mechanical resonance. When the simulation result with air backing (no mechanical clamping) was overlaid, it was noticed that the impedance spectroscopy matches well with the measurement at low and high frequencies, with the exception of noticeable peak at resonant frequency of roughly 6 MHz and its harmonics. Upon clamping and loading one side of PZT with PCB (FR-4), it was seen that a significant dampening of the resonant peaks from air backing. Despite a lack of observable resonance in the measurement, a small blimp around 6 MHz was observed, and the mechanical quality factor Q_m can be calculated using the following equations,

$$Q_m = \frac{f_a^2}{2Z_r C_p (f_a^2 - f_r^2)}$$

where f_a and f_r represent anti-resonant (where impedance is maximized) and resonant frequency (where impedance is minimized), Z_r represents an impedance at resonance, and C_p is the low-frequency capacitance. The calculated quality factor from the measurement is roughly 4.2 compared to 5.1 in simulation. According to the datasheet, the unloaded Q of the PZT is ~500, indicating that FR-4 backing and wire-bonds are causing significant degradation of the quality factor. Despite the drastic reduction in the mechanical Q of the PZT crystals, experiments showed that the backscattered signal level only decreased by roughly ~19.

[0298]   In the electrical characterization setup, the VNA has a built-in signal generator to provide the input necessary for characterization. In order to perform acoustic characterization of

PZT, acoustic waves were generated and launched onto the sample to use as an input. This can be achieved with commercially available broadband ultrasonic transducers.

[0299]   FIG. 20 shows the composition of a representative transducer, which consists of a piezoelectric active element, backing, and wear plate. The backing is usually made from a material with high attenuation and high density to control the vibration of the transducer by absorbing the energy radiating from the back face of the active element while the wear plate is used to protect the transducer element from the testing environment and to serve as a matching layer.

[0300]   Ultrasonic power transfer tests were performed using the home-built setup shown in FIG. 21. A 5 MHz or 10 MHz single element transducer (6.3 mm and 6.3 mm active area, respectively, ~30 mm focal distance, Olympus, Waltham, MA) was mounted on a computer-controlled 2-axis translating stage (VelMex, Bloomfield, NY). The transducer output was calibrated using a hybrid capsule hydrophone (HGL-0400, Onda, Sunnyvale, CA). Assembly prototypes were placed in a water container such that transducers could be immersed in the water at a distance of approximately 3 cm directly above the prototypes. A programmable pulse generator (33522B, Agilent Technologies Santa Clara, CA) and radio frequency amplifier (A150, ENI, Rochester, NY) were used to drive transducers at specified frequencies with sinusoidal pulse trains of 10-cycles and a pulse-repetition frequency (PRF) of 1 kHz. The received signals were amplified with a radio frequency amplifier (BT00500-AlphaS-CW, Tomco, Stepney, Australia), connected to an oscilloscope (TDS3014B, Tektronix, Beaverton OR) to collect ultrasound signal and record them using MATLAB.

[0301]   FIG. 22A and FIG. 22B show a representative measurement of the output power of the 5 MHz transducer as a function of the distance between the surface of the transducer and the hydrophone (z-axis). The peak pressure in water was obtained at ~33 mm away from the transducer's surface (FIG. 22A), while the de-rated peak (with 0.3 dB/cm/MHz) was at ~29 mm (FIG. 22B). FIG. 23A shows the de-rated XZ scan of the transducer output, which show both near-field and far-field beam patterns and a Rayleigh distance or a focal point at ~29 mm, matching the de-rated peak in FIG. 22B. FIG. 23B shows a XY cross-sectional scan of the beam at the focal point of ~29 mm, where the 6 dB beamwidth measured roughly 2.2 mm.

[0302]   The total integrated acoustic output power of the transducer at various frequencies over the 6 dB bandwidth of the beam was nominally kept at a spatial-peak temporal-average

I_{SPTA} of 29.2 μW /cm^2, resulting in a total output power of ~1 μW at the focal point, with a peak rarefaction pressure of 25 kPa and a mechanical index (MI) of 0.005. Both the de-rated I_{SPTA} and MI were far below the FDA regulation limit of 720 mW /cm^2 and 1.9, respectively (FDA 2008).

[0303] FIG. 19A shows the measured power delivery efficiency of the fully assembled prototype with cable loss calibrated out for various implantable device transducer sizes as compared to analytical predictions made for this same setup. Measured results matched the simulated model behavior very closely across all transducer sizes, with the exception of a few smaller transducer dimensions, likely due to the sensitivity to transducer position and the ultrasound beamwidth. The measured efficiency of the link for the smallest PZT crystal (127 μm)^3 was 2.064 x 10^{-5}, which resulted in 20 .64 pW received at the transducer nominally. A maximum of 0.51 μW can be recovered at the transducer if the transmit output power density was kept at 720 mW/cm^2. Such low power level harvested by the PZT is mainly due to the extreme inefficiency of broadband transducers that were used for the experiments; dedicated, custom-made transducers at each transducer dimension with optimal electrical input impedance could result in more than 2 orders of magnitude improvement in the harvested power level as predicted by the simulation model.

[0304] The frequency response of electrical voltage harvested on a (250 μm)^3 PZT crystal is shown in FIG. 19C. The resonant frequency was measured to be at 6.1 MHz, which matches the shift in the resonant frequency predicted for a cube due to Poisson's ratio and the associated mode coupling between resonant modes along each of the three axes of the cube. Furthermore, the calculated Q of 4 matched the electrically measured Q of the PZT.

[0305] The experimental result indicate that the analytical model for power coupling to very small PZT nodes using ultrasound is accurate down to at least ~100 μm scale and likely lower. It remains to be seen just how mall a transducer can be fabricated before loss of function. Note that measurements of even smaller nodes (< 127 μm) were limited not by the prototype assembly process but by commercial availability of PZT substrates. Moving forward, the considerable volume of research and techniques that has gone into micro- and nanoelectromechanical RF resonators was be used (see Sadek et al., *Wiring nanoscale biosensors with piezoelectric nanomechanical resonators*, Nano Lett., vol. 10, pp. 1769-1773 (2010); Lin et al., *Low phase noise array-composite micromechanical wine-glass disk oscillator*, IEEE Elec. Dev. Meeting, pp. 1-4 (2005)) and thin-film piezoelectric transducer (see Trolier-McKinstry et al., *Thin film*

piezoelectrics for MEMS, J. Electroceram., vol. 12, pp. 7-17 (2004)) to facilitate extremely small (10's of μm) transducers and to truly assess the scaling theory.

Example 5 – Beamforming Using Interrogator Ultrasonic Transducer Array

[0306]   In this example, an ultrasonic beamforming system capable of interrogating individual implantable sensors via backscatter in a distributed, ultrasound-based recording platform is presented. A custom ASIC drives a 7 x 2 PZT transducer array with 3 cycles of 32V square wave with a specific programmable time delay to focus the beam at the 800μ m neural dust mote placed 50mm away. The measured acoustic-to-electrical conversion efficiency of the receive mote in water is 0.12% and the overall system delivers 26.3% of the power from the 1.8V power supply to the transducer drive output, consumes 0.75 μJ in each transmit phase, and has a 0.5% change in the backscatter per volt applied to the input of the backscatter circuit. Further miniaturization of both the transmit array and the receive mote can pave the way for a wearable, chronic sensing and neuromodulation system.

[0307]   In this highly distributed and asymmetric system, where the number of implanted devices outnumbers the interrogating transceivers by an order of magnitude, beamforming can be used to efficiently interrogate a multitude of implantable devices. Research into beamforming algorithms, trade-offs, and performance in the implantable device platform has demonstrated that cooperation between different interrogators is useful for achieving sufficient interference suppression from nearby implantable devices. See Bertrand et al., *Beamforming approaches for untethered ultrasonic neural dust motes for cortical recording: a simulation study*, IEEE EMBC, 2014, pp. 2625-2628 (Aug. 2014). This example demonstrates a hardware implementation of an ultrasonic beamforming system for the interrogator and implantable device system shown in Fig. 2A. The ASIC (see, e.g., Tang et al., *Integrated ultrasonic system for measuring body-fat composition*, 2015 IEEE International Solid-State Circuits Conference – (ISSCC) Digest of Technical Papers, San Francisco, CA, 2015, pp. 1-3 (Feb. 2015); Tang et al., *Miniaturizing Ultrasonic System for Portable Health Care and Fitness*, IEEE Transactions on Biomedical Circuits and Systems, vol. 9, no. 6, pp. 767-776 (Dec. 2015)), has 7 identical channels, each with 6 bits of delay control with 5 ns resolution for transmit beam-forming, and integrates high-voltage level shifters and a receive/transmit switch that isolates any electrical feed-through.

[0308] The ASIC operates with a single 1.8V supply and generates a 32V square wave to actuate piezoelectric transducers using integrated charge pumps and level shifters. The system delivers ~32.5% of the power from the 1.8V supply to the 32V output voltage and ~81% from 32V to the output load (each transducer element is 4.6 pF). The ASIC block diagram is shown in FIG. 2A; the circuit details to enable such low energy consumption per measurement can be found in Tang et al., *Integrated ultrasonic system for measuring body-fat composition*, 2015 IEEE International Solid-State Circuits Conference – (ISSCC) Digest of Technical Papers, San Francisco, CA, 2015, pp. 1-3 (Feb. 2015). The ASIC is fabricated in 0.18μ m CMOS with high voltage transistors. The chip area is $2.0mm^2$ and includes the complete system except for the digital controller, ADCs, and two off-chip blocking capacitors.

[0309] The design of a transducer array is a strong function of the desired penetration depth, aperture size, and element size. Quantitatively, the Rayleigh distance, R, of the array can be computed as follows:

$$R = \frac{D^2}{4\lambda}$$

where D is the size of the aperture and λ is the wavelength of ultrasound in the propagation medium. By definition, Rayleigh distance is the distance at which the beam radiated by the array is fully formed; in other words, the pressure field converges to a natural focus at the Rayleigh distance and in order to maximize the received power, it is preferable to place the receiver at one Rayleigh distance where beam spreading is the minimum.

[0310] The frequency of operation is optimized to the size of the element. A preliminary study in a water tank has shown that the maximum energy efficiency is achieved with a (800 $\mu m)^3$ PZT crystal, which has a resonant frequency of 1.6 MHz post-encapsulation, resulting in λ ~950 μm. The pitch between each element is chosen to be an odd multiple of half wavelength in order to beamform effectively. As a result, for this demonstration of beamforming capabilities, the overall aperture is ~14mm, resulting in the Rayleigh distance of 50mm. At 50mm, given the element size of 800 μm, each element is sufficiently far from the field (R = 0.17mm); therefore, the beam pattern of individual element should be omni-directional enough to allow beamforming.

[0311] There are several transmit and receive beamforming techniques that can be implemented. In this example, time delay-and-sum transmit beamforming algorithm is chosen,

such that the signals constructively interfere in the target direction. This algorithm is capable of demonstrating beam-steering and maximal power transfer to various implantable devices. In order to accommodate backscatter communication to multiple implantable devices simultaneously, more sophisticated algorithms may be required. These can include delay-and-sum beamforming, linearly constrained minimum-variance beamforming, convex-optimized beamforming for a single beam, 'multicast' beamforming w/ convex optimization, maximum kurtosis beamforming, minimum variance distortionless response robust adaptive beamforming, polyadic tensor decomposition, and deconvolution of mote impulse response from multi-Rx-channel time-domain data. The detailed treatment of one aspect of this problem is described in Bertrand et al., *Beamforming approaches for untethered ultrasonic neural dust motes for cortical recording: a simulation study*, IEEE EMBC, 2014, pp. 2625-2628 (Aug. 2014).

[0312] Each of the 7 channels is driven by 3 cycles of 32V square wave with a specific programmable time delay such that the energy is focused at the observation distance of 50mm. The time delay applied to each channel is calculated based on the difference in the propagation distance to the focus point from the center of the array and the propagation speed of the ultrasound wave in the medium.

[0313] Ultrasim was used to characterize the propagation behavior of ultrasound wave in water with the 1D array described above. Simulated XY (FIG. 24A) and XZ (FIG. 24B) cross-sectional beam patterns closely match the measurement as shown, despite not modeling the PDMS encapsulation.

[0314] Water is used as the medium for measuring the beamforming system as it exhibits similar acoustic properties as the tissue. Pre-metalized Lead Zirconate Titanate (PZT) sheets (APC International, Mackeyville, PA) are diced with a wafer saw to 800 μm x 800 μm x 800 μm crystals (parallel capacitance of 4.6 pF each), which is the size of each transmit element. Each PZT element is electrically connected to the corresponding channel in the ASIC by using a conductive copper foil and epoxy for the bottom terminal and a wirebond for the top terminal. The array is encapsulated in PDMS (Sylgard 184, Dow Corning, Midland, MI) to protect the wirebond and provide insulation. The quality factor of the PZT crystal post encapsulation is ~7. The array is organized into 7 groups of 2 x 1 elements, with the pitch of ~$5/2\lambda$ ~2.3mm. The array measures approximately 14 mm x 3 mm. Finally, the entire assembly is encased in a

cylindrical tube with the diameter of 25 mm and the height of 60 mm and the tube is filled with water.

[0315] The transducer array's 2D beam pattern and output are calibrated using a capsule hydrophone (HGL-0400, Onda, Sunnyvale, CA). The hydrophone is mounted on a computer-controlled 2D translating stage (VelMex, Bloomfield, NY). The hydrophone has an acceptance angle (-6dB at 5MHz) of 30°, which is sufficient to capture the beam given the transmission distance of 50 mm and the scan range (±4 mm).

[0316] The measured XY cross-sectional beam pattern with the overlay of the array is shown in FIG. 32A. The applied delay for each transducer in the array (element) is shown in FIG. 24B. The -6dB beamwidth at the focal point is 3.2 mm ~ 3λ. The flexibility of the ASIC allows for both wide and granular programming of the delays. The peak pressure level of the array at 50mm before and after beamforming is ~6kPa and ~20kPa, respectively. The 3X in the transmitted output pressure wave after beamforming matches the simulation. The simulation also verifies that the Rayleigh distance of the array is at 50 mm as shown in FIG. 24C.

[0317] Additionally, in order to verify the capability to interrogate multiple implantable devices, it was verified the beam steering capability of the array as shown in FIG. 25A (showing beam steering at three different positions in the XY-plane), with the time delay for each beam position shown underneath in FIG. 25B. The 1D beam steering matches very closely with the simulation, as shown in FIG. 25C. Note that the beam steering range is limited to ±4 mm due to the mechanical construct of the array, rather than the electronic capability.

[0318] The hydrophone is replaced with an implantable device (with a 800 μm x 800 μm x 800 μm bulk piezoelectric transducer) and placed at the transmission distance of 50 mm to verify the power link. The open-circuit peak-to-peak voltage measured at the mote is 65 mV, for a transmit pulse-duration of 2.56 μs. The spatial peak average acoustic power integrated over the -6dB beamwidth at the focal point is 750 μW, which is 0.005% of the FDA safety limit. The maximum harvestable power at the mote is 0.9 μW, resulting in the measured acoustic-to-electrical conversion efficiency of 0.12%. The measured result is in agreement with the link model (see Seo et al., *Model validation of untethered ultrasonic neural dust motes for cortical recording*, J. Neurosci. Methods, vol. 244, pp. 114-122 (2015)). The system delivers 26.3% of the power from the 1.8V power supply to the transducer drive output (defined as driving efficiency) and consumes 0.75μ J in each transmit phase.

