18 Simulation of Electric Stimulation for Bone Growth

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18.1 Introduction

Osseointegration is a surgical procedure that provides direct skeletal attachment between an implant and host tissue with proven success in dental, auricle, and transfemoral implants. However, one challenge with using natural biological fixation is attaining a strong skeletal interlock at the implant interface, a prerequisite for long-term implant function. To prevent osseointegration failure at the bone-implant construct with a two stage procedure, extensive periods of restricted load bearing are required to allow for sufficient bone remodeling and prevent overloading. However, loosening at the bone-implant interface from osteopenia, stress shielding, and a lack of loading are potential concerns which must be addressed.

Due to their limited residual limb length caused by explosive devices, veterans with combat related injuries form an especially relevant population who require the development of new tools to enhance the success of osseointegration. Improvements in medical care and evacuation strategies have led to an increase in survival rates, resulting in an elevated number of veterans with amputations that require follow-up care and extensive rehabilitation. The relative youth and otherwise good health of these amputees make them an ideal population for aggressive rehabilitation, but also reveal the limitations of current technologies of prosthetic attachment. Current European rehabilitation programs for transfemoral amputees with osseointegrated implants require slow progressive weight bearing determined subjectively by clinicians. While this method is advocated for two stage surgical procedures, “the development of new surfaces and clinical techniques has enabled a marked reduction of the initial healing period, even to the point of an immediate/early loading of implants that show high primary stability.” In addition, the physical limitations of warrior amputees using sockets include: heat/sweating in the prosthetic socket, skin irritation, and inability to walk on challenging terrain. To further complicate rehabilitation efforts, a significant number of returning service men and women have short residual limbs for which socket technology is not suitable.

Utilizing metallic implants as a means of biological fixation has been the objective of orthopedic surgeons over the past two centuries. However, controlling osteogenesis at the implant interface, which is essential for providing strong skeletal fixation, remains challenging. Regulated electrical stimulation has proven effective in fracture healing and non-traumatized bone models, but has not been investigated in a percutaneous osseointegrated implant system. One advantage of the veteran patient population is that an orthopedic implant protrudes from the residual limb functioning as an exoprosthesis attachment and may operate as a potential cathode for an external electrical stimulation device.

Therefore, the objective of the proposal is to build upon the previous, well proven, clinical success of electrically induced bone growth used to augment fracture healing and expand this technology to accelerate osseointegration in the percutaneous model for veteran and warrior amputees. Since osseointegration technology is still fairly new for lower extremity amputees and not utilized clinically in the United States, ways to increase its efficiency are still developing. The investigator is addressing this limitation by developing an Osseointegrated Intelligent Implant Design (OID) system which has been awarded a United States provisional patent with the University of Utah Technology Commercialization Office as a novel rehabilitation tool to improve osseointegration technology. The addition of electrical stimulation may increase the rate, magnitude, and quality of initial skeletal attachment to the osseointegrated prosthetic stem.
18.1.1 Research question / hypotheses:

To validate the general hypothesis that electrical stimulation will increase skeletal attachment, a two phase project has been designed that utilizes in vitro, in vivo, and in silico modalities to confirm the safety and efficacy of this technology prior to implementation in veteran and warrior amputees. The specific hypotheses for this model are founded on histological assessment, mechanical testing, and finite element analysis. The research hypothesis from the Bloebaum group that is most relevant to the Center is that

**Finite element based simulation analysis of veteran and warrior amputee residual limbs imaged with computed tomography scans will reveal that safe and effective current densities and electric fields will be attainable at the bone-implant interface.**

To evaluate this hypothesis by creating the necessary simulation infrastructure, the Center proposes the following technical aims:

**Aim 1:** Develop segmentation and mesh generation support that is adapted to orthopedic applications like this one and to facilitate the rapid generation of accurate geometric models of amputees and the implants and stimulation electrodes required for these modeling applications. (Image Based Modeling TRD)

**Aim 2:** Accelerate the computations required to simulate electric fields and current densities for any selected boundary conditions of implant and skin surface electrodes and provide extensive visualization of the results that include certainty and parameter sensitivity. (Simulation and Visualization TRDs)

**Aim 3:** Develop estimation and optimization strategies for locating skin surface electrodes in ways that maximize the growth potential for electrical stimulation of osseointegration. (Estimation TRD)

18.2 Background

The remaining biomedical hypothesis that drive the Bloebaum group are as follows:

**Hypothesis 2:** Electrical stimulation will increase the mineral apposition rate of cortical bone at the periprosthetic interface when compared to control implants.

