# HHMI Faculty Research Award (FRA)

## Cover Sheet

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<th>Title</th>
<th>Mathematical models to predict nerve activation to develop a treatment for phantom limb pain.</th>
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<tr>
<td>Name of PI</td>
<td>Katharine Polasek</td>
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<td>Department of PI</td>
<td>Engineering</td>
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<tr>
<td>Name(s) of collaborators</td>
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</tbody>
</table>
| Undergraduates Associated with Project: (Give names if known or simply numbers if students are not yet identified) | John Boss  
Payton Hoff  
Brooke Draggoo  
TBA |
| Projected start date | January 2015 |
| Projected end date | December 2015 |
| Total Budget Requested | $14,641 |
Phantom limb pain adversely affects 64% of amputees and most treatment options are ineffective. The long term goal of my research is to develop a non-invasive, home-based therapy for treating phantom limb pain. This proposal focuses on the development of mathematical models for predicting effective electrode configurations and stimulation parameters in order to activate different portions of the nerve. Following this work, an algorithm will be developed to assign stimulation levels to each electrode and eliminate the need for perfect electrode placement.

The first objective of this proposal is to determine which physiological and/or anatomical differences between motor and sensory axons explain the selective activation of sensation that has been found experimentally. These differences will be used in a mathematical model to predict axon firing and explain the different excitation.

The second objective of this proposal is to determine an electrode configuration that predicts differential activation of the nerve. A previously-developed anatomical 3D model of the arm will be combined with the model from the first objective. This combination of models will be used to evaluate different electrode configurations. An effective electrode array will allow adjustment of the relative electrode activations to change which part of the nerve is active.

This funding will provide significant summer research experience for at least two Hope students and further the field of biomedical engineering.
PROJECT DESCRIPTION

Significance of Work

Phantom limb pain is a post-amputation phenomenon involving pain and/or extreme discomfort in the missing limb. In 2005 there were about 41,000 upper limb amputees and 623,000 lower limb amputees in the United States alone [1]. An estimated 64% of these individual have some form of phantom limb pain that significantly affects their daily life [3]. Conventional pain reduction strategies such as medication or neural revision surgery have had limited success [2].

Mirror therapy and Transcutaneous Electrical Stimulation (TENS) are two experimental treatments options for phantom limb pain. Mirror therapy is a visual treatment that allows subjects to see their intact limbs reflected in a mirror as if they were the phantom limbs [4]. Subjects attempt to move both limbs simultaneously and receive visual input from the mirror that they are successful. In one study, the therapy was given 15 minutes a day and subjects reported significant improvement over the four weeks and beyond [5]. TENS has been used to treat a variety of painful conditions with inconsistent results compared to placebo. Mulvey et al. used trial and error electrical stimulation of the residual limb in amputees in an attempt to reduce pain in either the phantom or the stump. While not a controlled study, they found a decrease in pain after a single session when TENS sensations were evoked in the phantom limb [6].

The therapy being developed here will combine these two concepts by electrically activating sensation in the missing limb that matches visual information about the limb (Figure 1). It is hypothesized that this simultaneous visual and somatosensory information will decrease pain in the phantom limb. **The goal of this research is to develop a non-invasive, home-based therapy for treating phantom limb pain. This proposal focuses on the development of mathematical models to predict effective electrode configurations and stimulation parameters to activate different portions of the nerve.**

![Figure 1: Example of treatment.](image)

Electrodes are applied over the nerves at the elbow to elicit sensation in hand with synchronous visual confirmation of the sensation. In this example pressure is applied to the thumb of the prosthesis to give visual confirmation of the stimulated sensation.

Objectives

Differential activation of axons can usually be predicted by location (axons closer to the stimulating electrode are activated prior to those further away) or diameter (larger diameter axons at the same distance are activated prior to smaller axons). Mechanoreceptor axons, the subset of sensory axons being targeted, range in diameter from 6-12 µm, smaller than the 12-20 µm diameter motor axons. However, surface electrical stimulation at the elbow near the median nerve produces sensation in the hand prior to visible muscle contraction. Based on computer simulations of our experimental conditions, location alone does not explain the activation of smaller mechanoreceptors prior to larger motor fibers. **The first objective of this**
proposal is to determine which physiological and/or anatomical differences between motor and sensory axons can be used to explain the selective activation of sensation.