[0319] The ultrasonic backscatter communication capability of the system is verified by measuring the difference in the backscattered voltage level as the input to the backscatter circuit (see Seo et al., *Model validation of untethered ultrasonic neural dust motes for cortical recording*, J. Neurosci. Methods, vol. 244, pp. 114-122 (2015)), and is adjusted with a DC power supply. The transmit time and the period of the system are 3 μs and 80 μs, leaving a ~77 μs window for reception. A 2 x 1 element in the center of the array is used for receiving the backscatter. The output of the receive crystals is amplified and digitized for processing. The measured backscatter sensitivity is ~0.5% per volt applied to the input of the backscatter circuit, which is in agreement with the simulation. The overall performance of the system is summarized in Table 4.

Table 4: Summary of System Performance

Supply voltage	1.8 V
Output voltage	32 V
Number of channels	7
Operating frequency	1.6 MHz
Charge pump + level shifter efficiency	26.3%
Acoustic-to-Electrical efficiency	0.12%
Backscatter change	0.5 %/V
Energy per transmit phase	0.75 μJ

[0320] The measurements with the ultrasonic beamforming system suggest that transmit beamforming alone can provide sufficient signal-to-noise ratio (SNR) to enable multiple sensors interrogation in the implantable device platform. The decrease in the SNR with the miniaturization of the dust mote can be largely mitigated by implementing receive beamform. Furthermore, in order to increase the rate of interrogation, one could explore an alternative means of multiplexing, such as spatial multiplexing where multiple motes are interrogated simultaneously with the same transmit beam. However, it is important to consider the system design tradeoff between processing /communication burden to power consumption. Additionally, sufficient suppression of interferences from nearby dust motes is necessary to achieve the required SNR.

[0321]   The acoustic-to-electrical efficiency at 0.12% currently dominates the efficiency

($\frac{P_{harvested}}{P_{1.8V\ supply}}$) of the overall system. Despite such low efficiency of the power link, if ~1% of the

FDA safety regulation (spatial peak average of 1.9W/cm^2) can be outputted, it is possible harvest

up to 0.92V peak-to-peak voltage and 180 μW at the 800 μm ultrasonic transducer 50 mm away

in water.

[0322]   Furthermore, the low efficiency of the power link in this demonstration is attributed

to such large transmission distance, as determined by the array aperture and the element size. For

peripheral nerve intervention, for example, the desired transmission distance is approximately 5

mm, which includes the thickness of skin, tissue, etc. In order to be at the far field of the array,

the aperture should be ~4.4mm. Further scaling of each element can reduce the overall

dimensions of the array aperture and the transmission distance down to the desired 5 mm.

Simulation indicates that acoustic-to-electrical efficiency up to 1% can be achieved in water with

a 100 μm receive ultrasonic transducer.

[0323]   For transmission in tissue, assuming 3dB/cm/MHz loss in tissue, FIG. 26 shows the

scaling of both link efficiency and received power level given operation at 1% of the FDA safety

limit. Despite this rather conservative loss, at 100 μm, the simulation indicates that it is possible

to harvest up to 0.6V peak-to-peak voltage and 75 μW. Therefore, wireless power transfer in

tissue using this platform is feasible. Furthermore, this power level is sufficient to operate highly

efficient, low-power energy harvesting circuits and charge pumps, similar to the ASIC presented

here, to output voltages that are suitable for electrically stimulating nearby neurons and detecting

physiological conditions using sensors.

Example 6 – Tracking of Movement and Temperature Drift of Implantable Devices

[0324]   An implantable device was manufactured with on a 50 μm thick polyimide flexible

printed circuit board (PCB) with a ultrasonic transducer piezocrystal (0.75 mm x 0.75 mm x 0.75

mm) and a custom transistor (0.5 mm x 0.45 mm) attached to the topside of the board with a

conductive silver paste. Electrical connections between the components are made using

aluminum wirebonds and conductive gold traces. Exposed gold recording pads on the bottom of

the board (0.2 mm x 0.2 mm) are separated by 1.8 mm and make contact on the nerve or muscle

to record electrophysiological signals. Recorded signals are sent to the transistor's input through

micro-vias. Additionally, some implants were equipped with 0.35 mm-wide, 25 mm-long,

flexible, compliant leads with test points for simultaneous measurement of both the voltage across the piezocrystal and direct wired measurement of the extracellular potential across the electrode pair used by the ultrasonic transducer (this direct, wired recording of extracellular potential as the ground truth measurement is referred to below, which is used as a control for the ultrasonically reconstructed data). The entire implant is encapsulated in a medical grade UV-curable epoxy to protect wirebonds and provide insulation. A single implantable device measures roughly 0.8 mm x 3 mm x 1 mm. The size of the implants is limited only by our use of commercial polyimide backplane technology, which is commercially accessible to anyone; relying on more aggressive assembly techniques with in-house polymer patterning would produce implants not much larger than the piezocrystal dimensions (yielding a ~1 mm^3 implant).

[0325]   An external, ultrasonic transceiver board interfaces with the implantable device by both supplying power (transmit (TX) mode) and receiving reflected signals (receive (RX) mode). This system is a low-power, programmable, and portable transceiver board that drives a commercially available external ultrasonic transducer (V323-SU, Olympus, Waltham, MA). The transceiver board exhibited a de-rated pressure focus at ~8.9 mm (FIG. 27A). The XY cross-sectional beam-pattern clearly demonstrated the transition from the near-field to far-field propagation of the beam, with the narrowest beam at the Rayleigh distance (FIG. 27B). The transducer was driven with a 5 V peak-to-peak voltage signal at 1.85 MHz. The measured de-rated peak rarefaction pressure was 14 kPa, resulting in a mechanical index (MI) of 0.01. De-rated spatial pulse peak average (I_{SPPA}) and spatial peak time average (I_{SPTA}) of 6.37 mW/cm^2 and 0.21 mW/cm^2 at 10 kHz pulse repetition were 0.0034% and 0.03% of the FDA regulatory limit, respectively (Food and Drug Administration, 2008). The transceiver board was capable of outputting up to 32 V peak-to-peak and the output pressure increased linearly with the input voltage (FIG. 27C).

[0326]   The entire system was submerged and characterized in a custom-built water tank with manual 6 degrees-of-freedom (DOF) linear translational and rotational stages (Thorlabs Inc., Newton, NJ). Distilled water was used as a propagation medium, which exhibits similar acoustic impedance as tissue, at 1.5 MRayls. For initial calibration of the system, a current source (2400-LV, Keithley, Cleveland, OH) was used to mimic extracellular signals by forcing electrical current at varying current densities through 0.127 mm thick platinum wires (773000, A-M Systems, Sequim, WA) immersed in the tank. The neural dust mote was submerged in the

current path between the electrodes. As current was applied between the wires, a potential difference arose across the implant electrodes. This potential difference was used to mimic extracellular electrophysiological signals during tank testing. To interrogate the neural dust mote, six 540 ns pulses every 100 μs were emitted by the external transducer. These emitted pulses reflect off the neural dust mote and produce backscatter pulses back towards the external transducer. Reflected backscatter pulses were recorded by the same transceiver board. The received backscatter waveform exhibits four regions of interest; these are pulses reflecting from four distinct interfaces (FIG. 28A): 1) the water-polymer encapsulation boundary, 2) the top surface of the piezoelectric crystal, 3) the piezo-PCB boundary, and 4) the back of the PCB. As expected, the backscatter amplitude of the signals reflected from the piezoelectric crystal (second region) changed as a function of changes in potential at the recording electrodes. Reflected pulses from other interfaces did not respond to changes in potential at the recording electrodes. Importantly, pulses from the other non-responsive regions were used as a signal level reference, making the system robust to motion or heat-induced artifacts (since pulses reflected from all interfaces change with physical or thermal disturbances of the neural dust mote but only pulses from the second region change as a function of electrophysiological signals). In a water tank, the system showed a linear response to changes in recording electrode potential and a noise floor of ~0.18 mVrms (FIG. 28B). The overall dynamic range of the system is limited by the input range of the transistor and is greater than >500 mV (i.e., there is only an incremental change in the current once the transistor is fully on (input exceeds its threshold voltage) or fully off). The noise floor increased with the measured power drop-off of the beam; 0.7 mm of misalignment degraded it by a factor of two (N = 5 devices, FIG. 28C). This lateral mis-alignment-induced increase in the noise floor constitutes the most significant challenge to neural recordings without a beamsteering system (that is, without the use of an external transducer array that can keep the ultrasonic beam focused on the implanted dust mote and, thus, on-axis). On axis, the implantable device converted incident acoustic power to electrical power across the load resistance of the piezo with ~25% efficiency. FIG. 28D plots the off-axis drop-off of voltage and power at one Rayleigh distance for the transducer used in this example. Likewise, FIG. 28E plots the change in effective noise floor as a function of angular misalignment.

Example 7 – Digital Communication Link Between Implantable Device and Interrogator

[0327]   A system including an implantable device and an interrogator having a transducer array is validated with a bench-top setup mimicking an in-vivo environment. Ultrasound coupling gel serves as a tissue phantom due to its acoustic impedance which is similar to that of target biological tissues (approximately 1.5 MRayl). An implantable device with a bulk piezoelectric transducer with direct connections to the two electrodes contacting the transducer is placed in the tissue phantom, and the interrogator transducer array is coupled to the gel. Both elements are attached to precision controlled stages for accurate positioning. The transducer array is placed 14 mm away from the dust mote, which corresponds to a 18.6 μs round-trip time of flight assuming an acoustic velocity of 1,540 m/s in ultrasound coupling gel. The transducer array is excited with six 1.8 MHz, 0-32 V rectangular pulses, and the backscatter signal is digitized with 2000 samples at 17 Msps and 12-bits of resolution. For time-domain backscatter inspection, complete backscatter waveforms are filtered in real time on the device and sent to the client through a wired, serial connection. In normal operation, the complete modulation extraction algorithm is applied to the backscatter data on the device in real-time, compressing the backscatter signal to four bytes. The processed data is transmitted through Bluetooth's SSP protocol to a remote client and streamed through the GUI in real-time.

[0328]   FIG. 29A shows the filtered backscatter signals collected with the described experimental setup. Signals are collected while the dust mote piezocrystal electrodes are in the shorted and opened configurations. The change in impedance due to the switch activity results in a backscatter peak amplitude that is 11.5 mV greater in the open switch configuration, a modulation depth of 6.45 %. (FIG. 29B). The long duration of the echo from the mote indicates transducer ringing despite a damping backing layer. While the under-damped transducer system response does spread out the backscatter signal in the time-domain, demodulation is successful as long as the backscatter from the implanted device is captured within the ROI.

[0329]   Using pulse-amplitude-modulated non-return to zero level coding, a backscatter sensor mote is modulated to send a predetermined 11-character ASCII message ("hello world"). The modulation of the device's acoustic impedance is achieved by shunting the piezoelectric transducer across a digitally controlled switch where a high level corresponds to the open configuration and a low level corresponds to the closed configuration. FIG. 30 shows the modulated values on the transducer and the corresponding extracted modulation values of the interrogator. The absolute value and noise margin of the extracted signal values depend on a

variety of factors such as mote distance, orientation, and size; however, the extracted waveform remains representative of the modulated signal on the dust mote, varying by a linear scaling factor.

[0330] Wirelessly transmitting the extracted backscatter value of the implantable device modulated by "hello world" demonstrates the device's real time communication link with implanted devices. Interrogation of a two state backscatter system provides a robust demonstration of the system's wireless communication link with both an implantable sensor and a remote client. This wireless communication link invites developments toward closed-loop neuromodulation systems to connect the brain with external devices.

CLAIMS

1. An implantable device, comprising:

a body about 5 mm or less in length in the longest dimension, comprising:

(a) an ultrasonic transducer configured to emit an ultrasonic backscatter encoding information relating to an impedance characteristic of a tissue based on a modulated current flowing through the ultrasonic transducer;

(b) an integrated circuit comprising:

(i) a variable frequency power supply electrically connected to a first electrode and a second electrode;

(ii) a signal detector configured to detect an impedance, voltage, or current in a circuit comprising the variable frequency power supply, the first electrode, the second electrode, and the tissue; and

(iii) a modulation circuit configured to modulate the current flowing through the ultrasonic transducer based on the detected impedance, voltage, or current; and

the first electrode and the second electrode configured to be implanted into the tissue in electrical connection with each other through the tissue.

2. The implantable device of claim 1, wherein the signal detector is electrically connected to the first electrode and the second electrode.

3. The implantable device of claim 1, wherein the signal detector is electrically connected to a third electrode and a fourth electrode configured to be implanted into the tissue in electrical connection through the tissue.

4. The implantable device of any one of claims 1-3, wherein the signal detector is configured to detect an impedance magnitude or an impedance phase angle.

5. The implantable device of any one of claims 1-4, wherein the signal detector is configured to detect an impedance magnitude and an impedance phase angle.

6. The implantable device of any one of claims 1-5, wherein the signal detector is configured to detect a voltage magnitude or a voltage phase.

7. The implantable device of any one of claims 1- 6, wherein the signal detector is configured to detect a voltage magnitude and a voltage phase.

8. The implantable device of any one of claims 1-7, wherein the signal detector is configured to detect a current magnitude or a current phase.

9. The implantable device of any one of claims 1-8, wherein the signal detector is configured to detect a current magnitude and a current phase.

10. The implantable device of any one of claims 1-10, wherein the integrated circuit comprises a digital circuit.

11. The implantable device of claim 10, wherein the digital circuit is configured to operate the modulation circuit.

12. The implantable device of claim 10 or 11, wherein the digital circuit is configured to transmit a digitized signal to the modulation circuit, wherein the digitized signal is based on the detected impedance, current, or voltage.

13. The implantable device of any one of claims 10-12, wherein the digital circuit comprises a processor and a non-transitory computer-readable storage medium storing one or more programs configured to be executed by the one or more processors, the one or more programs comprising instructions for determining the impedance characteristic of the tissue based on the detected current or voltage.

14. The implantable device of any one of claims 10-13, wherein the digital circuit comprises a processor and a non-transitory computer-readable storage medium storing one or more programs

configured to be executed by the one or more processors, the one or more programs comprising instructions for determining an impedance magnitude or an impedance phase angle.

15. The implantable device of any one of claims 1-14, wherein the ultrasonic backscatter encodes an impedance magnitude.

16. The implantable device of any one of claims 1-15, wherein the ultrasonic backscatter encodes an impedance phase angle.

17. The implantable device of any one of claims 1-16, wherein the ultrasonic backscatter encodes an impedance magnitude spectrum comprising a plurality of impedance magnitude measurements taken at different current frequencies.

18. The implantable device of any one of claims 1-17, wherein the ultrasonic backscatter encodes an impedance phase angle spectrum comprising a plurality of impedance phase angle measurements taken at different current frequencies.

19. The implantable device of any one of claims 1-18, wherein the integrated circuit comprises a power circuit.

20. The implantable device of any one of claims 1-19, wherein the integrated circuit comprises an analog-to-digital converter (ADC).

21. The implantable device of any one of claims 1-20, wherein the variable frequency power supply is configured to supply a current at a plurality of different frequencies at about 10 Hz or more.

