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14. ABSTRACT This project is focused on the development of a radically new class of prosthetic devices that will mimic more closely the full range of sensory and motor capabilities of natural limbs. To this end, we have made initial progress on four integrated projects to advance the development of neuroprosthetic limbs including: 1) creation of a sensory neural interface to provide amputees with tactile and kinesthetic feedback from their prosthetic limb, 2) improving the biocompatibility of implanted neural interface electrodes, 3) development of a virtual reality training and testing system for neuroprosthetic limbs, and 4) development of prosthetic hardware testing equipment and procedures. To date, we have completed pilot experiments to characterize the somatotopic organization of neurons in the dorsal root ganglia for the creation of a sensory feedback neural interface. We have completed pilot experiments to evaluate histologically the tissue response to electrodes implanted chronically in DRG, dorsal roots, and spinal cord. We have designed and developed a virtual reality training system based on BCI2000, creating custom software to greatly extend the functionality of BCI2000. Finally, we have developed a test jig to determine compliance with ISO standards for prosthetic hardware, and we have begun testing prosthetic feet.					
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INTRODUCTION

Advances in body armor and life-saving technology have increased survival rates of severely injured military personnel. Unfortunately, the survivors of improvised explosive devices used in gulf conflicts are often left with amputations and/or spinal cord injuries. The increase in amputations and paralysis among military personnel requires significant advances in prosthetics and functional electrical stimulation (FES) systems such that the soldiers can return to the field if they desire or to productive civilian lives. This project is focused on the development of a radically new class of prosthetic devices that will mimic more closely the full range of sensory and motor capabilities of natural limbs. By providing a communication link between the prosthesis and the user's nervous system, our goal is to integrate the prosthetic limb as a natural component of the user's sensorimotor apparatus. Significant progress has been made toward this goal, but there is still much work to be done, particularly in the areas of restoring sensory feedback, improving the electrode-neuron interface, user-training, and prosthetic durability. Project 1 deals directly with the issue of providing somatosensory input to soldiers with amputation or paralysis. Project 2 deals with improving the chronic stability of the neural interface and will test novel polymer surface modification methods for improving the long-term reliability of the implanted microelectrodes. Although neural control is the ultimate goal of our work, we believe that there is useful control information available in the muscles of the residual limb. Project 3 uses virtual reality to place patients in an environment with a simulated neuroprosthesis. In this environment, we can discover the degree of remaining electromyographic (EMG) signal content and begin to train patients to control their neuroprosthetic. In this way, the virtual environment serves two important purposes: 1) testing algorithms for myoelectric and/or neural control, and 2) training the user on neuroprosthetic control. This new class of prosthetic devices will literally look, feel, and function like natural limbs, but their internal construction will include complex machinery, motors, sensors, and control instrumentation. Therefore, durability is a major concern, especially since users will be more able to engage in rigorous physical activities. Through our interactions with soldiers returning to duty after amputation, we know that current prosthetics do not stand up to the harsh use of active amputees. Project 4 is designed to rigorously test currently available and newly design prosthetics to understand the components that fail and the ways to remediate these failures. In addition, we will build devices that can track prosthetic use and thus provide information on the use in terms of both distance traveled and force imparted.

BODY

Project 1. Develop a somatosensory neural interface (SSNI)

The overall goal of project 1 is to restore natural sensations of limb posture and movement through multichannel microstimulation of the normal afferent pathways involved in proprioception. Two objectives must be met to achieve this overall goal. First, we must identify an appropriate location in the somatosensory nervous system for implanting microelectrode arrays to stimulate afferent neurons. The ideal site for microstimulation is one in which the neurons for each body location (somatotopy) and afferent modality (e.g. muscle spindles, tendon organs) are colocated, allowing a single electrode to activate multiple neurons of a similar class (i.e. homonymous afferents). We will examine the somatotopic organization of afferent fibers at the DRG, dorsal root, and dorsal root entry zone levels of adult rats to create detailed somatotopic maps for each level.

Multiple independent channels are needed to convey limb-state information for the whole limb, and we must evaluate the extent to which afferent microstimulation conveys meaningful information to the brain. Our second objective will be to quantify the amount of information that can be transmitted by multichannel afferent microstimulation. This will be tested in a cat model.

Objective 1: Characterize somatotopic organization of primary afferent neurons in the DRG, dorsal roots, and dorsal root entry zone of spinal cord.

Results: We have completed 5 pilot experiments in rats to develop the procedures for mapping the receptive field locations and receptor types in the DRG. We adapted our DRG recording procedures for the cat to do similar procedures in the rat. Briefly, these procedures involve making a small laminectomy at the L4/L5 level. Reference and ground electrodes for the recording system are placed in the epidural space along the spinal cord. Next, a recording electrode is positioned in a micromanipulator. The tip of the electrode is inserted into the DRG near the center. Starting superficially, neural recordings are made at various depths, moving in 50 μm steps from the dorsal to the ventral surface of the DRG. At each depth, the receptor field location and receptor type are noted for all neurons recorded at that site. Figure 1C,D show the map of limb-segment areas that are used to document the receptive field locations.

Plans: We have determined that the most reliable and accurate procedure for creating these maps will be to use a multisite electrode array that allows concurrent sampling from multiple locations across the depth of the tissue. We have identified an electrode array from NeuroNexus Technologies that is suitable for these experiments (see Figure 1B). Subsequent experiments will be performed with multi-site electrode arrays of this type.