One requirement of a home-based therapy is that the user be able to apply electrodes to the skin and obtain the desired sensation. To accomplish this, an array of electrodes with adjustable relative activations is needed. In the summer of 2014, an anatomically-based 3D finite element model of the arm was developed for the purpose of developing such an array. This model includes different tissue properties for the skin, fat, muscles, bones and blood vessels. It can be used to calculate voltages inside the nerve from each electrode on the skin surface. Then, axon models such as the one developed in the first objective will be used to help identify which portions of the nerve are active. The second objective of this proposal is to determine an electrode configuration that predicts differential activation of the nerve.

Methods

Many different mathematical models have been developed to predict axon behavior, the simplest of which includes ion channels at the nodes of Ranvier and assumes that the myelin in between the nodes is a perfect insulator. The most common model used to predict the effect of electrical stimulation is the MRG model (Figure 2A) [7]. This is a multi-compartment model where the compartments include not only the nodes, but also different intermodal regions. To date this model has been used to predict activation of axons in peripheral nerves and in the spinal cord [8-10] but its channel properties were derived from motor axons. In order to compare excitability between motor and sensory axons, the original MRG motor axon model will be modified to create a sensory axon model. The Bostock model (Figure 2B) is a two-compartment model with a single node and internodal space that was developed to investigate how neurons respond to ischemia [11] and was later used to explain differences between behavior of motor and sensory axons [12]. These two models will be combined to compare the response of sensory and motor axons to electrical stimulation. Since this will be a novel model, it is likely that the parameters from the Bostock model will not initially give expected results and further investigation will be needed to reproduce the experimental findings in simulation. Completion of this objective will also help determine which differences between the types of axon explain the different excitabilities.

![Mathematical models of axons](image)

**Figure 2:** Mathematical models of axons. (A) Multi-compartmental model developed by McIntyre Richardson and Grill which includes ion channels in the intermodal regions. (B) Two-compartmental model developed by Bostock and used to explore differences between motor and sensory axons.
The model was originally written in NEURON, a neuroscience software package [13]. In the summer of 2014, my students and I combined this program with Matlab to run simulations using external voltage fields. To test these new models, the extracellular voltages at each position along the axon will be calculated from a point source electrode placed 500 µm away. Given these voltages, NEURON will be used to determine whether an action potential fired. By varying the stimulation values the activation threshold can be estimated. A sensitivity analysis will then be performed on each membrane parameter to determine which ones contribute most significantly to the threshold.

The second objective will be met using a finite element software package called Ansys Maxwell. Maxwell loads a 3D CAD model of the arm and allows assignment of different electrical properties to different tissue types (Figure 3). This model will be used to look at which portions of the nerve are activated with different electrode configurations. The model in has two large electrodes on the skin, the cathode in red and the anode in black. Since electrode movement has resulted in variations in sensation location, the goal is to find a single electrode configuration that can mimic the movement of electrodes. Two sample electrode configurations are shown in Figure 4, which include several cathodic electrodes with a single anodic electrode.

![Figure 3: The arm modeled in Maxwell. The median nerve cross section is shown on the left.](image1)

![Figure 4: Sample electrode configurations. The smaller electrodes (orange) in each panel are the cathodes and the larger rectangle (blue) is the anode.](image2)

For each electrode configuration, the voltage inside the nerve will be calculated using Maxwell. For axons placed within each fascicle (purple circles in inset of Figure 3), NEURON will use the voltages along the axon to predict firing. The specific organization of the axons and fascicles in the median nerve vary from person to person. The arrangement and size of fascicles within the nerve has been found to affect axon firing [14] so this variation will need to be taken into account. A range of nerve cross sections, with different number and size of fascicles will be tested based on reported values. Ten to twenty-five fascicles will be included, ranging in size from 0.2 to 1 mm diameter [15, 16]. Simulations will be run with axons from mechanoreceptors (6-12 µm) randomly placed within the fascicles. We will look for evidence that multiple fascicles or groups of fascicles can be selectively activated using different electrode positions.

Since this is a model of realistic anatomy but not the anatomy of the person we are testing, the effect of changing electrode locations will be used to guide electrode location and relative activations in actual experiments rather than to prescribe set values.
Expected Outcomes

The first objective will look at describing how the physiological differences in the axon types could explain their excitability differences. This will be useful for our modeling problem but will also be a significant contribution to the field of neuroscience knowledge.

The second objective will give the preliminary information necessary to create an algorithm to control sensation location. After choosing the best electrode configurations, the model will be used to develop a simple way for the user to adjust which part of the nerve is active. This algorithm will then be validated experimentally prior to use in a home-based system for individuals with phantom limb pain.

Potential Difficulties

Preliminary findings with sensory and motor axon models have not replicated our experimental results. It is possible that further investigation will not improve this outcome. If this occurs, the second objective can still be tested using the motor axon model and looking at how the different electrode locations activate different portions of the nerve.