22. The implantable device of any one of claims 1-21, wherein the body has a volume of about 5 mm^3 or less.

23. The implantable device of any one of claims 1-22, wherein the ultrasonic transducer is configured to receive ultrasonic waves that power the implantable device.

24. The implantable device of any one of claims 1-23, wherein the ultrasonic transducer is configured to receive ultrasonic waves that encode instructions for selecting a current frequency.

25. The implantable device of any one of claims 1-24, wherein the ultrasonic transducer is configured to receive ultrasonic waves from an interrogator comprising one or more ultrasonic transducers.

26. The implantable device of any one of claims 1-25, wherein the ultrasonic transducer is a bulk piezoelectric transducer, a piezoelectric micro-machined ultrasonic transducer (PMUT), or a capacitive micro-machined ultrasonic transducer (CMUT).

27. The implantable device of any one of claims 1-26, wherein the implantable device is implanted in a subject.

28. The implantable device of claim 28, wherein the subject is a human.

29. The implantable device of any one of claims 1-28, wherein the implantable device is implanted in the tissue.

30. The implantable device of any one of claims 1-28, wherein the first electrode and the second electrode are implanted in the tissue, and the body is attached to an implantable tissue support structure.

31. The implantable device of any one of claims 1-30, wherein the tissue is a bone, a bone fracture site, an injured soft tissue, or an infected tissue.

32. The implantable device of any one of claims 1-31, wherein the implanted device is at least partially encapsulated by a biocompatible material.

33. The implantable device of claim 32, wherein at least a portion of the first electrode and the second electrode are not encapsulated by the biocompatible material.

34. The implantable device of any one of claims 1-33, wherein the implantable device further comprises a non-responsive reflector.

35. A system comprising one or more implantable devices according to any one of claims 1-34 and an interrogator comprising one or more ultrasonic transducers configured to transmit ultrasonic waves to the one or more implantable devices or receive ultrasonic backscatter from the one or more implantable devices.

36. The system of claim 35, wherein the system comprises a plurality of implantable devices.

37. The system of claim 36, wherein the interrogator is configured to beam steer transmitted ultrasonic waves to alternatively focus the transmitted ultrasonic waves on a first portion of the plurality of implantable devices or focus the transmitted ultrasonic waves on a second portion of the plurality of implantable devices.

38. The system of claim 36, wherein the interrogator is configured to simultaneously receive ultrasonic backscatter from at least two implantable devices.

39. The system of claim 36, wherein the interrogator is configured to transit ultrasonic waves to the plurality of implantable devices or receive ultrasonic backscatter from the plurality of implantable devices using time division multiplexing, spatial multiplexing, or frequency multiplexing.

40. The system according to any one of claims 36-39, wherein the interrogator is configured to be wearable by a subject.

41. A method of measuring impedance characteristic of a tissue in a subject, comprising:

receiving ultrasonic waves that power one or more implantable devices comprising an ultrasonic transducer; an integrated circuit comprising a power supply and a signal detector configured to detect an impedance, voltage, or current; and a first electrode and a second electrode in electrical connection with each other through the tissue;

converting energy from the ultrasonic waves into a first electrical current;

transmitting the first electrical current to the integrated circuit;

applying a second electrical current through the tissue;

detecting an impedance, voltage, or current of a circuit formed by the power supply, the first electrode, the second electrode, and the tissue;

modulating the first electrical current based on the detected impedance, voltage, or current;

transducing the modulated first electrical current into an ultrasonic backscatter that encodes information related to impedance characteristic of the tissue; and

emitting the ultrasonic backscatter to an interrogator comprising one or more transducer configured to receive the ultrasonic backscatter.

42. The method claim 41, comprising:

applying the second electrical current through the tissue at a plurality of different current frequencies; and

detecting the current impedance, voltage, or current at the plurality of different current frequencies.

43. A method of monitoring or characterizing a tissue a subject, comprising:

transmitting ultrasonic waves from an interrogator comprising one or more ultrasonic transducers to one or more implantable devices comprising an ultrasonic transducer, an integrated circuit comprising a variable frequency power supply and a signal detector configured to detect an impedance, voltage, or current; and a first electrode and a second electrode in electrical connection with each other through the tissue;

receiving from the one or more implantable devices ultrasonic backscatter that encodes information related to impedance characteristic of the tissue at a plurality of different current frequencies.

44. The method of any one of claims 41-43, wherein the information related to impedance comprises information related to impedance at a plurality of different frequencies

45. The method of any one of claims 41-44, wherein the signal detector is electrically connected to the first electrode and the second electrode.

46. The method of any one of claims 41-44, wherein the signal detector is electrically connected to a third electrode and a fourth electrode configured to detect the impedance, voltage, or current.

47. The method of any one of claims 41-46, wherein the power supply is a variable frequency power supply.

48. The method of any one of claims 41-47, comprising determining the impedance based on the determined current or voltage.

49. The method of any one of claims 41-48, comprising determining an impedance magnitude and an impedance phase angle.

50. The method of claim 49, wherein the ultrasonic backscatter encodes the determined impedance magnitude and impedance phase angle.

51. The method of any one of claims 41-50, wherein the ultrasonic backscatter encodes the determined voltage or the determined current.

52. The method of any one of claims 41-51, comprising monitoring or characterizing the tissue during a healing process.

53. The method of any one of claims 41-52, comprising comparing the information related to impedance characteristic of the tissue at the plurality of different current frequencies to a reference to characterize a tissue disease, an infection in the tissue, or a tissue injury.

54. The method of any one of claims 41-53, comprising:

receiving the ultrasonic backscatter that encodes information related to impedance caused by the tissue at the plurality of different current frequencies at a first time point;

receiving the ultrasonic backscatter that encodes information related to impedance caused by the tissue at the plurality of different current frequencies at a second time point; and

comparing the information related to impedance caused by the tissue at the plurality of different current frequencies at the first time point and at the second time point to monitor a tissue disease, an infection in the tissue, or a tissue injury.

55. The method of any one of claims 41-54, wherein the tissue is bone, a bone fracture, or a soft tissue.

56. The method of any one of claims 41-55, wherein the method comprises monitoring or characterizing a bone fracture, a bone disease, scar tissue, or an ulcer.

57. The method of any one of claims 41-56, wherein the method comprises monitoring or characterizing a bone disease that causes pathological fracturing.

58. The method of any one of claims 41-56, wherein the method comprises monitoring or characterizing a tissue subject to compartment syndrome.

59. The method of any one of claims 41-56, wherein the method comprises monitoring or characterizing the tissue after a surgery.

60. The method of any one of claims 41-56, wherein the method comprises monitoring or characterizing a bone graft implant or spinal fusion.

61. The method of any one of claims 41-60, comprising implanting the one or more implantable devices in the subject.

62. The method of any one of claims 41-61, wherein the subject is a human.

63. The method of any one of claims 41-61, comprising determining a location or movement of the one or more implantable devices.

64. The method of any one of claims 41-61, wherein the ultrasonic backscatter comprises a digitized signal.

External Transceiver
-Long Range Transmitter
-Trans-Cranial Comm
-ASIC / Memory
-Data Processing
-Battery

Skull

Sub-Dural Interrogator
-Ultrasound Transceiver
 to Neural Dust
-Transcranial Transceiver
 for External Comm
-Polymer Encapsulant

Dura

Neural Dust
Polymer Encapsulation
Recording Sites
CMOS Front
End
Piezo
Drive
Electrodes
$\lambda/2$

Cortex

FIG. 1

1.8V Supply

ASIC

Charge Pump (1.8V to 32V)

FPGA

Digital Control

Delay
Control

Level-
Shifter

0-32V

Pre-Amp

0-1.8V

T/Rx

Data Capture

Amps → ADCs

Transducer Array

Beamforming

Backscatter

Neural Dust Motes

FIG. 2A

2/21

User Interface

Storage Medium

Input/Output

Power Supply

Integrated
Circuit

FIG. 2B

Bluetooth

BT
to
Serial

3.3V Power Sub-
System

LiPo
Battery

uC

ASIC

1.8V

Digital
Controls

Charge Pumps (1.8V to 32V)

7

Delay
Control

Level-
Shifter

DSP

0-32V

0-1.8V

T/Rx

7

Transducer Array

ADCs

3

Amps

BPF

3

7.2MHz   600kHz

FIG. 3A

FIG. 3B

FIG. 3C

FIG. 3D

FIG. 3E

Interrogator Transducer

Tissue   Miniaturized
          Ultrasonic
Carrier   Transducer   Sensor

Backscatter   Implantable Device

FIG. 4

FIG. 5A
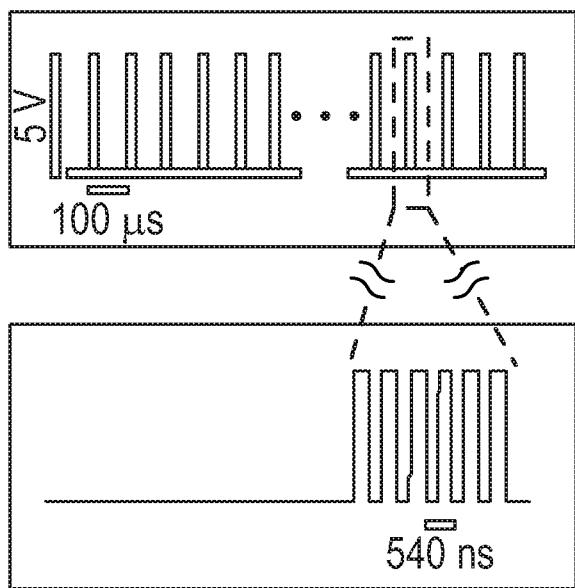
FIG. 5C
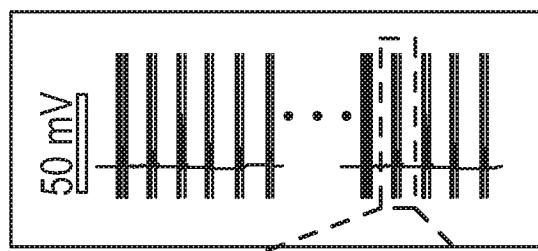
FIG. 5B
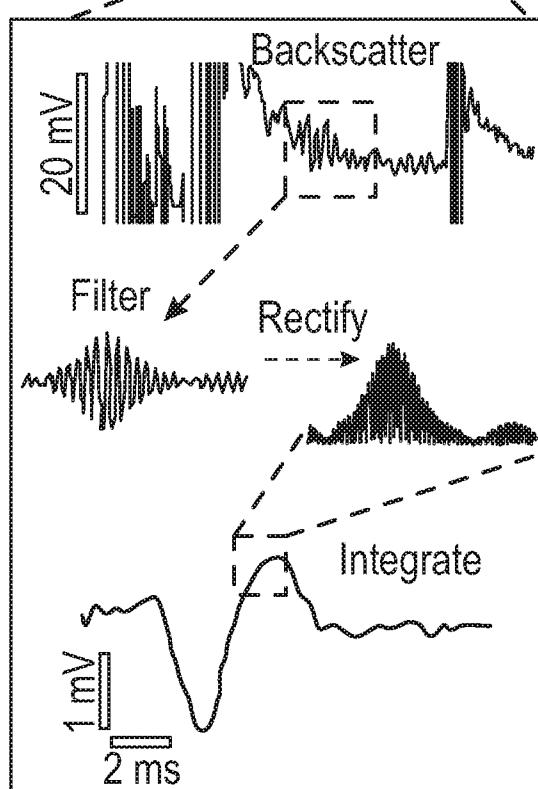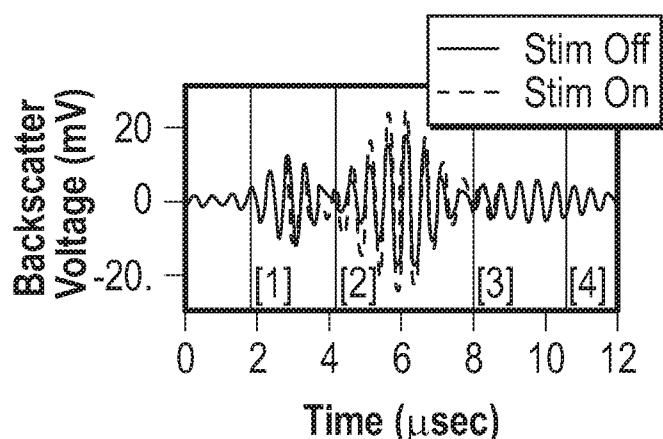
FIG. 5E

FIG. 5D
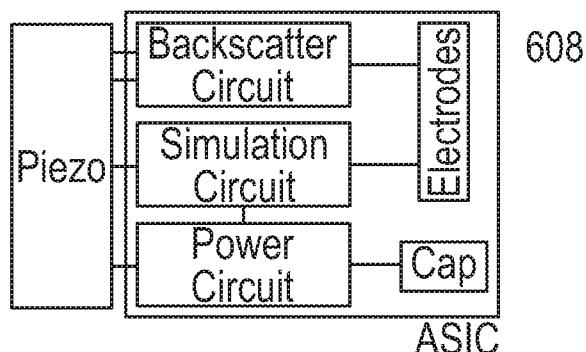
FIG. 6
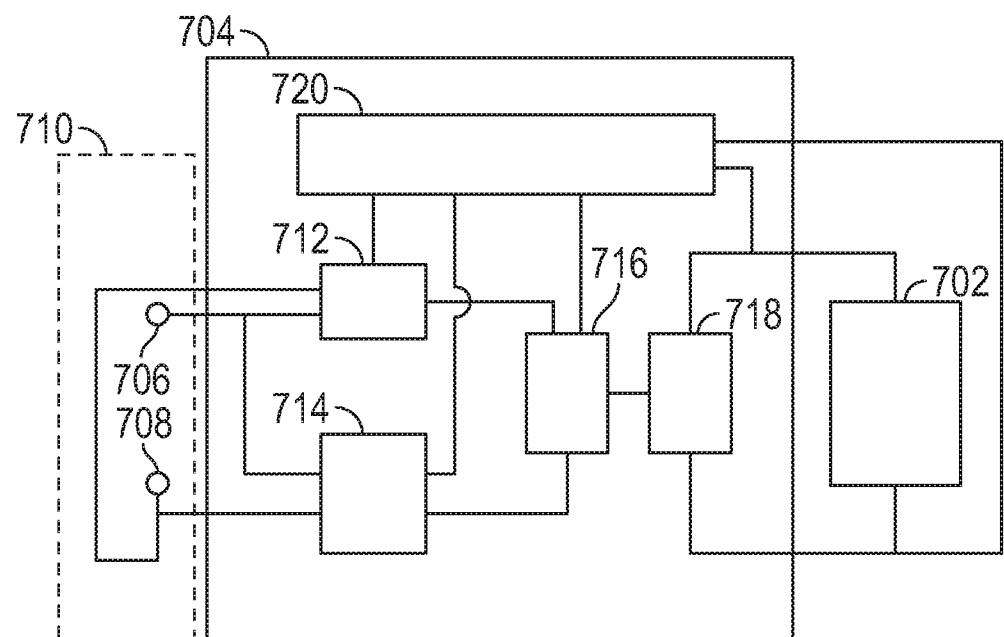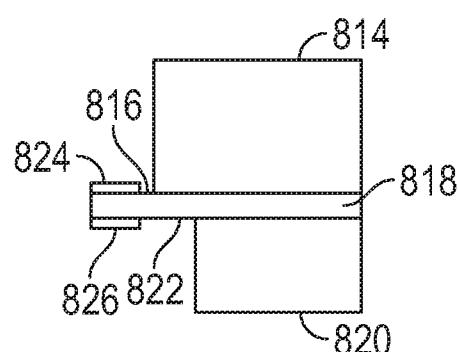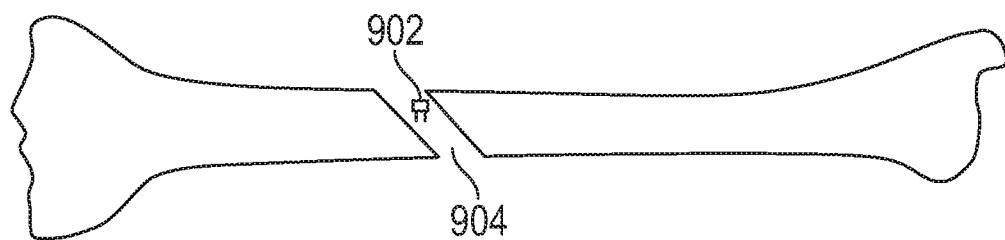
FIG. 7A