**Hypothesis 3:** Enhanced bone remodeling, signified by differences in gray levels analysis from scanning electron microscopy (SEM) will demonstrate expedited remodeling near the electrical implants compared to contralateral controls.

**Hypothesis 4:** Higher forces will be required to remove implants in the medullary canal when subjected to controlled physiologic mechanical push out tests of the electrical implants.

Shortly after Galvani discovered that an accidental electrostatic shock resulted in muscle fiber contraction of an immobilized animal, electrical stimulation drastically altered the field of medicine. While the exact reason for the phenomenon was largely unknown at the time, advancements in modern science have demonstrated that endogenous electrical signaling affects tissue growth, repair, and regeneration. In general, all animals are complex electrodynamic systems with large but stable gradients that direct cell migration. Messages are transmitted from adjacent cells and the neighboring environment by a plethora of available mechanisms, including mechanical deformation which affects electrical polarization within a cell membrane.

Early research by Brighton and Friedenberg used the concept of electrical stimulation for bone regeneration in the 1960s and 1970s, demonstrating that direct current (DC) could be used to repair non-unions in a shorter period of time than traditional healing methods. Additional models have investigated bone formation with restrictive weight bearing, causing induced osteopenia, and using low-frequency electrical fields, stimulating osteogenesis with a thirty-one percent increase in osteogenic activity between controls and electrically stimulated limbs.

While researchers in the field of electrical stimulation have paved the way for understanding the mechanism for osteoblast matrix deposition with electrical stimulation, inadequate understanding has limited the expansion of this technology. While there are many cases of successful healing of non-unions and fracture healing models, examples of patient discomfort and failed attempts are replete in the literature. The problem with electrical stimulation occurs when scientists and clinicians control the wrong electric metrics and concentrate solely on current magnitudes. Previous researchers have looked to current as the “magic bullet” for fixing the approximate
500,000 non-unions which occur annually. However, repeatability between models has been limited due to joule heating complications and not determining current densities. In fact, all manufactured biomedical devices must be limited to a current density less than 2 mA/cm², as outlined by the International Electrotechnical Commission, to prevent localized tissue necrosis and patient discomfort.

The advantage of using veteran amputees with osseointegrated implants is that a percutaneous post serves as an ambulatory aid and may be developed as an exposed cathode for electrical stimulation. The presence of an osseointegrated implant does not require additional surgical procedures to insert electrical components, allowing the device to be controlled externally and preventing further risk of infection. Therefore, by understanding the method of current injection into the residual limb of veteran and warrior amputees, an electric field on the magnitude of 1–10 V/cm may be established, controlled, and measured at the implant interface. It is hypothesized that this will allow safe levels of electricity to be delivered, capable of inducing osteoblast migration and improving skeletal attachment. An electric field of this degree will increase the quantity and quality of bone at the implant interface and improve the prospects for accelerated rehabilitation and skeletal fixation for an amputee. Use of electrical stimulation has not been investigated as a modality to accelerate osseointegration in an intramedullary prosthetic implant and this technology presents numerous opportunities for translational research to improve patient care.

18.2.1 Investigator profile

Roy Bloebaum, Ph.D. is Research Professor and Albert and Margaret Hofmann Chair in Orthopedic Research at the University of Utah. He is internationally recognized as an expert in bone healing and total joint replacements. He holds positions as a research professor in Orthopedics, Bioengineering, and Biology. Dr. Bloebaum is a Research Career Scientist and Co-Director of the VA Bone and Joint Research Lab, which is a collaborative research program with the VA Salt Lake City Health Care System Research and Development Program and is mainly supported by the Veterans Health Administration Research and Development Merit Review Program. Dr. Bloebaum’s publications include over 115 peer reviewed manuscripts on bone and total joint replacement related topics and he has been a guest lecturer on these topics all over the world. Dr. Bloebaum’s current research focus is developing alternative prosthesis attachments for warrior amputees and this concept is funded in part by the DOD, TATRC, NIH and PRMRP.