Connection to other HHMI Programs

Several of my research students are participating in the FACES mentoring program, both as mentors and mentees. One of my new students is a freshman and was encouraged to come speak with me by her mentor, showing the benefit of connecting upper and lower classmen students from the beginning. Many of these FACES students, as part of the Society for Women Engineers, also helped organize and run the Middle School Girls Engineering Day last spring. This included a tour and demonstration in our research lab as well as a biomedical engineering project.

With this funding, I will be able to mentor two additional Hope engineering students on an innovative biomedical engineering project. This will help them to mature into leaders in STEM fields. One of my students last year was a HHMI Research Scholar and he is providing valuable mentorship and experiences as I increase the size of my research group.

Plans for External Funding To Continue Work

In June I submitted a R15 proposal to the National Institutes of Health for $225,000 over three years. I should hear back from them in the next month or so. I also plan to submit a proposal to the Michigan Space Grant Consortium, probably for both a student fellowship and a research seed grant.

Timeline

Spring 2015:  
• Verify that sensory axon parameters from the Bostock model match other experimentally reported values and convert to the correct form for the MRG model.
• Start evaluating different electrode configurations on the basis of differential activation of portions of the nerve.

Summer 2015:  
• Perform a sensitivity analysis to determine which parameters contribute significantly to the axon threshold.
• Combine the two models (if possible) to obtain the most accurate evaluation of electrode configuration.

Fall 2015:  
• Start developing an algorithm to adjust the relative stimulation levels of the electrodes as if the electrodes were being moved along the surface of the skin.
BIBLIOGRAPHY/REFERENCES
**Biographical Sketch of Katharine Polasek**

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**a. Professional Preparation**

University of Michigan, Ann Arbor, MI  
Mechanical Engineering  B.S.E.  2001

Case Western Reserve, Cleveland, OH  
Biomedical Engineering  M.S.  2003

Case Western Reserve, Cleveland, OH  
Biomedical Engineering  PhD  2007

**b. Appointments**

Assistant Professor of Engineering, Hope College, Holland MI, 2010-present  
Postdoctoral Fellow, Musculoskeletal Research training grant, CWRU, Clev. OH, 2008-10  
Research Associate, APT Center, CWRU, Cleveland OH, 2007-2008  
Graduate Research Assistant, Functional Electrical Stimulation Center, Clev. OH, 2001-07  
General Lab assistant, Otopathology Laboratory, University of Michigan, 1997-2000

**c. Publications**

Forst JC, Blok DC, Slopsema JP, Boss JM, Heyboer LA, Tobias CM, Polasek KH. Surface Electrical Stimulation to Evoke Referred Sensation, *Journal of Rehabilitation Research and Development* (submitted)


d. Synergistic Activities

Currently mentoring seven undergraduate students, six of them are from underrepresented
groups in the field of engineering
Faculty Advisor for Hope College Society for Women Engineers
Co-developed a program to increase recruitment and retention of female engineering
students at Hope College

e. Collaborations & Other Affiliations

(i) Susan Brown (Director, Center for STEM Inquiry, Hope College); Patrick Logan (Vice
President Orthotics/Prosthetics Corp., Mary Free Bed Rehabilitation Hospital); Matthew Schiefer
(Investigator & Adjunct Instructor, APT & FES Centers of Excellence, Case Western Reserve
University); Dustin Tyler (Associate Professor, Case Western Reserve University).

(ii) Graduate and Postdoctoral Advisors: Dr. Dustin J. Tyler and Dr. Robert F. Kirsch (Case
Western Reserve University).

(iii) Research Advisees: Johanna Forst (University of Rochester); Derek Blok (Wayne State
University).
CURRENT AND PENDING SUPPORT

Pending: NIH R15 5/2015-4/2018
Surface Electrical Stimulation of Referred Sensation with Future Application to the Treatment of Phantom Limb Pain.
The goal of this proposal is to develop a non-invasive treatment option for individuals with limb loss. Treatment will include electrical activation of sensation in the missing limb paired with matching visual affirmation of the sensation. Funding for 3 years was requested for a total of $225,000.
Role: PI

Towsley Research Scholar Program Runner up, Hope College 5/2013-5/2014
Sensory Stimulation for the Treatment of Neurological Disorders
The goal of this project was to develop sensory stimulation as a method of activating referred sensation. This award covers a 1 semester sabbatical and summer funding for 1 student.
Role: PI

Deans Start-up Funds, Division of Natural and Applied Sciences, Hope College 7/2010-12/2015