FIG. 7B

FIG. 8A

FIG. 8B

FIG. 9A

FIG. 9B

FIG. 10A

FIG. 10B

FIG. 11

1202 ┐
```
┌─────────────────────────────────────────────────────┐
│         Coat a surface with a polyimide layer.        │
└─────────────────────────────────────────────────────┘
```

1204 ┐
```
┌─────────────────────────────────────────────────────┐
│      Coat the polyimide layer with an a-SiC layer.    │
└─────────────────────────────────────────────────────┘
```

1206 ┐
```
┌─────────────────────────────────────────────────────┐
│         Etch one or more ports into the SiC layer.    │
└─────────────────────────────────────────────────────┘
```

1208 ┐
```
┌─────────────────────────────────────────────────────┐
│      Attach implantable device to the a-SiC layer.    │
└─────────────────────────────────────────────────────┘
```

1210 ┐
```
┌─────────────────────────────────────────────────────┐
│  Coat at least a portion of the exposed implantable device │
│                  with an a-SiC layer.                 │
└─────────────────────────────────────────────────────┘
```

1212 ┐
```
┌─────────────────────────────────────────────────────┐
│      Emboss the encapsulated implantable device.      │
└─────────────────────────────────────────────────────┘
```

FIG. 12

FIG. 13A

FIG. 13B

Silver Epoxy Cure Time vs Temperature
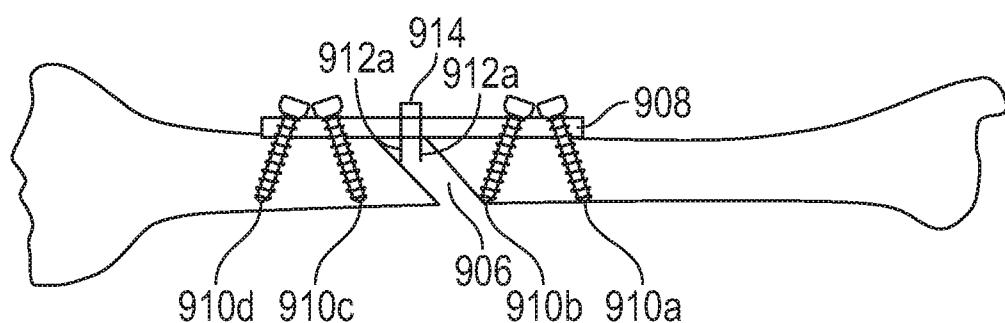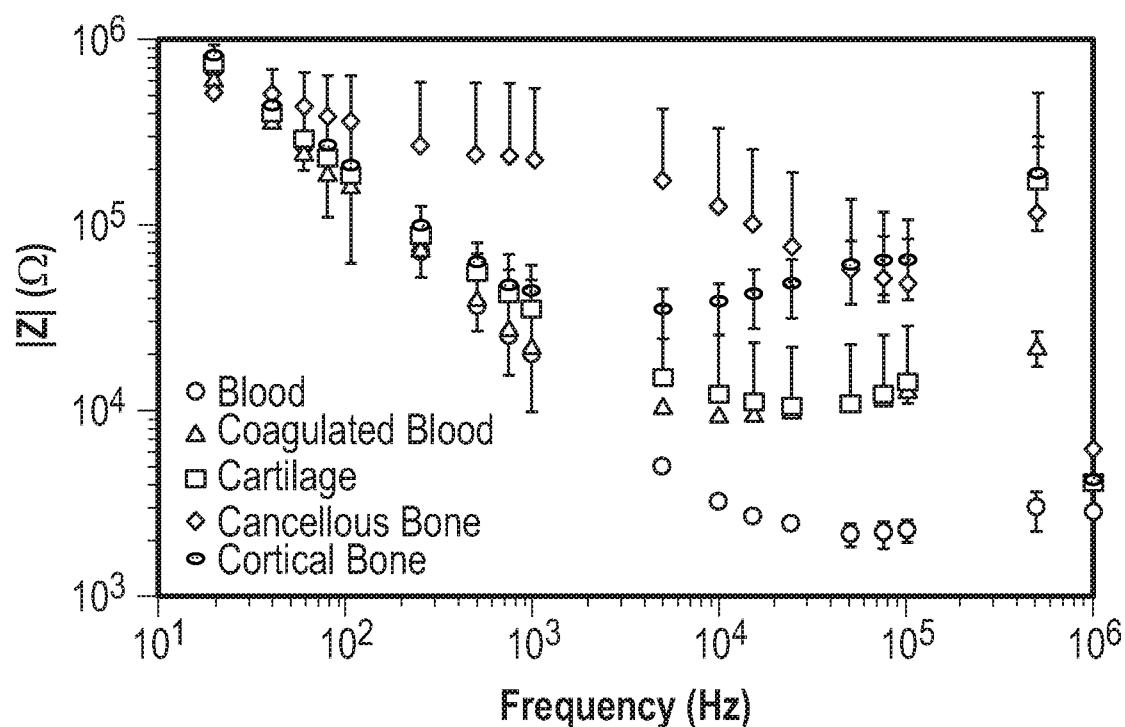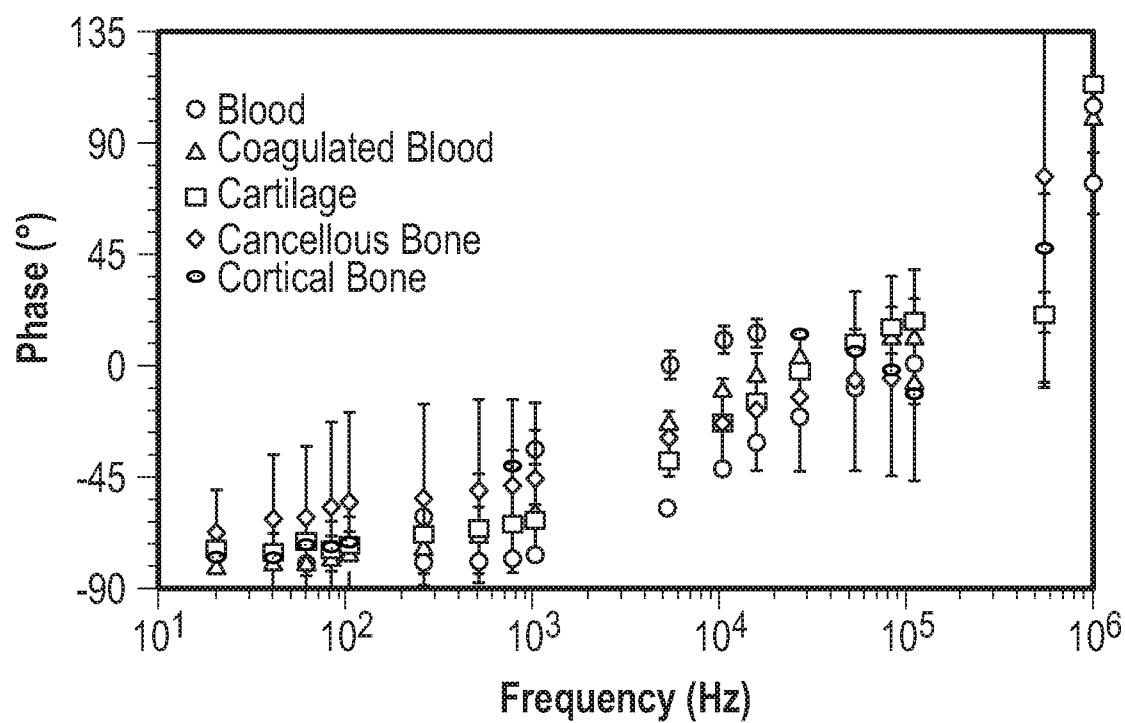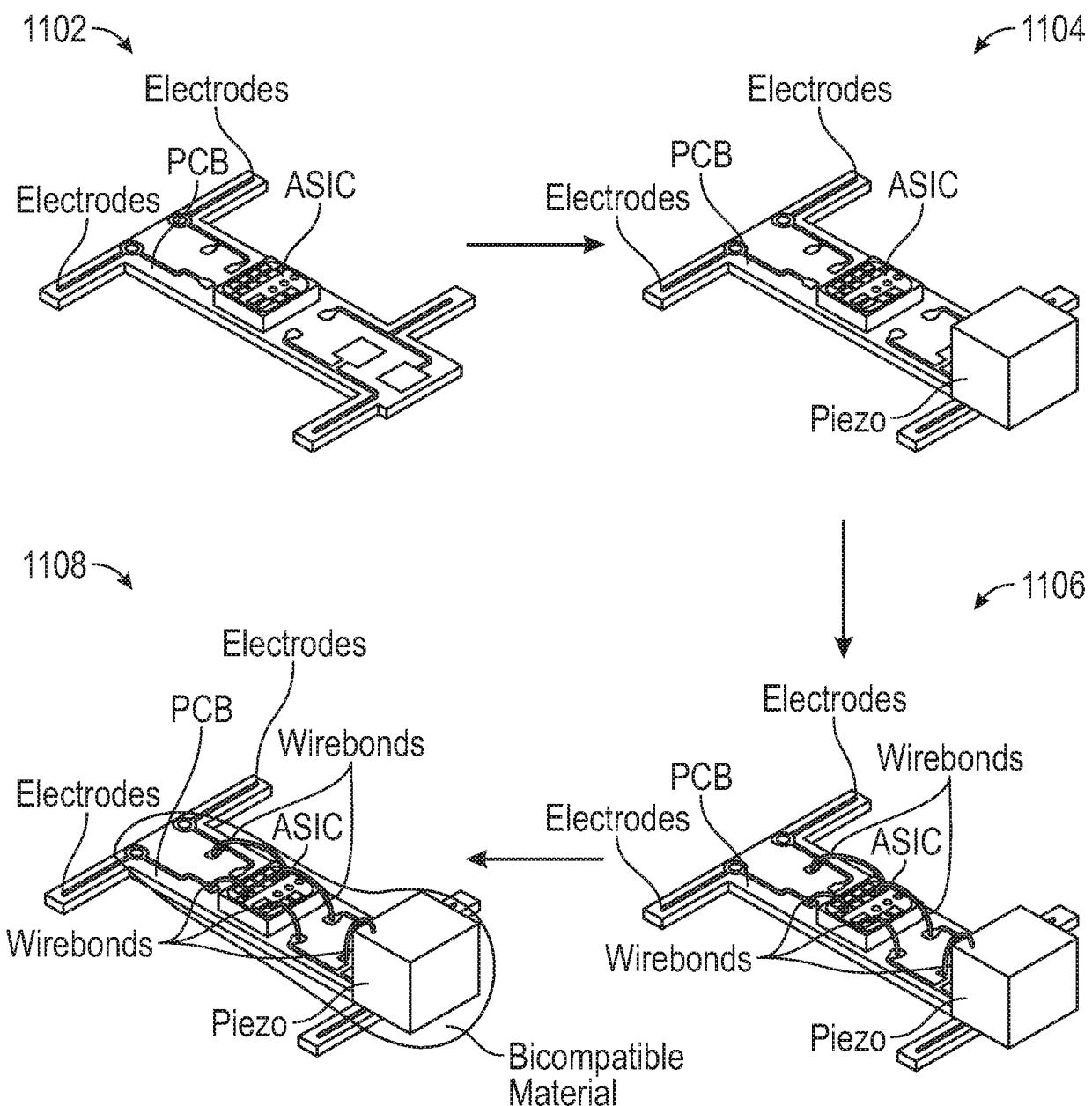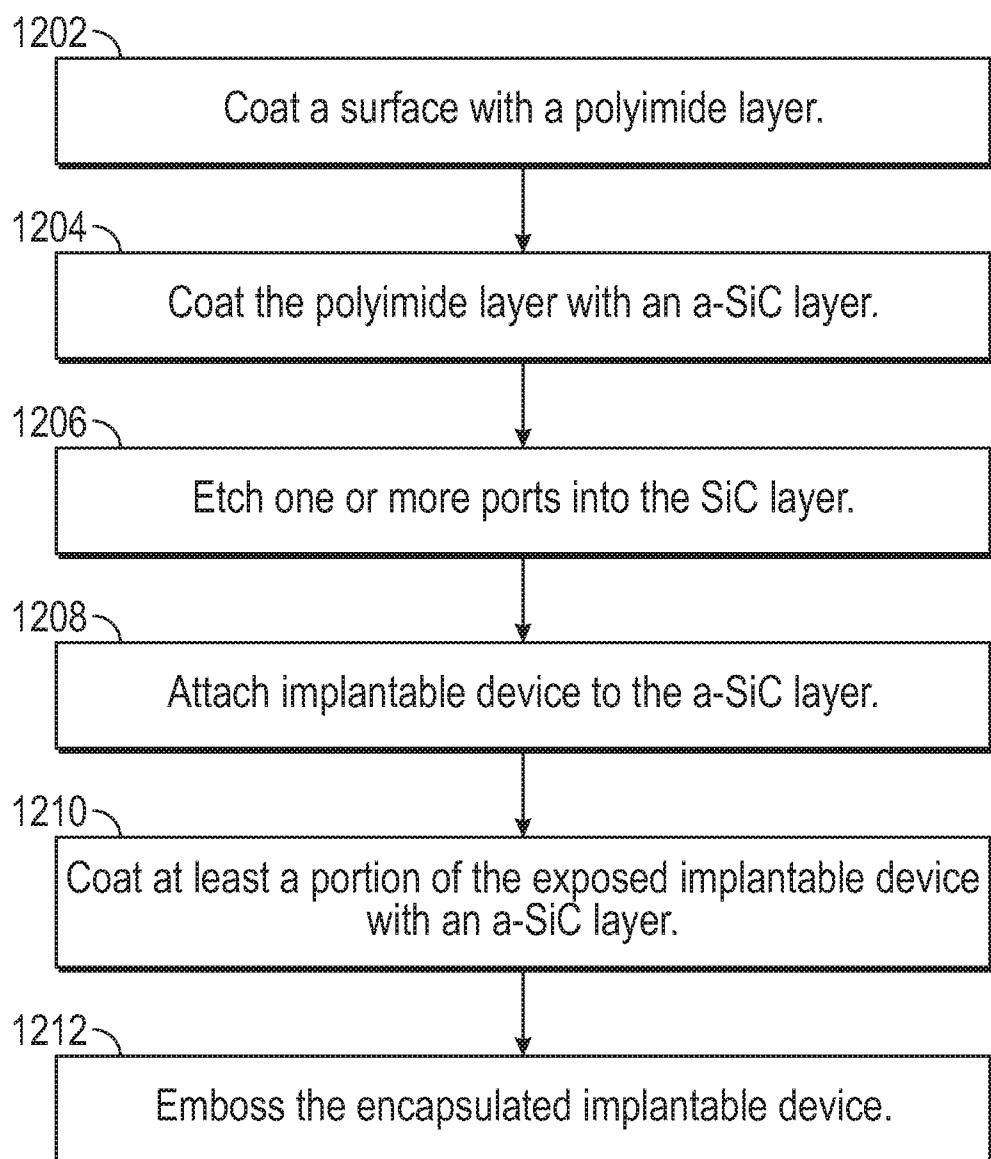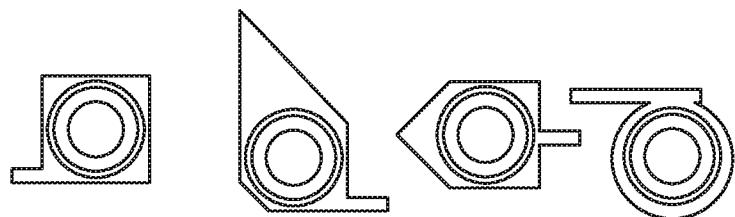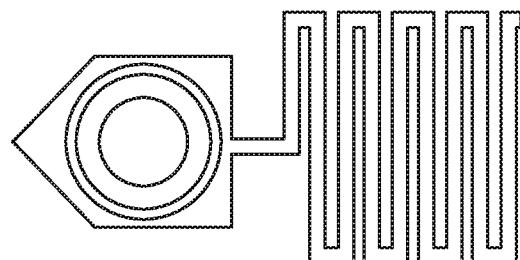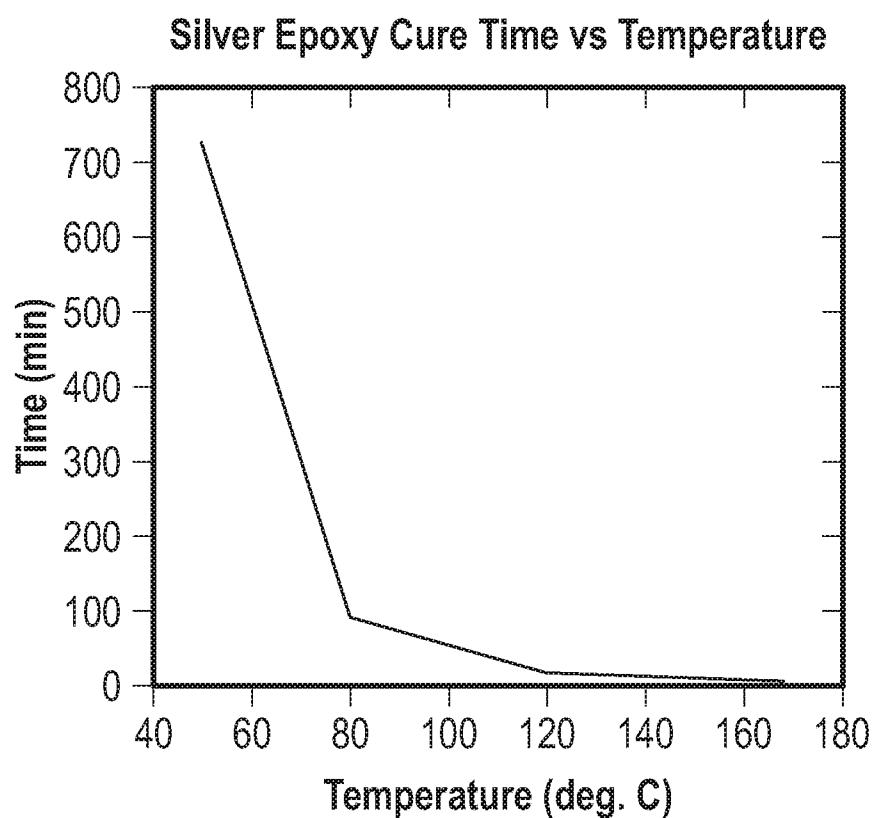
FIG. 14