Objective 2: Quantify the amount of information that can be transmitted by

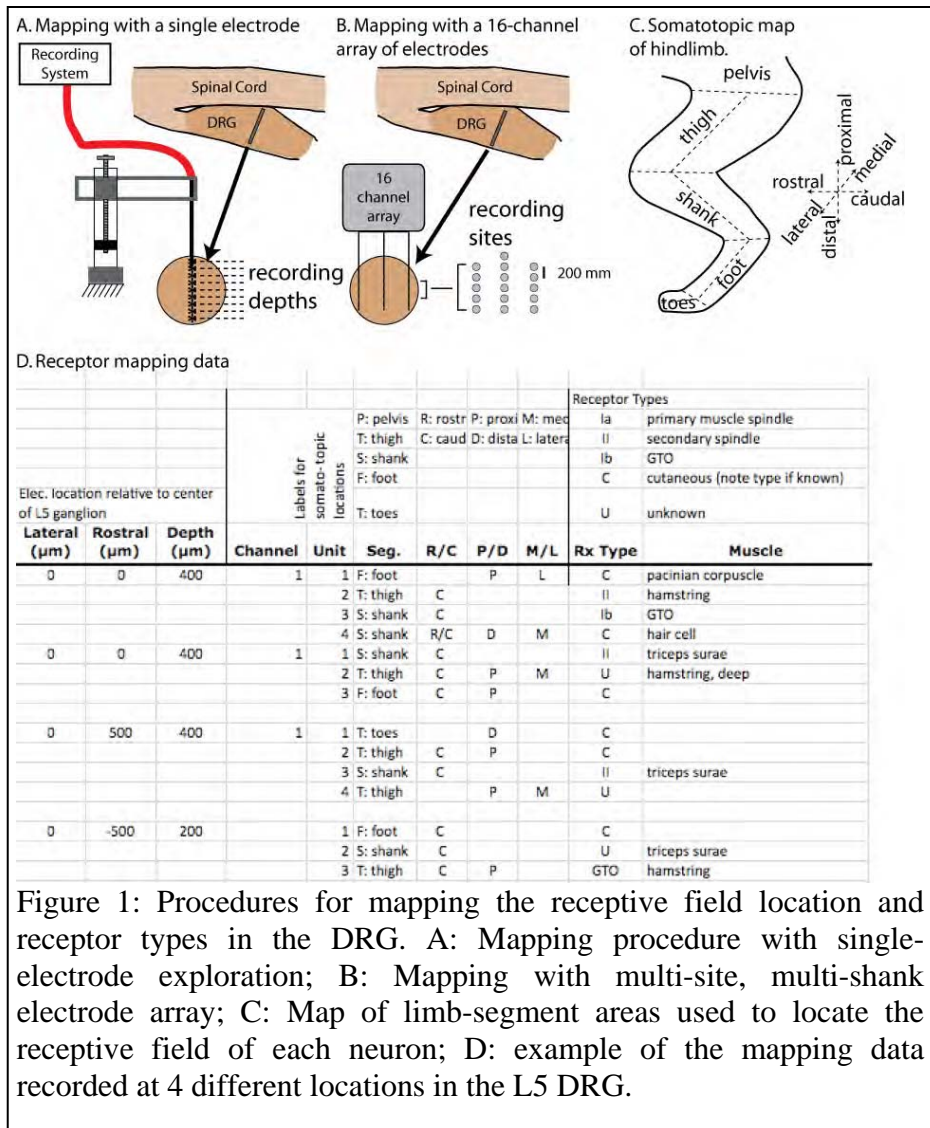


Figure 1: Procedures for mapping the receptive field location and receptor types in the DRG. A: Mapping procedure with single-electrode exploration; B: Mapping with multi-site, multi-shank electrode array; C: Map of limb-segment areas used to locate the receptive field of each neuron; D: example of the mapping data recorded at 4 different locations in the L5 DRG.

multichannel afferent microstimulation

Plans: We are currently developing the protocol for cortical recording and afferent microstimulation in cats. We will be submitting the protocol for review by the University of Pittsburgh IACUC in February, 2009. Once we receive approval from the Pitt IACUC, we will submit the protocol to the USAMRC. We expect to begin animal testing in May, 2009.

Project 2. Establishment of Neural interface stability and optimization

The implanted neural interface must remain stable throughout the lifespan of the user, but immune and inflammatory reactions at the implant site are known to degrade the performance of implanted microelectrodes. Since tissue reactions vary in different parts of the nervous system, our first objective is to compare the responses in the DRG, dorsal root nerve, and spinal cord. Our second objective is to test whether surface coating, with agents that encourage specific neuronal survival and growth and reduce inflammation, will be effective in improving the biocompatibility.

Objective 1: To compare the responses in the DRG, dorsal root nerve, and spinal cord.

First, we have investigated several commercially available neural electrode arrays and narrowed down to using the microelectrodes from Microprobe Inc for the planned experiments. These are stiff metal wire electrodes with parylene C coating that have shown to present good electrical performance and biocompatibility in neural tissue.

Several implantation experiments were done to develop and optimize the implantation, tissue processing and immunohistochemical protocols. Figure 2 and Figure 3 are representative H&E and immunofluorescent images of different implant sites. Electrodes were inserted on one side of the DRG or spinal cord and removed (serving as a stab wound control) and implanted on the contralateral side (implantation group) for 1 week.

