Smart Implant to Detect Fracture Healing

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Need and Industrial Relevance:

10-20% of fractures result in delayed or non-union, with this number rising to 46% when the injury occurs in conjunction with vascular damage. Current monitoring techniques (e.g. radiographs) are unable to diagnose delayed healing until late stages of fracture repair (months). We are currently developing a device that utilizes impedance spectroscopy to monitor progression of fracture healing, and have completed proof of concept trials in a mouse model to show that electrical signals correlate to specific stages of fracture healing. We now aim to develop a smart implant with integrated wireless capability for a larger preclinical animal model to acquire impedance maps across the fracture site.

Project Aims:

Specific Aim 1 – Develop sensor electronics that integrate impedance measurements and wireless capability

1a) *Replace the LCR meter with an impedance measurement chip solution*

We will first replace the LCR meter with the Analog Devices AD5933 chip. This can be tuned to our application and integrated with a microcontroller to enable us to take impedance measurements in an implant without the need for bulky equipment.

1b) *Establish wireless communication, data transfer and power transfer*

To produce a fully implantable sensor, we will utilize RF (radio frequency) technology to establish wireless communication and data transfer capability. To do this, we will incorporate components necessary to receive power passively from an external transceiver via RF power transfer.

Specific Aim 2 – Prototype sensor for a larger animal model

2a) *Use cadaveric tibias to model size restrictions and determine necessary dimensions*

Our *in vivo* study in a mouse model has validated our ability to track tissue changes in a fracture gap over the course of healing (**Figure 1**). In preparation for a future larger animal study, we will use cadaveric rabbit tibias to understand the size constraints for our sensor and build a prototype to scale. Rabbits are larger in size than rodents and have similar tibia load-bearing as humans.

2b) *Fully implant sensors in cadaveric rabbit hind limb to verify ability to collect data wirelessly*

In an *ex vivo* rabbit model, we can determine the optimal placement of the electrodes and the measurement technology within the surgical site. After fully implanting the sensor in a rabbit leg and suturing the skin closed above it, we can verify the sensor's ability to collect and transmit data wirelessly through the soft tissue.

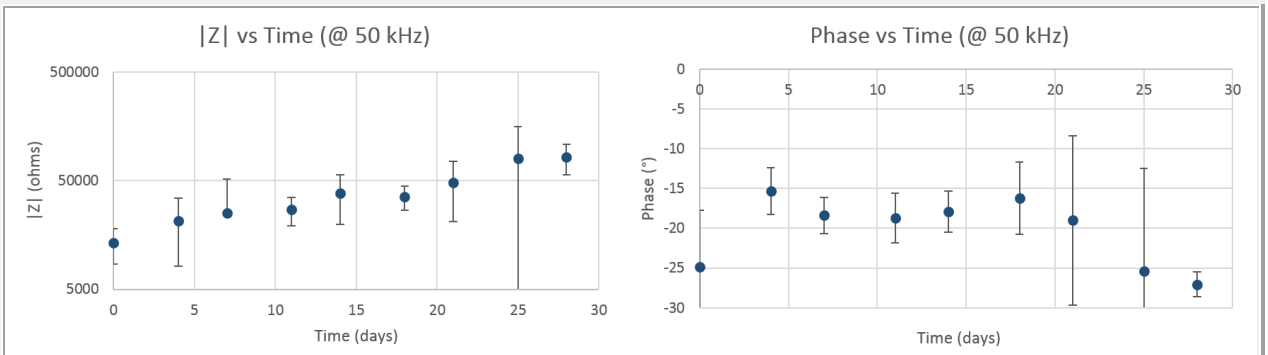

Figure 1 – Impedance magnitude (left) and phase angle (right) at 50 kHz measured from sensors implanted in mouse fractures (N=6) and measured over 28 days. Impedance magnitude, which reflects the conductivity of the tissues, rises as expected over the course of healing. The phase angle indicates that the measurements became more resistive (less negative) early on and became more capacitive (more negative) towards the later stages of healing.

Methods:

Methods 1a) *Replace the LCR meter with an impedance measurement chip solution*
The Analog Devices AD5933 chip has a programmable output voltage to a maximum frequency of 100 kHz, and can be set through a serial I^2C interface. The basic impedance measurement range covers 1 kΩ to 10 MΩ, but we can add capability of measuring from 100 Ω to 1 kΩ with additional circuitry. We will integrate this with a microcontroller to regulate at which frequencies impedance measurements should be taken and allow for measurements across multiple pairs of electrodes.

Methods 1b) *Establish wireless communication, data transfer and power transfer*
To achieve fully passive acquisition of impedance measurements in the body, the implanted device will require a mixer, matching network, and antenna. An exterior interrogator will send a carrier signal (i.e. at 2.4 GHz) to activate the recorder, which in turn will activate the microcontroller and impedance chip from Aim 1a to make measurements. These will be mixed with the carrier to generate 4.8 GHz signals that can be transmitted back to the interrogator, which also contains a highly coupled antenna. Post-processing and analysis can be done off-chip on a laptop.

Methods 2a) *Use cadaveric tibias to model size restrictions and determine necessary dimensions*
We will obtain cadaveric rabbit tibias from a butcher for testing. Using the boards developed in Aim 1, we will determine the minimum size of our sensor and the ideal way to integrate it into a tibia fixation model. We plan to explore multiple options, including designing the sensor in the form of a small bone screw that can be inserted through one of the center holes in a typical bone plate, and integrating the sensing electrodes around an intramedullary nail.

Methods 2b) *Fully implant sensors in cadaveric rabbit to verify ability to collect data wirelessly*
With the information garnered from Aim 2a, we will design and build devices for a rabbit model first using a 3D printer to allow for rapid prototyping. This will involve electrodes that sit in the fracture gap, and a small piece of hardware responsible for taking impedance readings and wirelessly transmitting the data that will likely be affixed to an implant. We will mimic this clinical situation by performing analogous surgery on a cadaveric rabbit tibia, and verify our system by testing it with an external transceiver that will passively power the internal hardware via RF. We expect that wireless measurements made with this implanted device will match measurements made using a gold standard Agilent E4980A LCR meter using wired connections.

Milestones:
Examples:

- Tune impedance chip for use in monitoring fractures for Aim 1a – February 28, 2017
- Design board incorporating wireless capabilities for Aim 1b – April 30, 2017
- Initial studies in cadaveric rabbit to determine dimensions for Aim 2a – May 31, 2017
- Build prototype for rabbit model – June 30, 2017
- Fully implant sensors in cadaveric rabbit for Aim 2b – July 31, 2017
- Submit journal manuscript – September 30, 2017

Deliverables:
Quarterly presentation updates:

- December 2016 – conference call
- Spring 2017 – Spring Symposium @ UT (conference call option for non-UT teams)
- June 2017 – conference call
- September 2017 – Fall Symposium @ UCSF (conference call option for non-UCSF teams)

Final written report including results - October 31, 2017
Specific work product (e.g. protocols, material, device, database)

- Prototype for larger animal model – June 30, 2017
- Journal article – submitted by September 30, 2017

General Budget Outline:

Personnel	$	8,000
Supplies	$	5,000
Prototyping	$	10,000
Specimens	$	10,000
Total Direct	$	33,000
Indirects (10%)	$	3,300
Total	$	36,300

Start Date:
October 2, 2016

End Date:
September 30, 2017