1. Start w/SCS
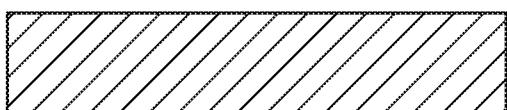
2. Spin PI Layer
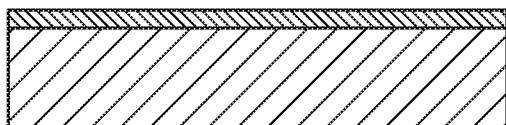
3. PECVD a-SIC
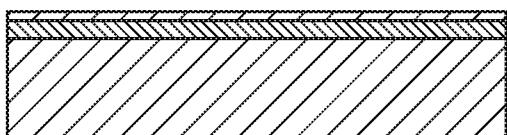
4. RIE Openings for Electrodes
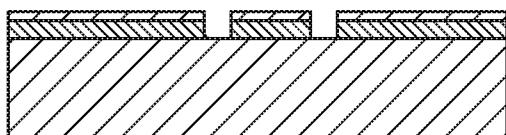
5. Evaporate Ruthenium and Plate Gold onto Electrode Sites
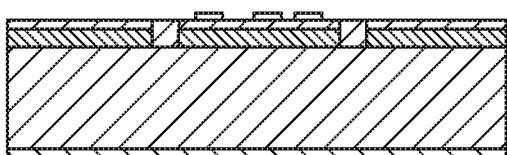
6. Die/Piezo Attach and Wirebond
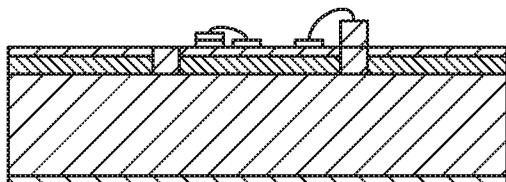
7. PECVD a-SIC Encapsulation
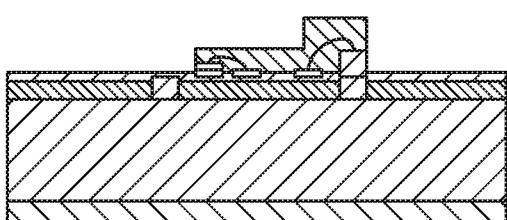
8. RIE Emboss Topside, Remove Film from Backside
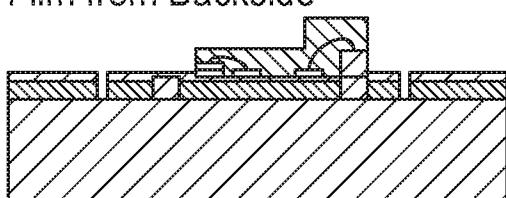
9. Dissolve Wafer (TMAH)

FIG. 15
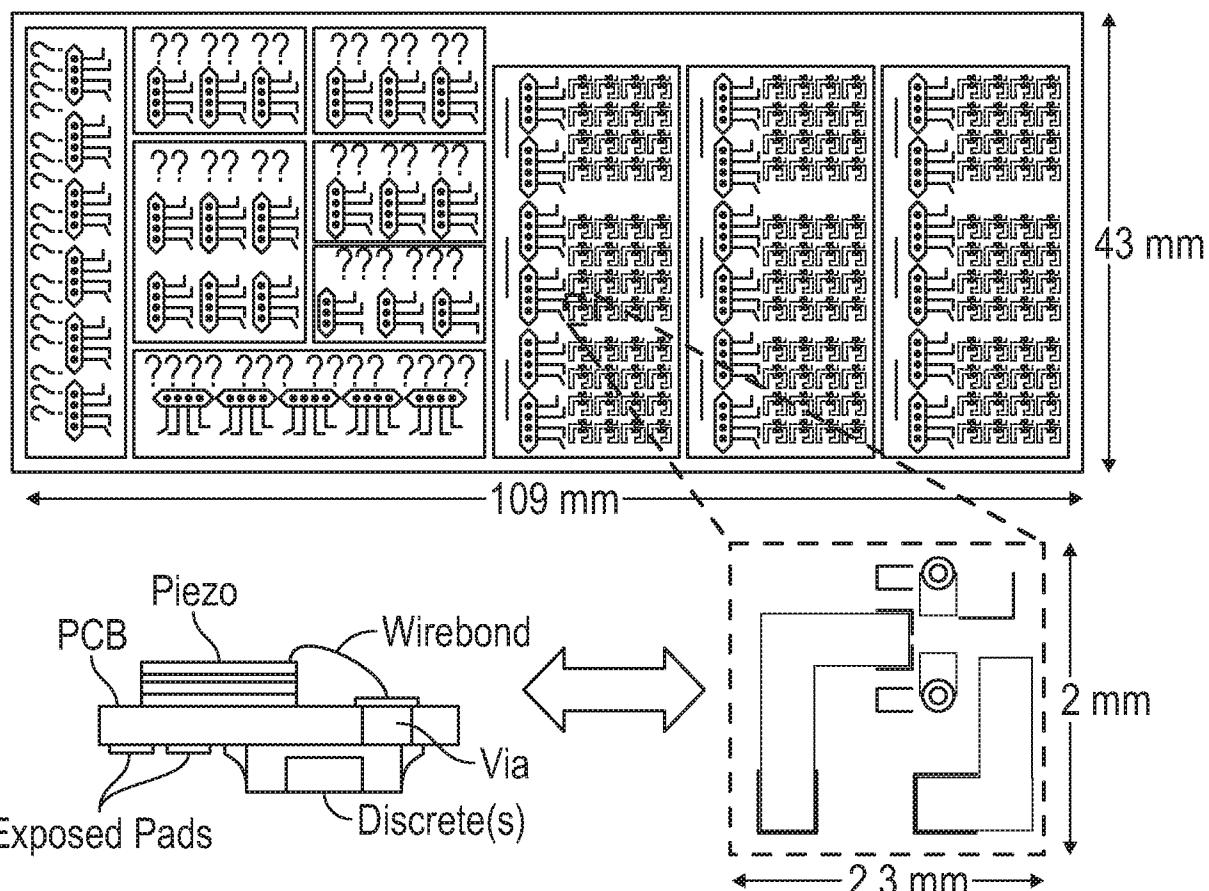
FIG. 16
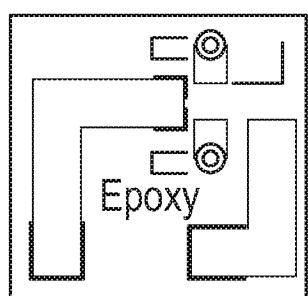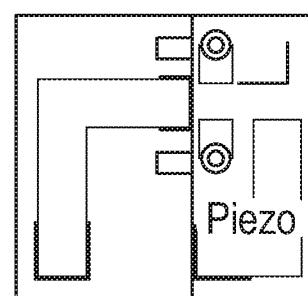
FIG. 17A   FIG. 17B
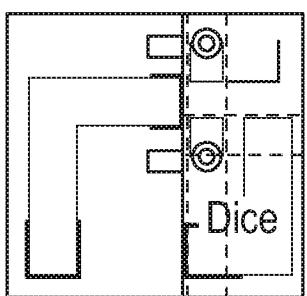
FIG. 17C   FIG. 17D   FIG. 17E
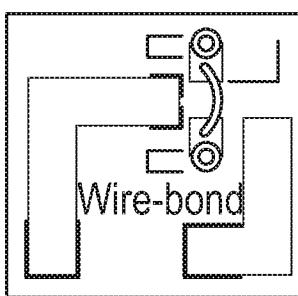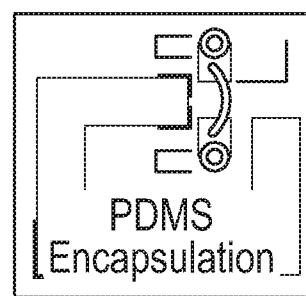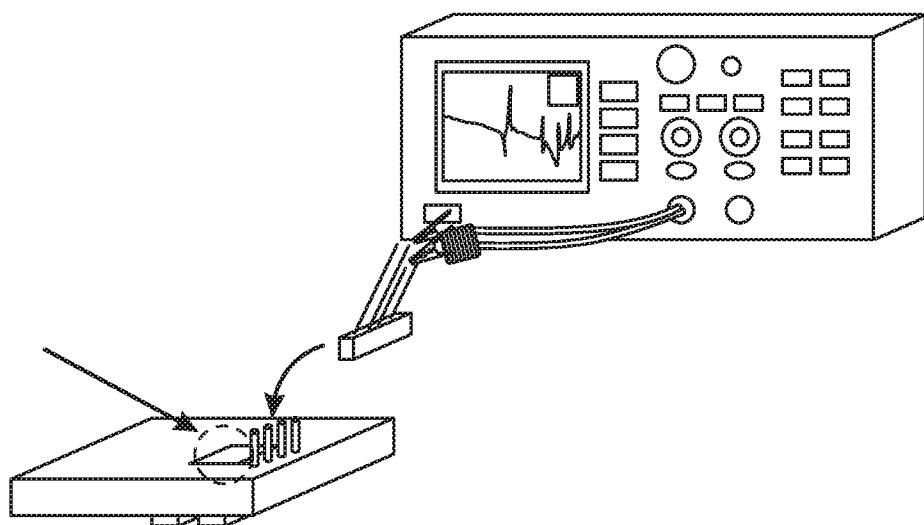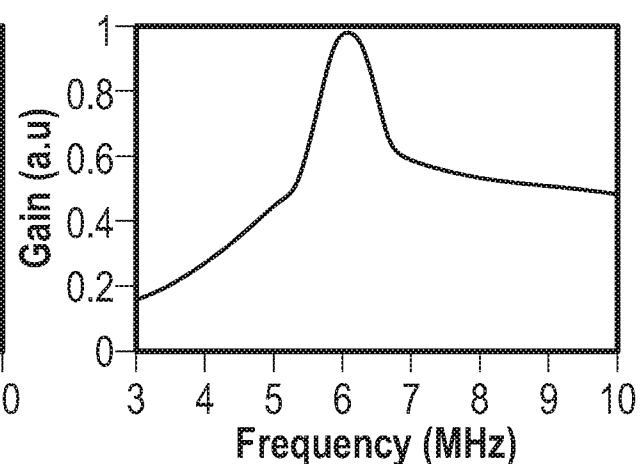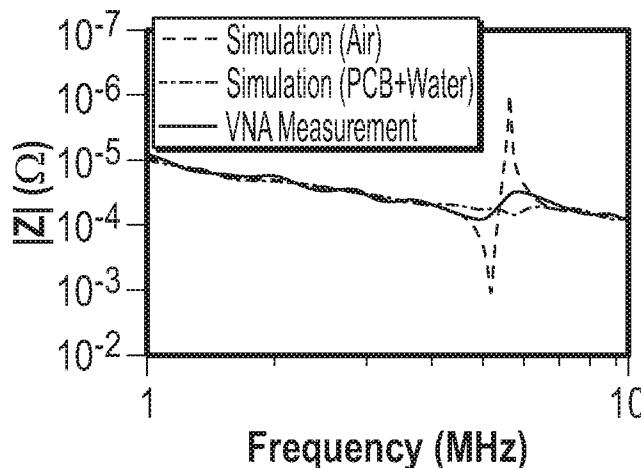
FIG. 18