Results: Differences are found between the stab wound and the 1-week implantation samples. This is expected as stab wound only causes an acute injury while the presence of implants could generate persistent stimuli causing more inflammatory tissue response. Similar results were found in previous work focused on brain tissue [1]. These preliminary results can by no means provide conclusive comparison due to the small sample size. However, they are here to demonstrate that we have developed solid implantation and staining protocols. The H&E staining provided a gross picture of the tissue inflammation and injury around the implant. The immunohistochemical marker for neuronal processes and

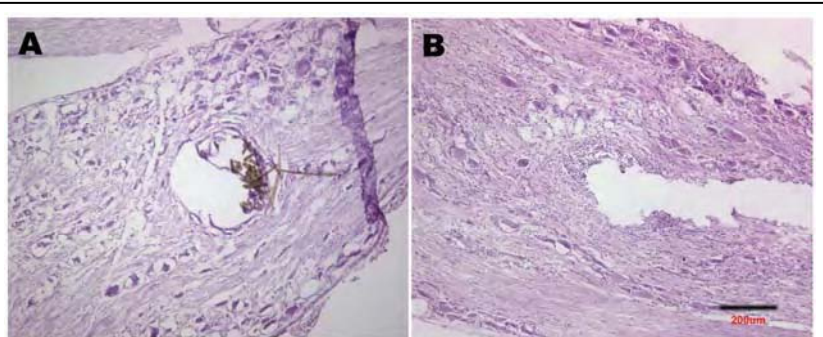


Figure 2: HE staining of the stab wound (A) and chronic implantation for 1 week (B) in DRG tissue. Tissue reaction to indwelling microelectrodes was characterized by a multilayered and densely packed region of cellular component, including many inflammatory cells (B). The pattern of reactivity around indwelling microelectrodes (B) differed from microelectrode stab wound controls (A), which consists of layers of cells surrounding the stab region with a much lower density and almost no inflammatory cells.

microglia further illustrated the cell type specific response.

Plans: Next, we plan to stain ECM matrix such as fibronectin and collagen (using Masson Stain) to obtain a more complete picture of tissue responses. Once these new staining protocols are finalized, we will be ready for a large-scale implantation experiments. The current plan is to examine 4 time points: 1 week, 2 week, 4 week and 12 weeks.

Objective 2: To test whether surface coating, with agents that encourage specific neuronal survival and growth and reduce inflammation, will be effective in improving the biocompatibility

Two types of coatings are being developed for the electrodes, one is for surface immobilization of neural adhesion molecules and the other is for the controlled release of anti-inflammatory drugs.

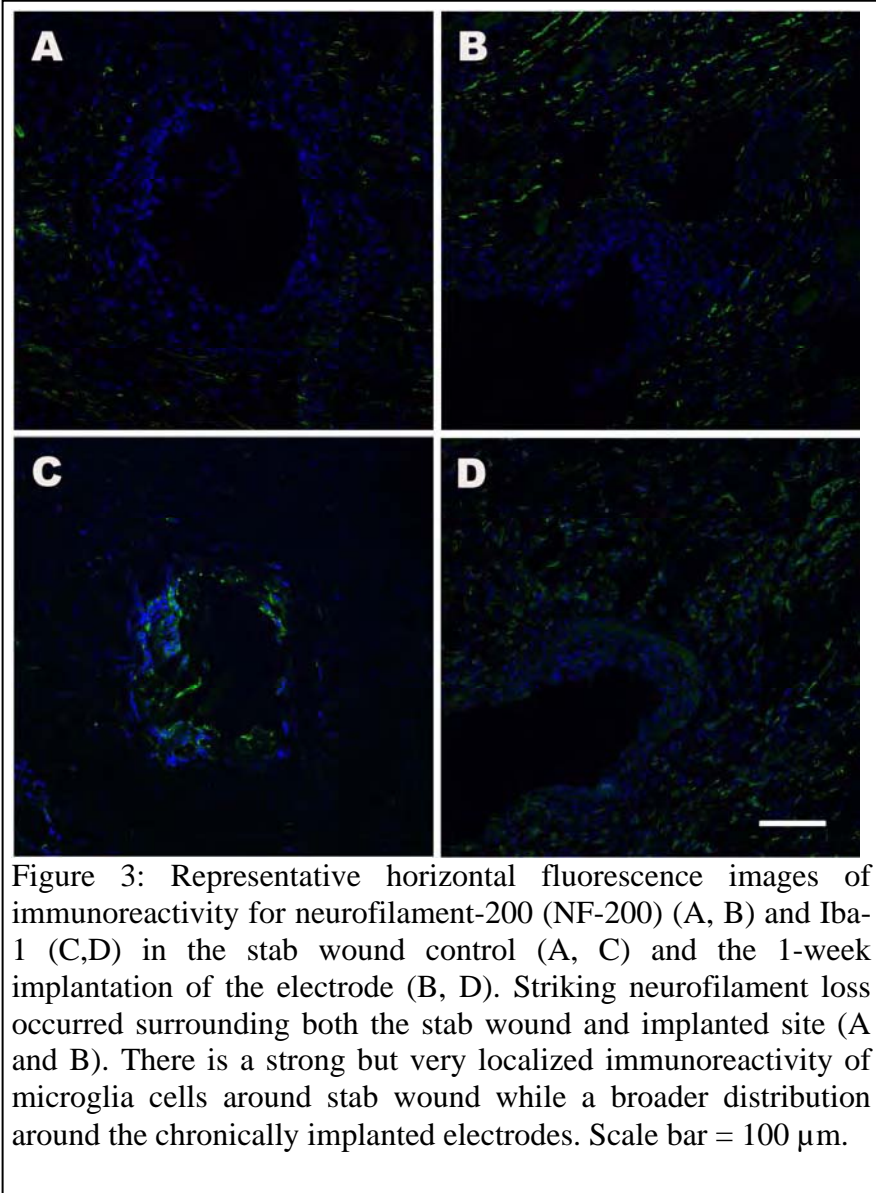
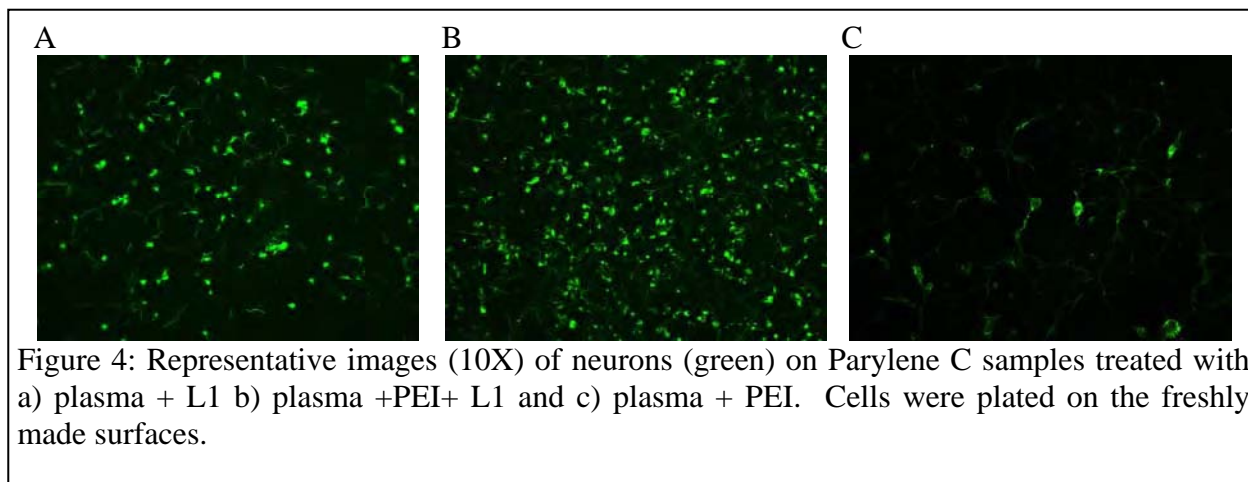