Since the osseointegration research has the potential to influence rehabilitation clinicians, orthopedic surgeons, and scientist alike, Dr. Bloebaum has established collaborative support with Dr. Joseph Webster M.D., (head of Rehabilitation for amputee care at the SLC VA), Dr. Peter Beck M.D., (orthopedic surgeon and voluntary staff physician for the SLC VA) and Dr. Larry Meyer, M.D., Ph.D. (Associate Chief of Staff for the SLC VA).

18.3 Significance

This DBP is extremely well aligned with the goals of the Center and will drive substantial progress in all of the TRDs. Thematically, the project builds on the established strengths of the Center in bioelectric fields, but expands the application of that knowledge into completely novel and highly significant directions. There are close parallels between this DBP and Dr. Triedman’s directed at simulating defibrillation in the heart (Section 19). Both DBPs require the creation of highly detailed, patient specific geometric models from image data and then seek to use these models to simulate the effects of artificially applied electric fields on biological tissues. Both DBPs require extensive support for image based modeling, for visualization of image data, and for sophisticated visualization of the simulation boundary conditions and their results. Both DBPs also share enormous potential for the creation of novel estimation approaches with which to predict ideal parameters for applying the external electric fields. In this DBP, the relevant parameters include the placement of the surface electrodes that form the anode for the application of stimulation and the value of the applied field. To further reinforce the similarity between this and the Triedman DBP, preliminary results included below were generated with Seg3D and SCIRun using many of the same specific tools and settings as the defibrillation project.

While progress on this DBP has already been substantial, there are many additional hurdles that the Center will need to address in the future, challenges that represent ideal test beds for all the TRDs. Specific examples of these challenges include the following:

Image based modeling: A major step in the work flow of this project is the creation of accurate and detailed geometric models from CT imaging of actual patients and animals used for validation.
Visualization: Visualization for this DBP includes both the viewing and quality control of the raw image data and the visualization of simulation results. Of special importance to this project is the need to capture uncertainty in the parameters of the model and visualize the consequences of this uncertainty in terms of relevant electric stimulation parameters. Investigators will need to determine the range of useful positions of the surface electrodes and the consequences of variations in those positions. The research will benefit greatly from visualizations of the impact of variations of the applied field strength and the impact of variations in electrode contact impedance. Investigators will wish to see these impacts displayed in terms of variations in electric potentials, spatial current densities, and the associated rates of bone growth. Thus there will be a need for highly integrated display of scalar, vector, and even tensor quantities that may be time dependent and have associated uncertainties.

Simulation: Simulation is at the very core of this project and virtually all proposed improvements in simulation infrastructure will assist with this DBP. Computation time is a significant limitation in problems such as this, in which many iterations will be required to determine optimized settings for relevant parameters. Thus, any progress on computational efficiency will have enormous impact. The problem is inherently multiscale in that it includes macroscopic application of electric fields through electrodes that are embedded in the bone and applied to the surface. The actual effect of the field, however, is entirely microscopic. Comprehensive simulation approaches must include multiple levels of interaction to provide comprehensive guidance, especially for implementing this approach in patients. The scope of experiments in humans is much less extensive than in animals so that the burden shifts to careful, patient specific simulation to ensure safe and effective translation of the technology. Validation and verification are essential elements of projects like this and the Center will support the quantitative comparison of experiments and simulation results that will both test and confirm the accuracy of simulation. We anticipate that such testing will drive new needs in the numerical solutions and computational implementation of those simulations.

Estimation: This DBP offers an ideal example of the need for estimation and optimization specific to the problem at hand and to the specific subject to which the therapy will be applied. Estimation can go beyond testing “What if?” and begin to answer the question “Which is best?”. Implementing appropriate schemes to carry out this estimation process will be challenging because there are few standard approaches that are guaranteed to provide the desired results. However, as with the defibrillation DBP (Section 19), we will develop and apply both existing and novel estimation and optimization approaches, measuring their effectiveness based on parallel numerical and experimental studies using both in silico and in vivo models.