FIG. 19A

FIG. 19B

FIG. 19C

14/21
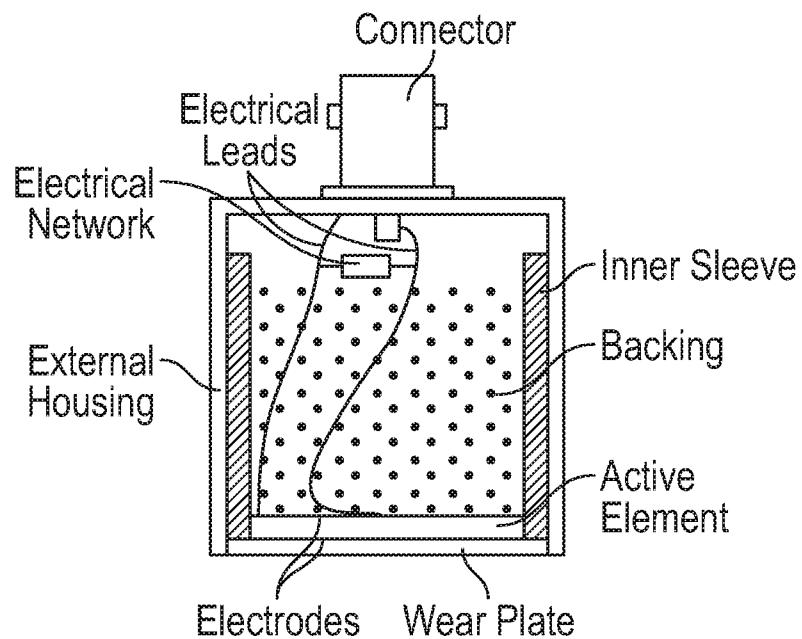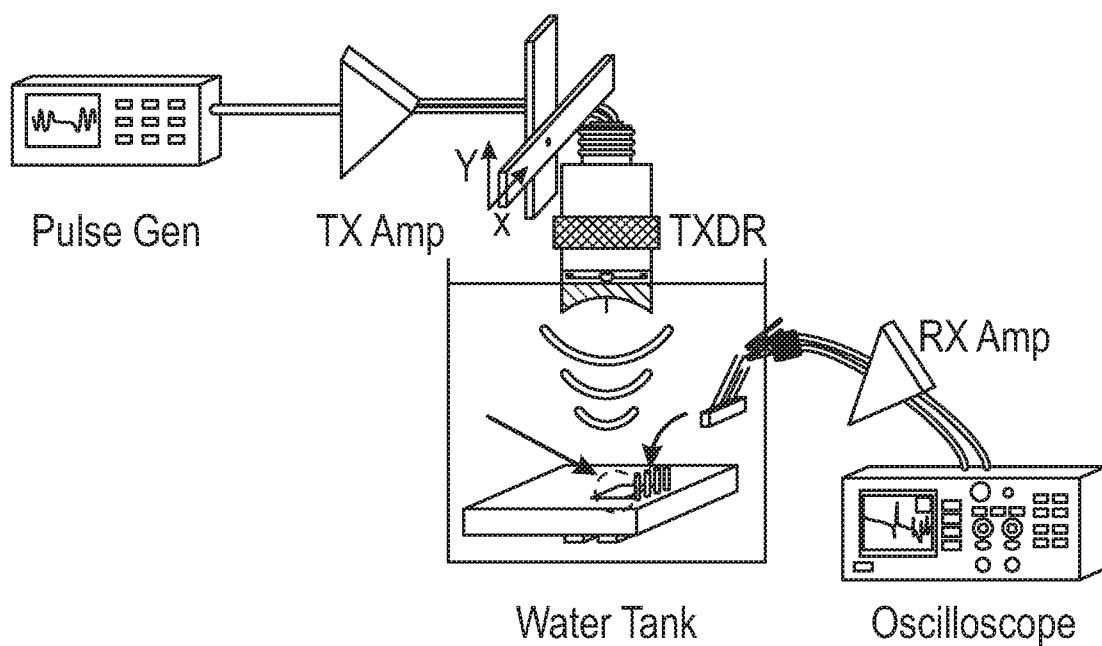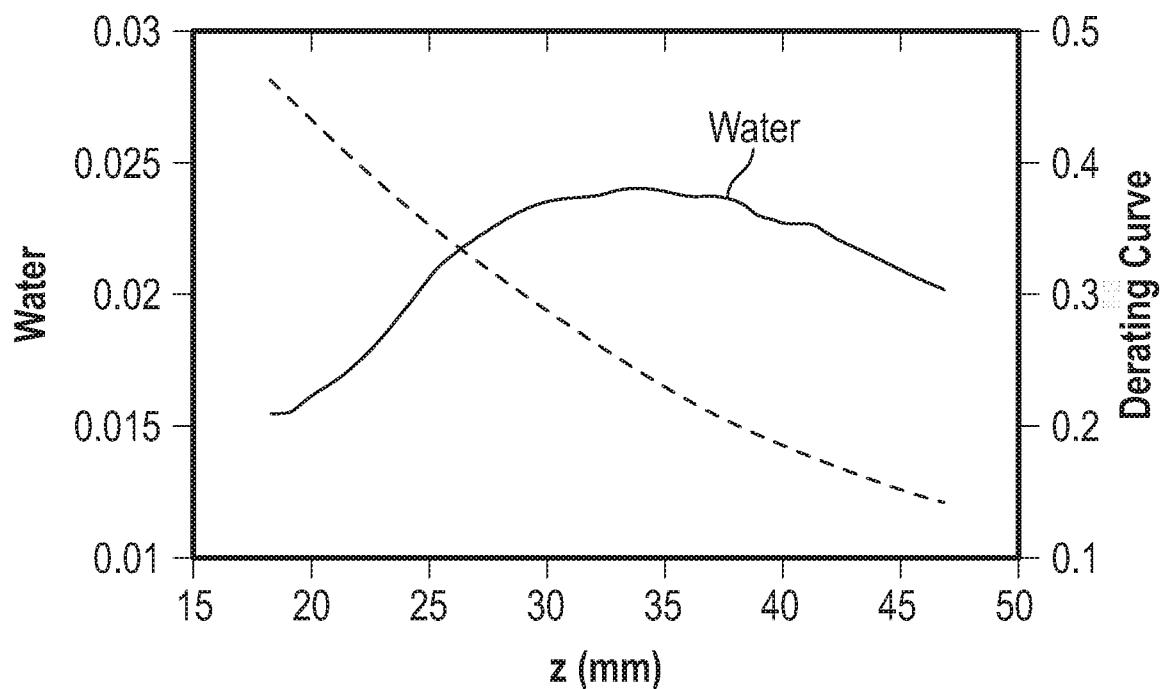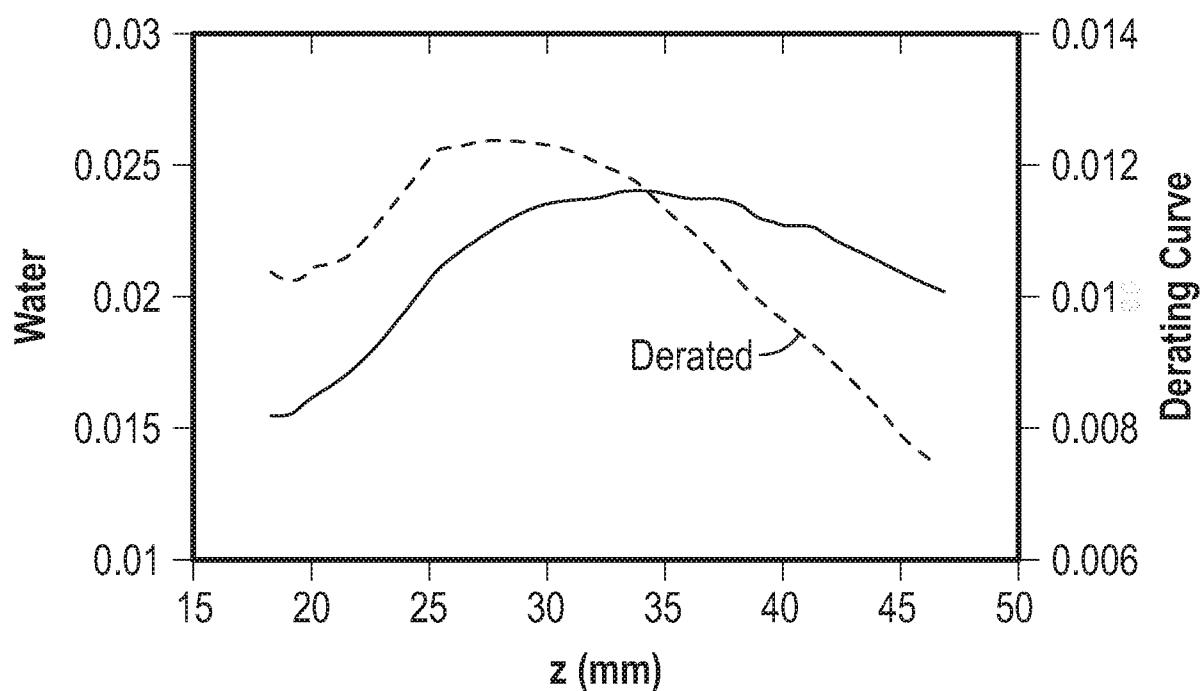
Connector

Electrical
Leads

Electrical
Network

Inner Sleeve

Backing

External
Housing

Active
Element

Electrodes   Wear Plate

FIG. 20

Pulse Gen   TX Amp   Y   X   TXDR

RX Amp

Water Tank   Oscilloscope

FIG. 21

FIG. 22A

FIG. 22B
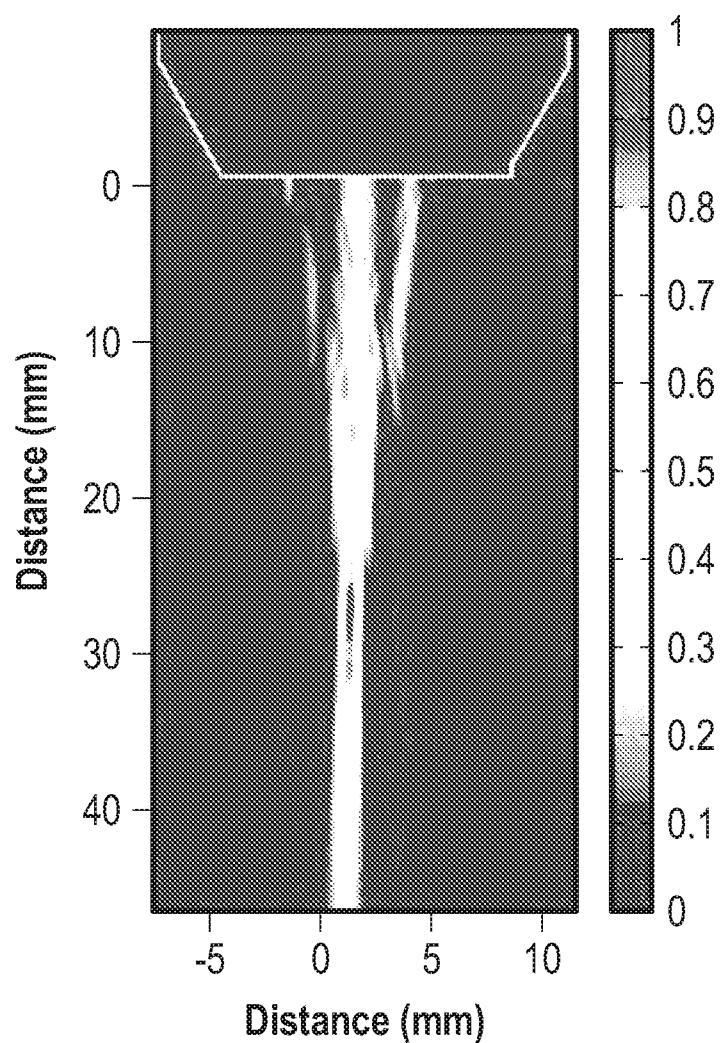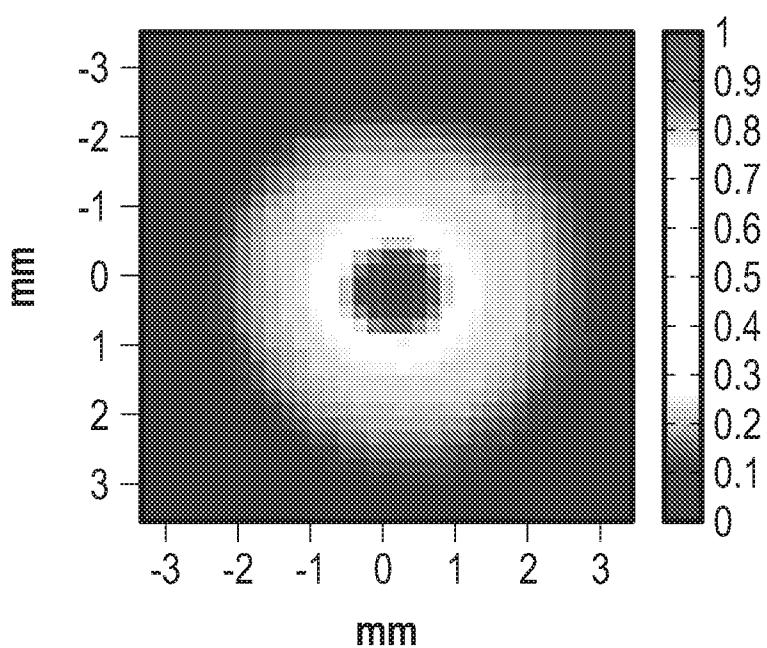
FIG. 23A