Figure 3: Representative horizontal fluorescence images of immunoreactivity for neurofilament-200 (NF-200) (A, B) and Iba-1 (C,D) in the stab wound control (A, C) and the 1-week implantation of the electrode (B, D). Striking neurofilament loss occurred surrounding both the stab wound and implanted site (A and B). There is a strong but very localized immunoreactivity of microglia cells around stab wound while a broader distribution around the chronically implanted electrodes. Scale bar = 100 μ m.

We have developed a surface immobilization method that can coat the surface of parylene C (insulating layer of the FMA electrodes) with neural adhesion molecule L1, which has shown in our previous work and by others to be potent in promoting neuronal health and growth while inhibiting glial cells. Several coating conditions were tested including: Parylene C + L1, Parylene C + plasma treatment (10 seconds) + L1 (1hr), and Parylene C + plasma treatment (10 seconds) + PEI (1hr) + L1 (1hr). Primary neuronal cells were plated on different surfaces and grown in culture for three days for evaluating the bioactivity of the coatings. Untreated parylene C samples do not support cell attachment and growth. Directly adsorbing L1 did not result in a neural adhesive surface probably due to the poor attachment of L1 on the untreated surface. Plasma treatment was found to be necessary and effective in promoting the attachment of the L1 protein onto the Parylene C surface, demonstrated by the excellent neuron attachment and neurite outgrowth. A layer of polyethyleneimine (PEI) added before adding the proteins further

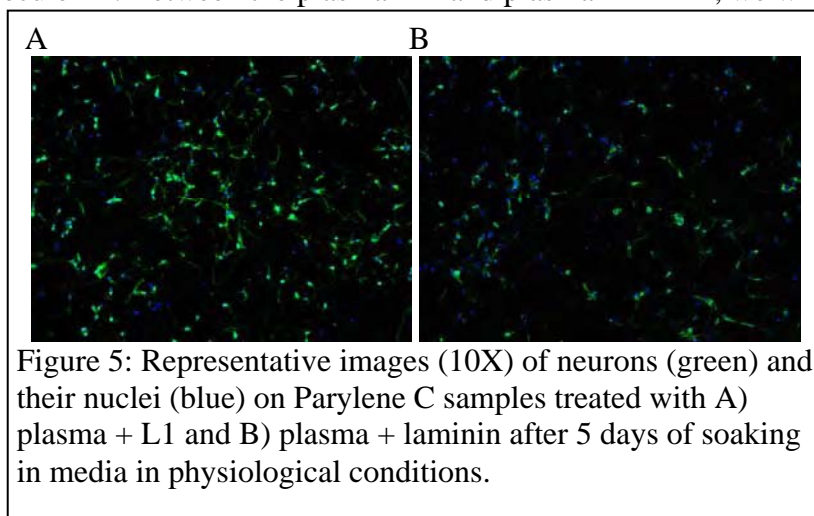


increased the neuronal attachment. Representative images are shown in Figure 4.

To test the stability of the coatings, the coated samples were soaked in the culture medium DMEM at 37°C for 5 days before the cell culture. The cell growth on the soaked samples was found to be as good as those on the freshly made samples, suggesting that the immobilized protein coatings were stable for at least 5 days in physiological conditions (Figure 5).

In conclusion, we have found a reliable way of coating the parylene C insulated electrode surface with neural adhesion molecule L1. Between the plasma+L1 and plasma+PEI+L1, we will use the former as the final procedure, as PEI itself may promote nonspecific protein adsorption and encourage glial cell attachment in vivo, which is not desired.

For the controlled release coating, our prior work has shown that we can incorporate dexamethasone in polypyrrole coatings deposited on the electrode surface and the drug can be electrically stimulated to



release [2]. We have since developed a nanostructured coating with significantly increased drug load and release efficiency [new publication by Luo and Cui, see “REPORTABLE OUTCOMES”].

Plan: The plasma+L1 coating treatment will be tested for tissue response *in vivo* in comparison to the non-treated electrodes. In addition, we will integrate the drug releasing coating in the electrode arrays and characterize the effect of drug release in minimizing inflammatory tissue reaction in the animals.

Project 3. Utilization of a virtual reality environment for prosthetic training and testing

A virtual environment will be created that will allow amputees to: 1) test simulated neuroprosthetics and control algorithms, and 2) practice using the neuroprosthetic in a virtual training environment. The main objective for the FY06 funding period is to design, acquire, and assemble a virtual reality system for training people to use an upper extremity neuroprosthesis (months 1-6). In months 3-12, we will develop and test the VR system with myoelectric control inputs, and test the system with upper extremity amputees performing simulated reaching tasks.