The Center will play an essential role in the simulation component of this DBP; without a full suite of appropriate software that is well matched to the specific application domain, progress by the investigators will be severely limited. For many aspects of this problem, standard tools do not exist, especially not for the proposed estimation approaches. It is also evident that simulation is highly integrated into the research proposed by the DBP team and has already played a role in showing viability of the entire concept (see below). We also note that simulation of bone growth by electric fields has been reported in the literature for many decades, but its impact has remained limited, in part, because of an absence of planning tools with which to create workable electrode configurations. The fact that the bone implant itself provides one of the electrodes for this application and that simulation provides a patient specific means of evaluating and selecting the location of the second electrode(s) makes this a breakthrough application that simply requires simulation for guidance and optimization.
18.4 Rationale and preliminary results

The basic computational approach in this DBP has been established through ongoing studies and documented in publications (see below), leaving little doubt about the basic rationale for our approach. We have shown that it is possible to create patient specific models from CT image data from amputees that form the basis of simulations of applied electric field for osseointegration. Together with the investigators of the project, we have demonstrated the need for customized models over schematic versions created by artificially truncating full-limb models. This need will be even greater in the planned studies of what is known as heterotopic ossification (HO), an overgrowth of mature osseous bone in neighboring soft tissue. HO is more likely to occur in victims of explosions; creating prosthetics for such patients requires extreme attention to the specific shape of the residual limb.

18.4.1 Preliminary results

Figure 18.1 shows an example of a residual limb imaged using CT and segmented with Seg3D. Also visible are the effects of heterotopic ossification, regions of bone that must be taken into account in creating patient specific models of the limb suitable for simulation.

![A B]

Figure 18.2: Simulation results for implantation. Panel A shows the volume rendered bone and trunk structure from a patient with the implanted electrode in the residual bone and the layout of external band electrodes applied to the skin surface. Panel B shows the resulting simulation results for the electric field strength along the electrode-bone interface.

Figure 18.2 shows an example of the trunk of a patient together with the electrode configuration and resulting simulations of electric field strength along the implanted electrode. The goal of the parameter estimation process is to locate the skin electrodes and apply appropriate electric potential to create a uniform electric field along the length of the implant.

18.5 Methods

The main goal of the Center collaboration with this DBP is to develop a comprehensive and validated computational infrastructure that will support the creation of patient specific models of the residual limbs of amputees to assist in the evaluation and treatment by means of osseointegration. This DBP is another example of the image based modeling and simulation pipeline that serves as a central framework of the Center’s research and development. This DBP will require support from all the TRDs to be maximally successful, which leads to the aims listed in Section 18.1.1.

Achieving each of these specific aims will require dedicated development and research within all Center TRDs; without the Center, the investigators will be unlikely to incorporate patient specific modeling and simula-
tion into their research, as the tools for efficient creation and simulation of these models are either not available or involve considerable costs. The alternative would be an enormous series of animal experiments, which would, at best, only partially mimic the conditions in actual human amputees. In order to validate and verify both the simulations and the effectiveness of the overall project, the research of the investigators includes animal experiments using a rabbit model with osseointegration implants placed in the hip and then connected with external portable circuitry that provides controlled application of stimulation currents. The stimulation electrodes were implanted into the proximal femur and the superior musculature in the hip.

![Acquire CT images](image1.png) ![Segmentation](image2.png) ![Compare measurements and simulation](image3.png) ![Identify implanted electrodes](image4.png)

Figure 18.3: Workflow for animal validation experiments. The figure shows the workflow for carrying out animal experiments to validate the concept of the electric stimulation of ossification around the metallic prosthetic implant. Image based simulation begins with CT imaging of the limb under study; segmentation of the relevant tissues of the limb, including implanted electrodes; construction of subject specific model; and simulation of electric field strength.