FIG. 23B
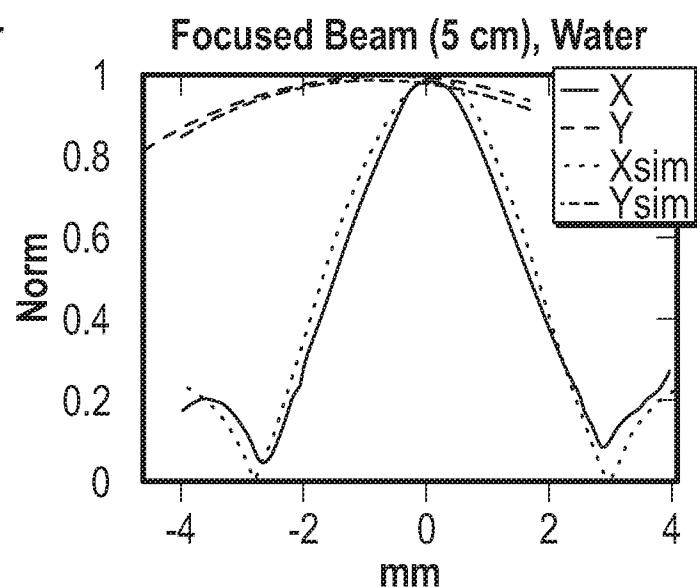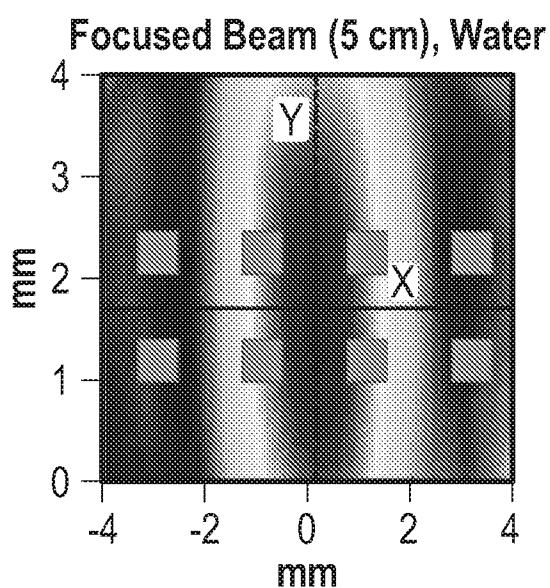
FIG. 24A

FIG. 24B

FIG. 24C

Focused Beam(5 cm),
Water

FIG. 25A

FIG. 25B

FIG. 25C

Transmission Distance = 5mm (-3dB/cm/MHz)

Transmitted Power=1.9W/cm² over 3.2mm Beam

FIG. 26

FIG. 27A

Near-Field

Rayleigh
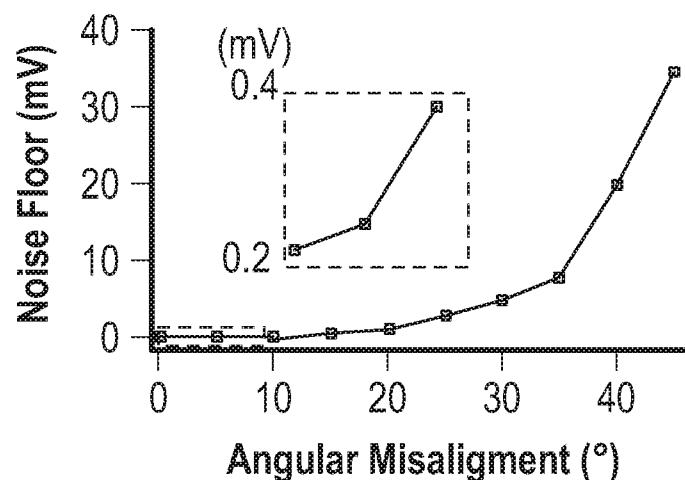
Far-Field
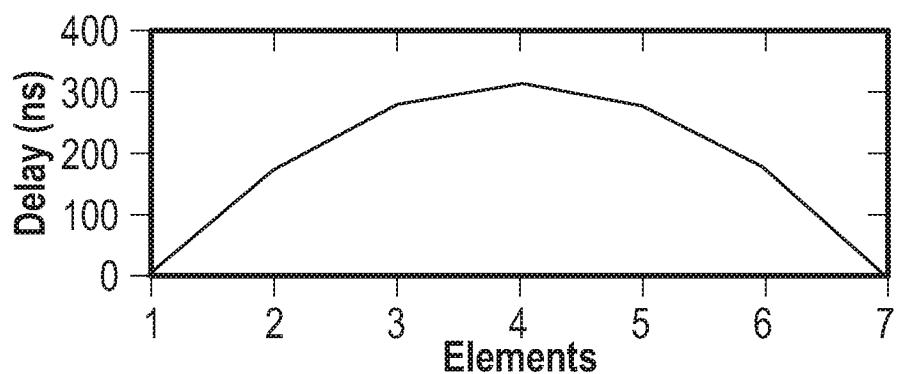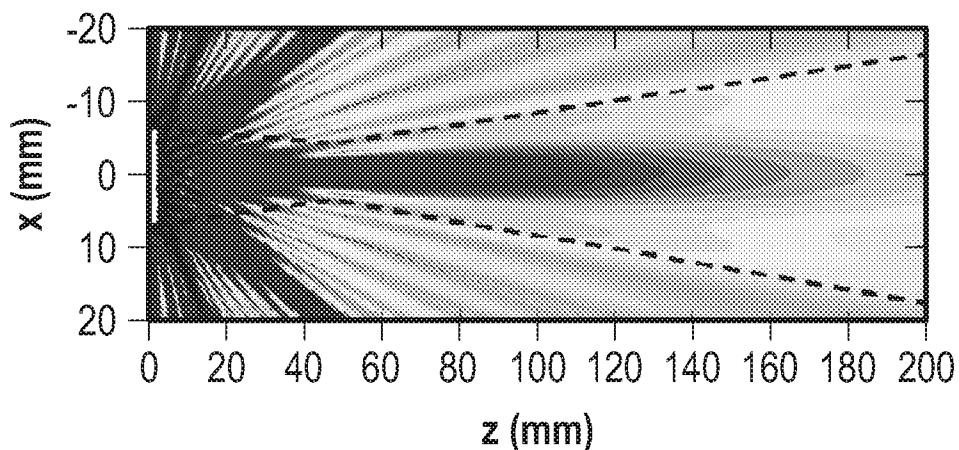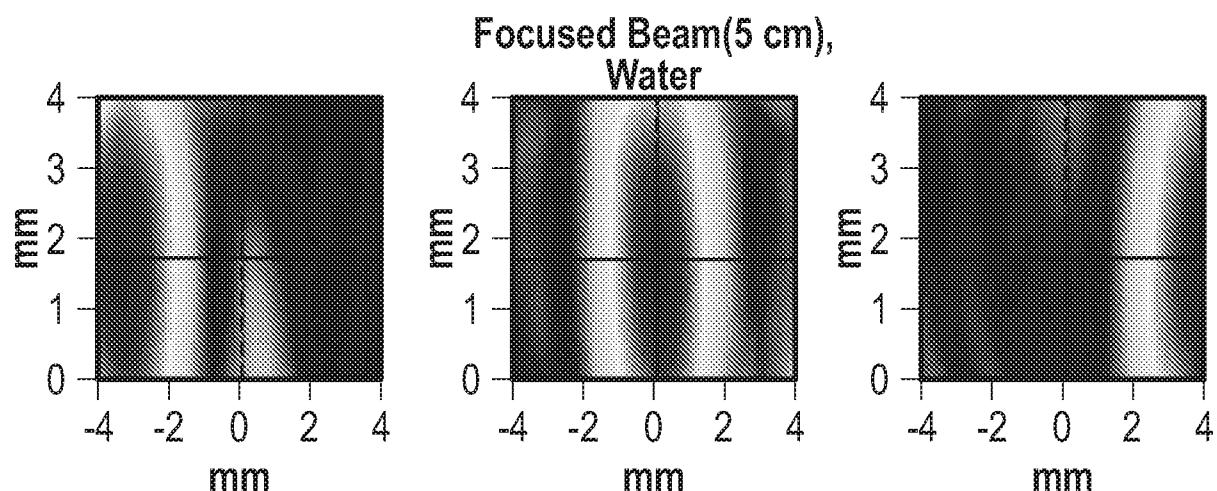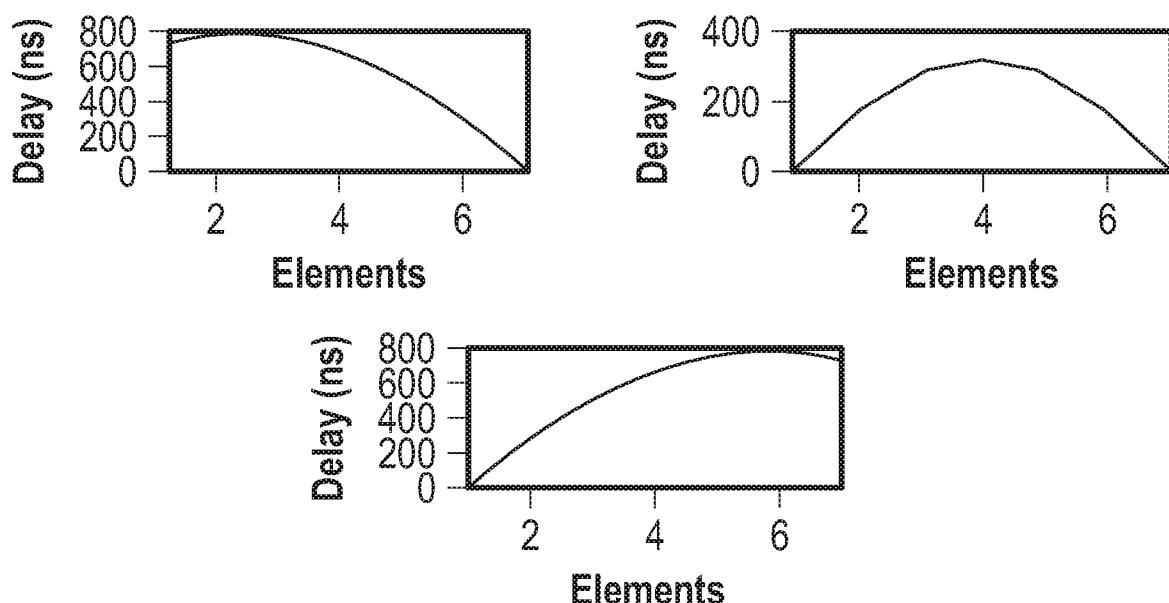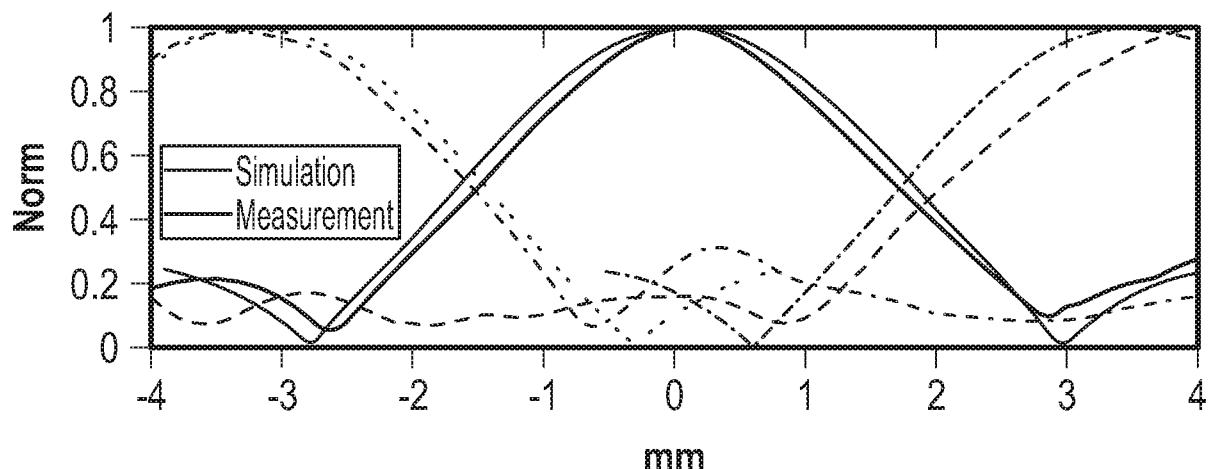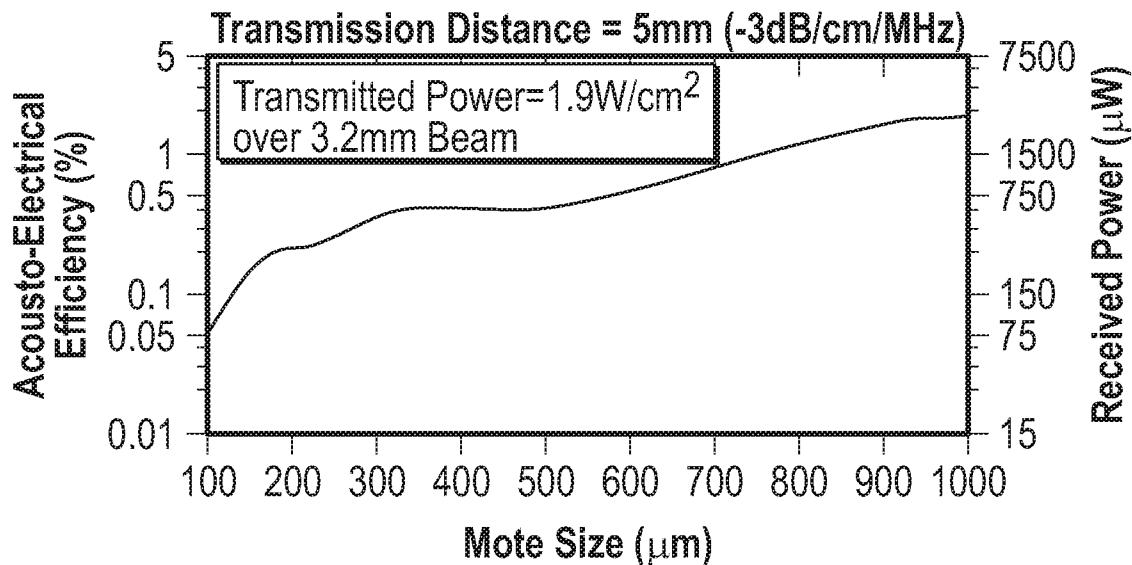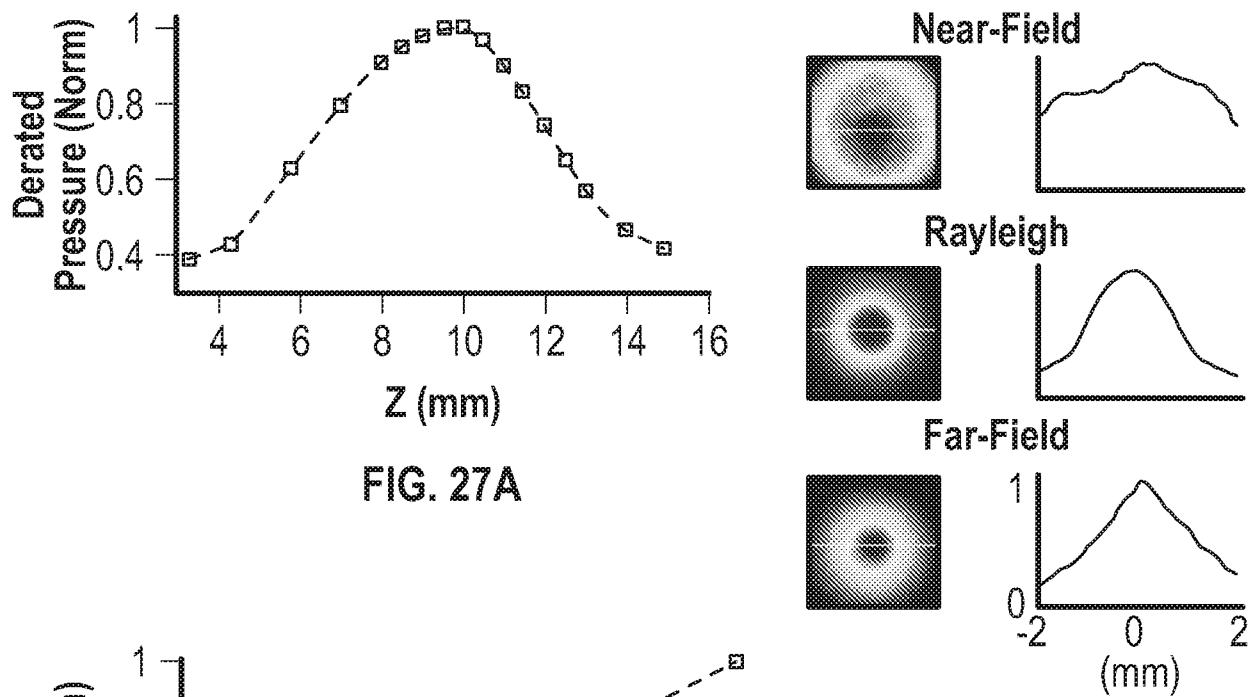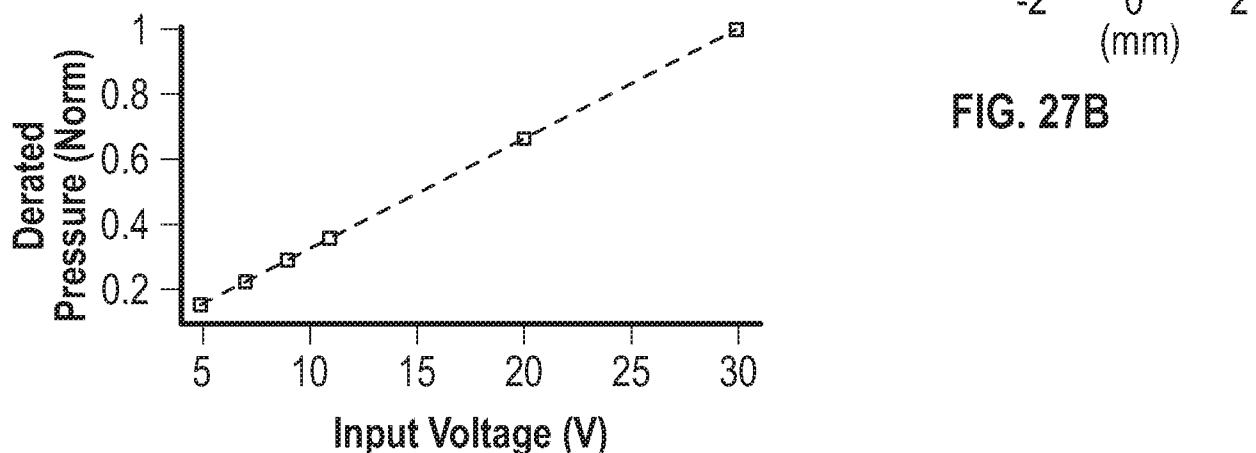
FIG. 27B