Objective 1: Design, acquire, and assemble a virtual reality system for training people to use an upper extremity neuroprosthesis.

We have acquired all the critical hardware and software components for the virtual reality training system (see Figure 6) as listed below:

1. 3-dimension real-time motion tracking system from PhaseSpace, Inc. This is a wireless active marker motion tracking system developed and marketed by the PhaseSpace, Inc. It includes four light-weight cameras and a base station running a real-time Linux operating system. All the cameras and the base station communicate with each other through a dedicated local network. Any clients can receive real-time motion data from the base station via local network, as well. All cameras were wall-mounted in the human subject testing room.
2. 16-channel EMG recording system from Delsys. The Delsys EMG system is one of the most widely used EMG recording systems in both clinical labs and research labs studying human movement and neuromuscular systems. This system is uniquely equipped with dry EMG surface electrodes, which greatly reduce setup time and skin irritation caused by conductive gels.
3. 64-channel brain-computer interface system from Guger Technologies. This 64-channel neural recording system is FDA-approved for recording physiological signals from humans, including EMG, EOG, EEG, and ECoG. This system can simultaneously sample 64-channels with a sampling rate up to 19k Hz.
4. 4-channel oscilloscope from Tektronix. This high-performance oscilloscope is frequently used for data visualization and system testing.
5. An MEG and fMRI compatible 2-axis joystick with USB interface. This joystick is specially designed to work with MEG and fMRI recordings. It has no metal or electronic components, and it uses fiber optics to transmit the movement signal from the MEG recording room to an outside base station.
6. BCI2000 software. This is an open-source software package based on C++. It is developed and maintained by the Wadsworth Center at Albany, New York. This is a general-purpose software package for neuroprosthetics and brain-computer interface research. It has three modules: signal source, signal processing, and application. These

three modules communicate with each other through the network with a well-define interface.

7. Virtual reality Toolbox from the MathWorks, Inc. The virtual reality toolbox from the MathWorks provides a high-level interface for users to easily create and manipulate virtual objects through either Matlab or Simulink interface in real-time.

Our virtual reality system uses BCI2000 as the base for signal acquisition, real-time myoelectric and neural signal decoding, and real-time control of 3-D cursor movement. The choice of BCI2000 is based on its open-source architecture and the well-defined interface between different modules. The goal is to make this virtual reality system flexible in the

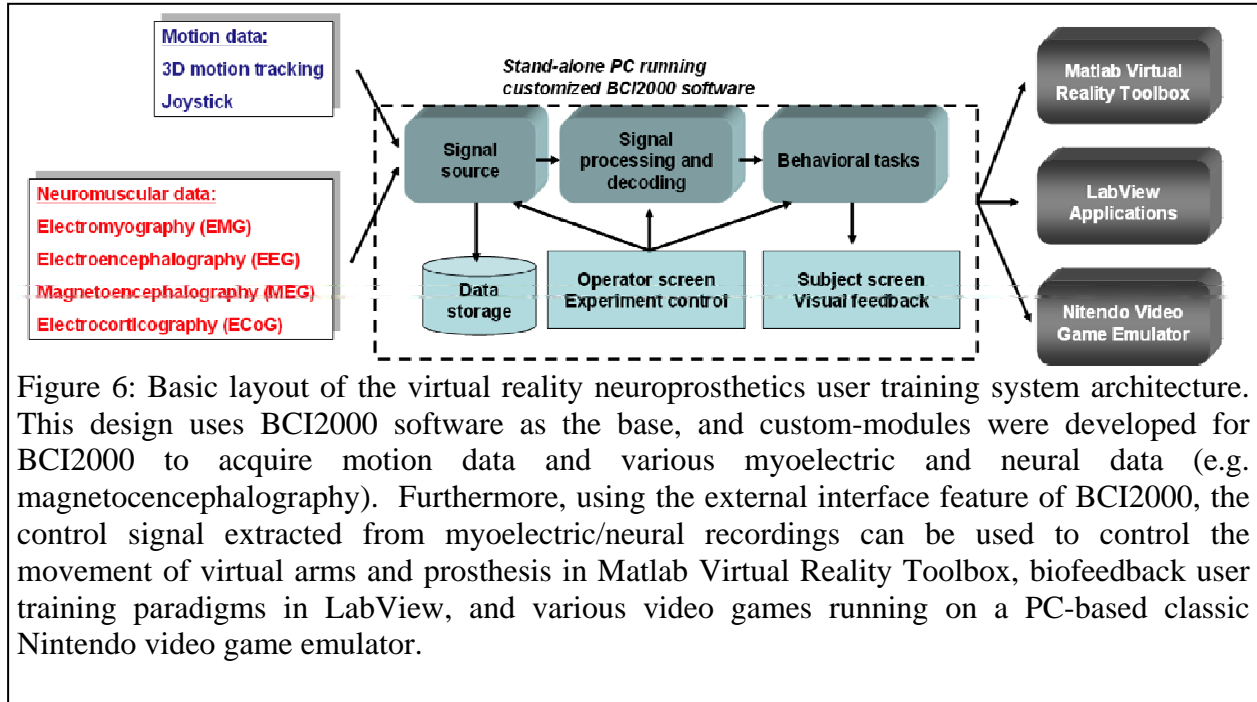


Figure 6: Basic layout of the virtual reality neuroprosthetics user training system architecture. This design uses BCI2000 software as the base, and custom-modules were developed for BCI2000 to acquire motion data and various myoelectric and neural data (e.g. magnetocencephalography). Furthermore, using the external interface feature of BCI2000, the control signal extracted from myoelectric/neural recordings can be used to control the movement of virtual arms and prosthesis in Matlab Virtual Reality Toolbox, biofeedback user training paradigms in LabView, and various video games running on a PC-based classic Nintendo video game emulator.