Figure 18.3 shows the workflow in animal experiments just beginning. Dr. Bloebaum and his group have developed a rabbit model in which they place metallic implants into and near the femur of the animal, respectively, and then apply a controlled current by means of external, portable electronics. Following a period of 3–6 weeks under constant stimulation, the animal is then anesthetized and receives multielectrode recording needles placed in the tissue near the femur; acute measurements provide the distribution of electric potential in the limb. The animal will then be sacrificed and the leg removed and imaged with CT. Using the steps in Figure 18.3, the investigators, using software from the Center, will create customized models and then carry out simulations to calculate the electric fields from the simulation electrodes and compare those results to the measurements. Histological evaluation of the femur after stimulation will also provide indications of the rate of bone growth into the surface of the implant as a function of the applied electric currents. Evaluation of these results will provide validation of both the concept of electrically stimulated bone growth into a metallic implant and the use of simulations to analyze and guide the location of the stimulus electrodes as well as the associated applied currents.

Once validated by animal studies, the simulation model will become a suitable tool with which to simulate different electrode locations and stimulation protocols. This model will further guide animal studies designed to fully mimic the application of this concept in humans. The model will also form the basis of estimation approaches seeking to optimize the parameters of the protocol within appropriate constraints. We will use
sensitivity analysis approaches described in the Simulation TRD, Section 11.3.6.2 to determine the critical parameters in the stimulation and determine optimal values for those parameters.

Concurrent with the animal studies will be simulation studies using image data from human amputees, with the goal of translating animal results to the development of viable clinical systems for osseointegration. Here, too, sensitivity studies and estimation approaches will provide a means of predicting optimized electrode locations and stimulation protocols.

The role of the Center, throughout these studies, will be to work closely with the investigators to modify and extend the software to support the study needs. Each of the computational steps have associated elements in the Center software suite. Many of the research and development goals described in the TRDs for this proposal will apply to this DBP. Specific examples include improvements in segmentation and mesh generation, enhanced efficiency of simulation software through GPU based approaches, and novel estimation approaches that seek to optimize parameters of the stimulation electrode design, placement, and protocol.

### 18.6 Impact

Improvements in medical care and evacuation strategies on the field of combat have led to an increased number of veterans surviving disastrous war related injuries. While the improved survival rate is a medical advance, many veterans are returning from combat with amputations that require complex follow-up care, extensive rehabilitation, and expensive prosthetic services. Available documentation has shown that there are now over 1000 warriors with major amputations who have returned from the two most recent major military operations overseas. Of these, approximately 15% have lost multiple limbs and a significant number of returning service men and women have short residual limb for which socket technology is not an option or is rejected by the patient. Such patients may be better served with percutaneous osseointegrated implants. The potential worldwide impact of this technology is enormous, as residual land mines and explosives continue to maim residents in a number of recent war zones.

Development of an OIID system to improve rehabilitation regimens and increase bone remodeling is a translational research initiative which can assist clinicians and patients alike. Establishing a standardized mechanism to assess electrical stimulation will help drive new product development and directly help veterans and warriors. The advantage of the proposed testing protocol is that robust histological and mechanical tests will be conducted and provide the a complete assessment of electrical stimulation in a controlled experiment. Aside from the scientific usefulness, expediting skeletal attachment will directly reduce the length of rehabilitation for veteran and warrior amputees using osseointegration technology. Current load bearing protocols require a waiting period of 12–18 months post-operative before full weight bearing. However, osseointegration will vary between persons and individual rehabilitation programs will be necessary.

The computational support to be developed by the Center for this project will be essential for the application to progress beyond proof of concept animal studies and to really approach clinical application. Patient specific models will be essential, as will sensitivity and optimization studies to determine the critical parameters and their values. The strategies developed for this DBP will also have impact on other projects within the Center and the wider community. The same sort of sensitivity and optimization will benefit the defibrillation DBP and a host of other studies in which electrical stimulation can mitigate pain, control motor control (the Deep Brain Stimulation DBP), or stimulate muscle contraction in the heart and skeletal muscles.

Progress in this project will yield a series of papers as well as the potential for product development. The project has already produced conference presentations and a journal article, with a second journal article in preparation. The potential for product development is clear and funding for the project comes in part from the Technology Commercialization Office of the University of Utah.