FIG. 27C
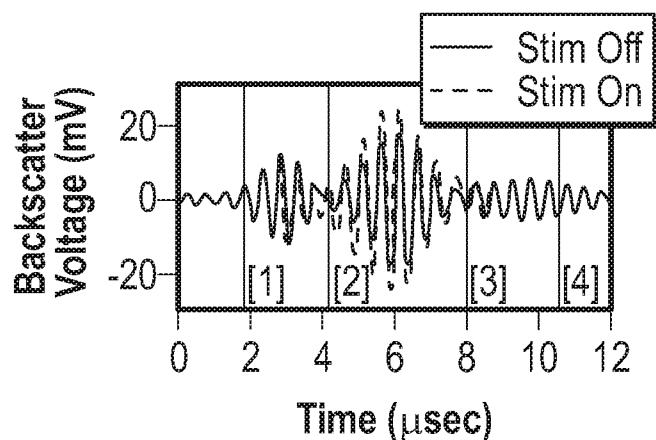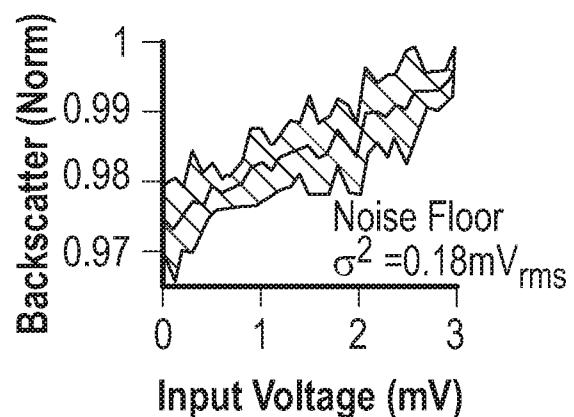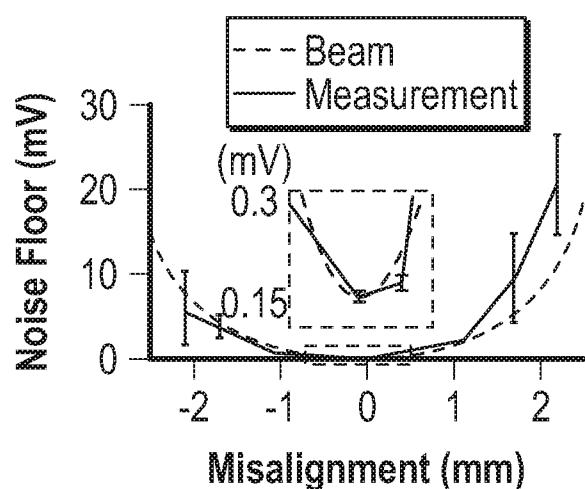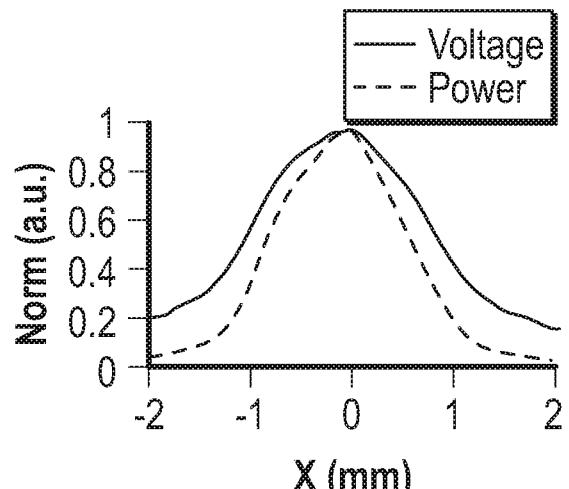
FIG. 28A

FIG. 28B

FIG. 28C

FIG. 28D

FIG. 28E
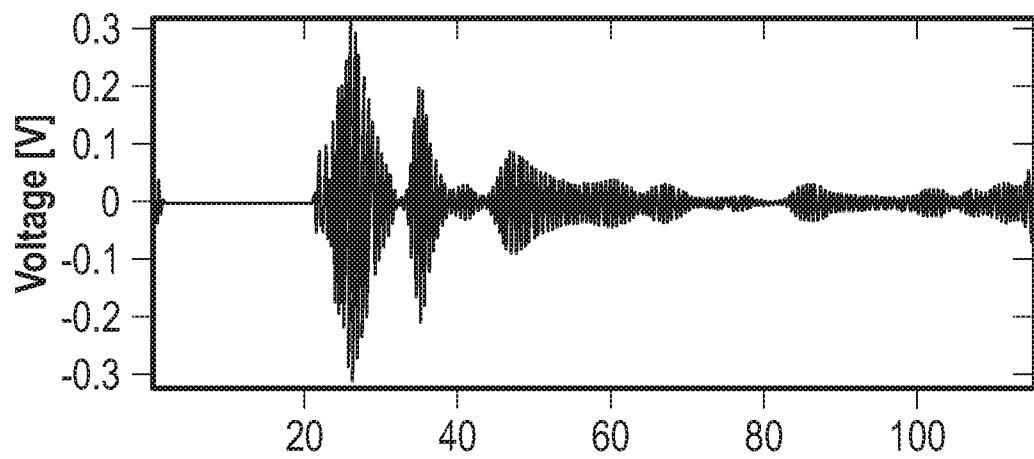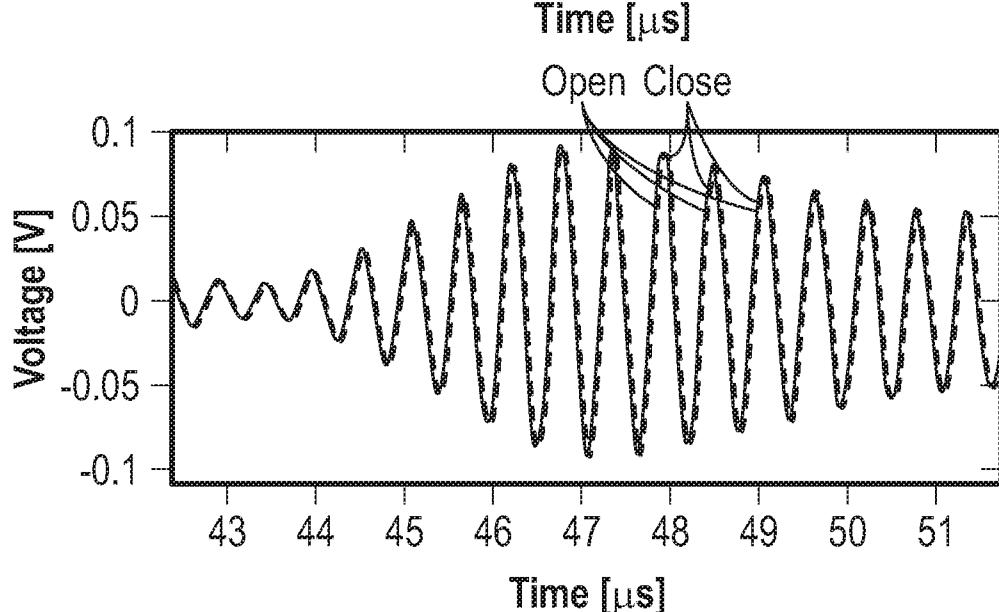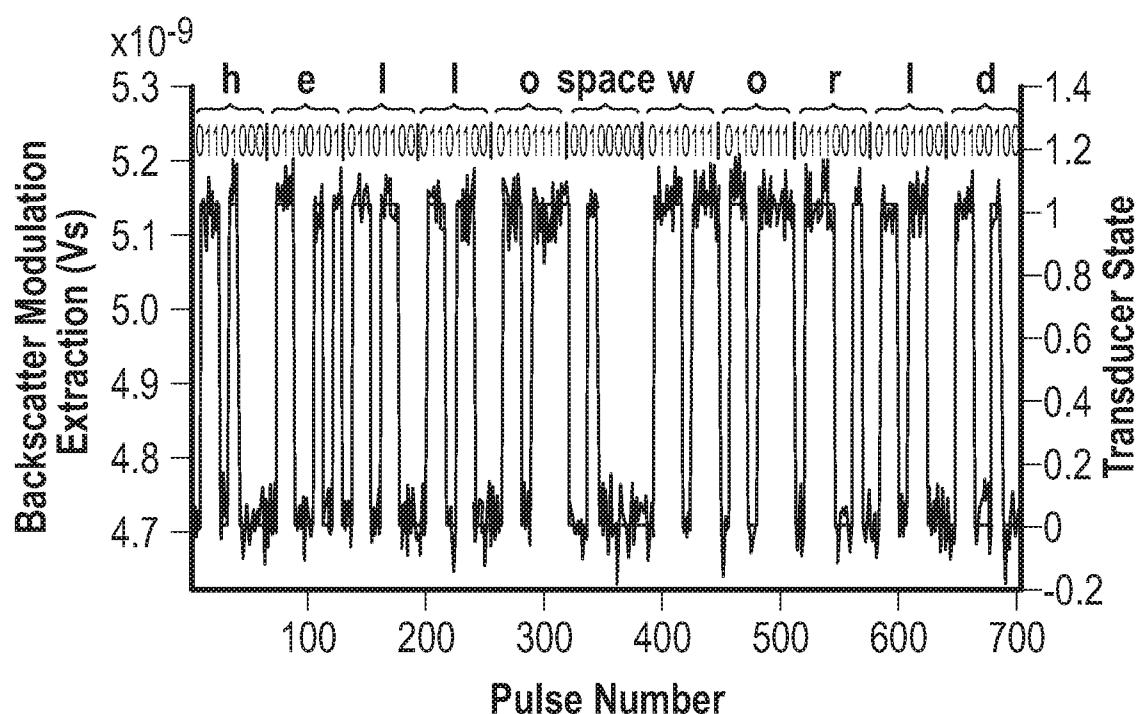
FIG. 29A

FIG. 29B

FIG. 30

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DONGJIN SEO ET AL: "Model validation of untethered, ultrasonic neural dust motes for cortical recording", JOURNAL OF NEUROSCIENCE METHODS., vol. 244, 1 April 2015 (2015-04-01), pages 114-122, XP055416347, NL ISSN: 0165-0270, DOI: 10.1016/j.jneumeth.2014.07.025 abstract; figures 1-9	1-62,64
Y	page 115, left-hand column, paragraph 1 - right-hand column, line 1 page 117, right-hand column, paragraph 1 - page 119, left-hand column, paragraph 1 page 120, right-hand column, paragraph 2 page 121, left-hand column, paragraph 2 - page 122, left-hand column, paragraph 1	63

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| X | Further documents are listed in the continuation of Box C. | | X | See patent family annex. |

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Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2017	13/11/2017

| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer Daoukou, Eleni |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/057868 A1 (MEDTRONIC INC [US]; CINBIS CAN [US]) 3 May 2012 (2012-05-03) paragraph [0030]	63
A	Michela Peisino: "Deeply implanted medical device based on a novel ultrasonic telemetry technology", , 17 May 2013 (2013-05-17), XP055178356, ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE Retrieved from the Internet: URL:https://infoscience.epfl.ch/record/186 391 [retrieved on 2015-03-23] page 63 - page 79	1-64
A	CELINSKIS DMITRIJS ET AL: "Wireless impedance measurements for monitoring peripheral vascular disease", 2014 36TH ANNUAL INTERNATIONAL CONFERENCE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY, IEEE, 26 August 2014 (2014-08-26), pages 6937-6940, XP032676031, DOI: 10.1109/EMBC.2014.6945223 [retrieved on 2014-11-02] abstract; figures 1,4 page 6937, left-hand column, paragraph 2 page 6937, right-hand column, paragraph 5 - paragraph 6 page 6938, right-hand column, paragraph 2 page 6940, left-hand column, paragraph 2	17,18, 21,24, 42,44, 47,53, 54,58
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A	WO 2007/090159 A1 (MEDTRONIC INC [US]; CHEN KAIMIN [US]; SCHMIDT CRAIG L [US]; MERRITT DO) 9 August 2007 (2007-08-09) page 10, paragraph 4 - page 11, paragraph 1	56
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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BERTRAND ALEXANDER ET AL: "Beamforming approaches for untethered, ultrasonic neural dust motes for cortical recording: A simulation study", 2014 36TH ANNUAL INTERNATIONAL CONFERENCE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY, IEEE, 26 August 2014 (2014-08-26), pages 2625-2628, XP032674549, DOI: 10.1109/EMBC.2014.6944161 the whole document -----	37,38

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WO 2007090159	A1	09-08-2007	NONE		