following perspectives: 1) it should be able to use various types of source signals, from non-invasive surface EMG signals to more invasive intracranial ECoG signals; 2) it should provide a rich set of applications or training paradigms for prosthesis user training. We developed multiple software programs to meet those requirements. For example, on the signal source side, in addition to testing the system using EMG, EEG, and ECoG signals, we also developed a prototype signal source module to interface BCI2000 with MEG, which is a non-invasive cortical recording method with high spatial and temporal resolution. On the application and training paradigm side, we have developed a hybrid user training module, which blends the user-generated control signal with a computer-generated assistive control signal. This is particular helpful in minimizing user frustration, especially during the initial training. Furthermore, we have developed external applications in Matlab Virtual Reality Toolbox and LabView. Another example of the richness of our training paradigm is that we can have users play classic video games using their EMG or neural signals, which will make the training process much more fun and engaging.

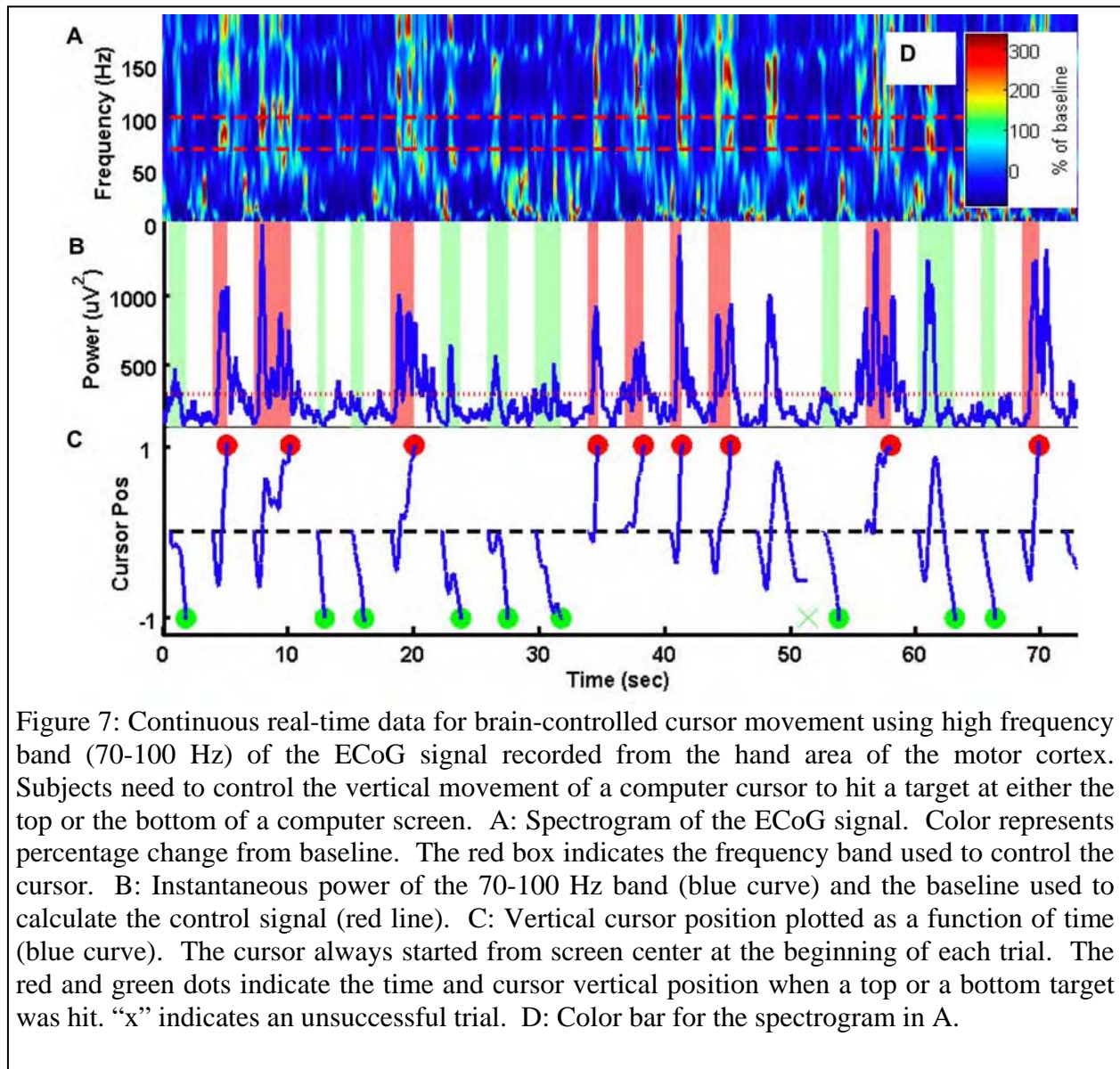
Plans:

- 1) Further development and testing of the virtual reality system to ensure that it functions reliably for all the training paradigms given any type of source signals.

- 2) Obtaining approval from Pitt IRB and Army Human Research Protection Office.
- 3) Collecting data from both able-bodied subjects and individuals with limb amputations.

Objective 2: Develop and test the VR system with myoelectric control inputs, and test the system with upper extremity amputees performing simulated reaching tasks.

In addition to our main effort in system integration and testing, we have started the process for human subject testing. The first step is to obtain appropriate human study approval from both the Institutional Review Board at University of Pittsburgh (Pitt) and the Human Research Protection Office of U.S. Army before conducting any experiments with able-bodied subjects and individuals with limb amputations. We have developed the human study protocol titled “Virtual reality (VR) environment for prosthetic training and testing”. TATRC regulatory expert, Dr. Jeffery Stephensen, has kindly reviewed our protocol and provided critical inputs to ensure that this protocol is in compliance with the requirement of the U.S. Army. This protocol has been submitted to Pitt IRB Office for review (Pitt IRB Protocol Number PRO08070220).



While the IRB protocol is being developed, we have conducted preliminary testing of the system using neural recordings such as MEG and ECoG. Figure 7 shows a continuous segment of data during a real-time brain-controlled cursor movement session. The subject was instructed to move a cursor either up or down toward the target. The subject controlled cursor movement using the ECoG signal recorded from an electrode sitting right on top of the hand area of the motor cortex. Within the first ten minutes' of training, the subject achieved an accuracy of 73% (The chance level is 50% for this 2-target task).

Project 4. Prosthetic hardware testing

Little objective or validated information exists about the quality and functional reliability of prostheses. The primary objective for the FY06 funding period is to develop and assemble a testbed for life-cycle testing of a variety of prosthetic feet. In months 1-6, we will design the testing apparatus and acquire and assemble the hardware and software for testing. We will also complete pilot testing with a small number of prosthetic limbs to validate the system.

Objective 1: Develop and assemble a testbed for life-cycle testing of a variety of prosthetic feet.

Objective 2: Complete pilot testing with a small number of prosthetic limbs to validate the system.

Results: We have completed the design and assembly of a test jig for ISO testing. Figures 8-10 show pictures of the testing apparatus. Also, we have ordered components to add torsional testing to MTS machine in conjunction with heel/toe loading. We have ordered the first set of prosthetic feet and have commenced testing to determine compliance with ISO standards. We have an IRB protocol pending review to collect field failure samples and to interview soldiers/veterans who have experienced prosthetic foot failures.

Plans: We will continue testing prosthetic feet and intend to complete tests on 3 feet. We are also planning to write software and build hardware to incorporate torsional component to tests. Within a few weeks, we hope to receive IRB approval and will begin scheduling interview sessions once we receive approval from the local IRB and the USAMRMC.

KEY RESEARCH ACCOMPLISHMENTS

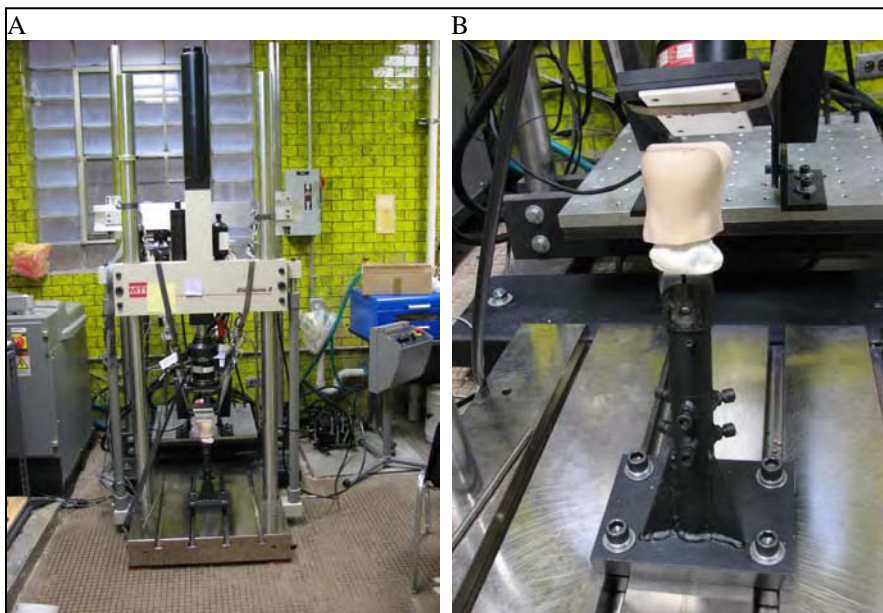


Figure 8: (A) The MTS Testing Machine simulates movement of two axis ankle-foot actuator using hydraulic power implementing displacement and force control for the angular movements or loads. (B) shows mounting of a prosthetic foot in the test jig.

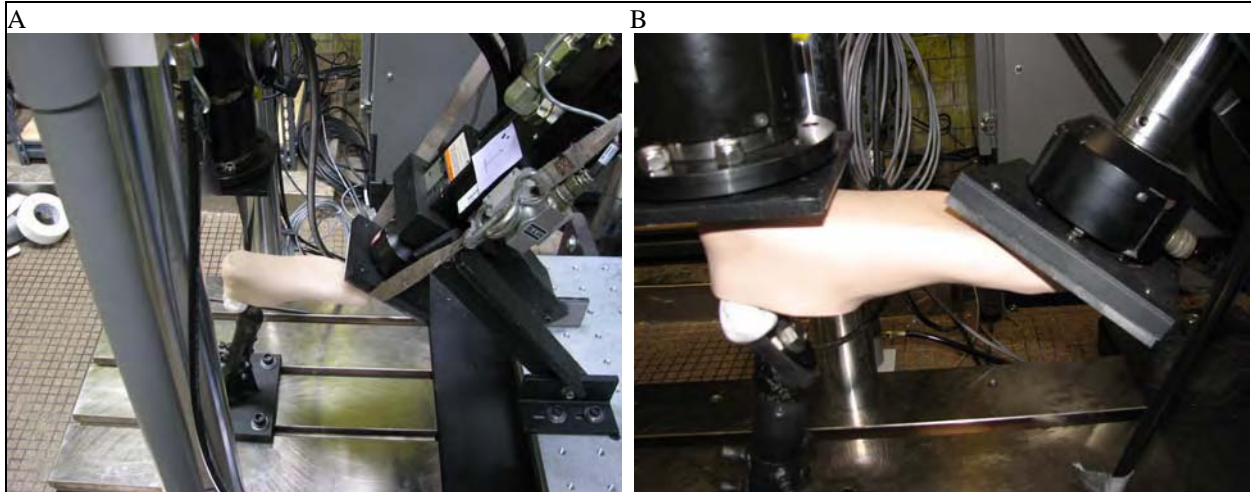


Figure 9: (A) The Cyclic Test is a dynamic fatigue test in which load is applied on the both heel and toe alternatively for a large number of cycles followed by final static force. (Like in heel strike and toe of in normal gait cycle). (B) The Proof Test is a static test for foot ankle unit in which maximum load is applied on heel and forefoot in one single time successively.

Project 1. Develop a somatosensory neural interface (SSNI)

-Completed pilot testing of experiments to evaluate somatotopic organization of primary afferent fibers in DRG, dorsal roots, and spinal cord.

Project 2. Establishment of Neural interface stability and optimization

-Completed several pilot experiments to evaluate histologically the tissue response to electrodes implanted chronically in DRG and spinal cord. Developed biocompatible coatings for the parylene C insulated electrodes.

Project 3. Utilization of a virtual reality environment for prosthetic training and testing

- Acquired all critical hardware and software components for the virtual reality system.
- Designed and developed the virtual reality training system based on BCI2000. Custom software was developed to greatly extend the functionality of BCI2000.
- Developed human study protocol and submitted to Pitt IRB for review.

Project 4. Prosthetic hardware testing

- Test jig completed to ISO testing.
- Testing has commenced to determine compliance with ISO standards.

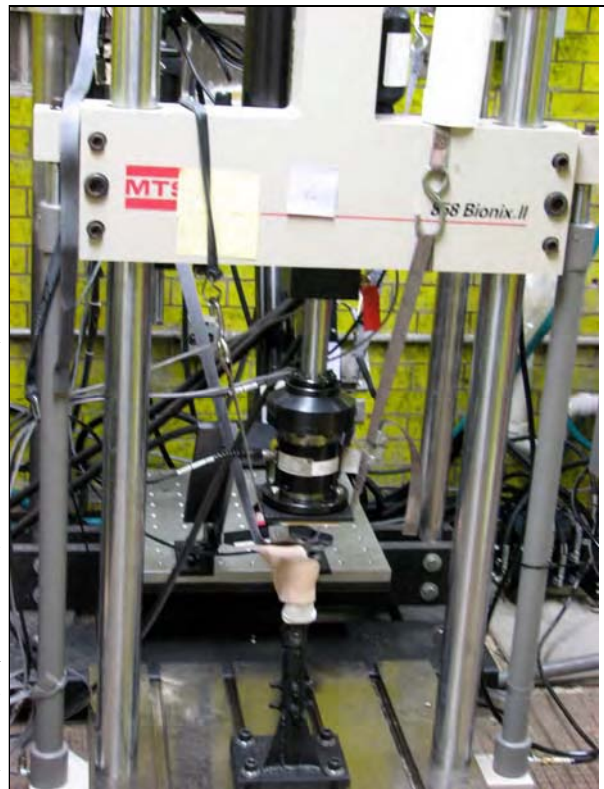


Figure 10: The Ultimate strength test is a Static test in which force is applied separately on heel and toe by actuator and load is increased gradually at the rate of 175N/ 20 second.

- IRB pending to collect field failure samples and to interview soldiers/veterans who have experienced prosthetic foot failures.
- Ordered components to add torsional testing to MTS machine in conjunction with heel/toe loading.

REPORTABLE OUTCOMES

A total of 8 conference abstracts and 1 full-length journal article were published in 2008. The citations are listed below, grouped according to project.

Project 1. Develop a somatosensory neural interface (SSNI)

Bourbeau DJ, Hokanson J, and Weber DJ. A computational model for examining activation of peripheral neurons by electrical microstimulation. In: *BMES 2008 Annual Fall Meeting*. St. Louis, MO: 2008.

Hokanson J, Wagenaar JB, and Weber DJ. Recruitment of DRG neurons by electrical microstimulation. In: *BMES 2008 Annual Fall Meeting*. St. Louis, MO: 2008.

Hokanson JA, Wagenaar JBW, and Weber DJ. Recruitment of DRG neurons by electrical microstimulation. In: *Society for Neuroscience Annual Meeting*. Washington, DC: 2008, p. 779.715.

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Wagenaar JB, Hokanson J, Ventura V, and Weber DJ. Real-time feedback control of functional electrical stimulation based on primary afferent recordings. In: *BMES 2008 Annual Fall Meeting*. St. Louis, MO: 2008.

Project 2. Establishment of Neural interface stability and optimization

Xiliang Luo and Xinyan Tracy Cui, Electrochemically controlled release based on nanoporous conducting polymers, *Electrochemistry Communications*, Volume 11, Issue 2, February 2009, Pages 402-404 (attached in the appendices)

Project 3. Utilization of a virtual reality environment for prosthetic training and testing

Degenhart AD, Sudre G, Collinger J, Chang C-L, Schwartz AB, Tyler-Kabara E, Weber DJ, and Wang W. Comparison of ECoG signal modulation between hand and brain-controlled cursor movement tasks. In: *Society for Neuroscience Annual Meeting*. Washington, DC: 2008, p. 779.716.

Sudre G, Degenhart A, Collinger J, Weber DJ, and Wang W. Modulation of MEG signals during overt and imagined wrist movement for brain-computer interfaces. In: *Society for Neuroscience Annual Meeting*. Washington, DC: 2008, p. 779.713.

Sudre G, Degenhart A, Collinger J, Weber DJ, and Wang W. MEG analysis of motor-related brain activity during overt and imagined wrist movement In: *BMES 2008 Annual Fall Meeting*. St. Louis, MO: 2008.

Project 4. Prosthetic hardware testing

Nothing to report.

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