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Neuromotor Prosthesis Development

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UNLIKE HUMAN LIMBS, TRADITIONAL, PASSIVE PROSTHESES have practically no ability to respond to anything but the most basic aspects of our movement intentions. In addition, traditional prostheses cannot communicate sensory information to the brain. Biohybrid limb research seeks to restore sensory and motor signals meant for natural limb function by creating an interface that provides two-way communication between the prosthetic limb and the nervous system. The goal of our research is to create a biohybrid interface that communicates directly with the nervous system.

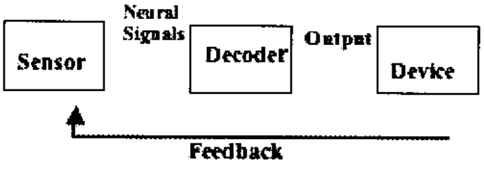
NEUROMOTOR PROSTHESES (NMPs)

In the human nervous system, sensory and motor information are represented in patterns of electrical impulses (neuronal action potentials), often called spikes. Research into these patterns has paved the way for the development of closed-loop neuromotor prostheses (NMPs), which have the potential to enable bidirectional interaction between the human nervous system and external devices. In the case of semiautonomous robots, such devices could be independent of the human body, but capable of communicating with and being controlled by human users. In the case of biohybrid limb prostheses, the devices themselves could replace limbs lost secondary to traumatic amputation, vascular or medical disease, and the ideal prosthesis would mimic both natural motion and sensation.

The emerging technology of NMPs combines cutting-edge biomedicine, neuroscience, mathematics, computer science, and engineering. This type of interface transcends earlier controllers because it is based on neural spiking, a source of information-rich, rapid, complex control signals from the nervous system. NMPs promise an entirely new paradigm for building bionic systems that can restore lost neurological functions.

For example, our team, together with a Brown spin-off company, Cyberkinetics Neurotechnology Systems, Inc. (CKI), has already created a system that records human brain signals, decodes them, and transforms them into movement commands. The system consists of a match head sized platform with 100 thread-thin electrodes that penetrate just into the surface of the motor cortex where commands to move the hand emanate. The pattern of complex neural signals is decoded by a rack of computers that displays the resultant output as the motion of a cursor on a computer monitor—as if the thoughts to move the hand had moved a computer mouse. This neural command signal has been used by persons with tetraplegia to control a computer for spelling[1], to run software, or to use assistive devices that control a television.[2] While computer cursor motion represents a form of virtual device control, this same command signal could be routed to any of a number of devices to command motion of paralyzed muscles or the actions of prosthetic limbs; indeed, simple robotic arm control has already been achieved in pilot studies[2] and we have achieved pre-

Figure 1. Basic elements of brain machine interface



This bidirectional system must have an interface to detect neural signals (Sensor), a decoder to transform the neural signal into a desired command signal, and a controlled device, such as a computer, robot, or muscle. For a closed-loop system, feedback reports error in uncertain environments.

liminary control of an electric wheelchair.[1] Joining expertise in human functional neurosurgery and neurology (Friehs and Hochberg), computer science and robotics (Black), neuroscience (Donoghue), and engineering (Nurmikko), this team has already completed initial work on potentially commercial elements of first-generation NMP technology now being developed through CKI.

To make further progress towards a useful product, the current pilot system must become miniaturized, wireless and fully implantable. Our team is developing these key elements of advanced NMP technology: integrated microscale signal processors, innovative broadband optical telemetry and powering, and miniaturized processors are all in development. Reliable signal control is also essential for day-to-day use. We are working on new mathematical models to transform a small sample of human neural recordings into a rich and useful control signal. In addition, we are working to create an interface that can provide sensation via low levels of patterned electrical stimulation to the sensory areas of the brain. In this way we hope to provide an NMP that creates two-way communication between machines and the nervous system.

Research and Translational Goals

This research provides the foundation for a system that could ultimately allow paralyzed people a greater degree of independence, communication and mobility if they were able to control – simply through their own movement intentions – computer, robotic, or prosthetic interfaces. Long-term goals include a new class of devices necessary for human NMPs to operate more effectively, and to elucidate the principles of their operation. Intermediate goals include the development of both control algorithms and user interfaces that would enable human neural control of robot navigation tasks or other complex interactions.

Modeling the Brain Computer Interface

The initial technology of Brain Computer Interfaces (Figure 1), of which NMPs are one type, consists of three key components: a neural interface, a decoding system, and a user interface (effector); a closed-loop system would be completed by a feedback signal from the effector to the brain. Feedback would be achieved by very low level electrical impulse sequences that attempt to activate a neural apparatus that participates in sensation. Core elements of the current research include:

1. An optimally designed and extensively tested microelectrode array. Microelectrode array fabrication incorporates controlled design and manufacturing of a one-hundred electrode sensor, a compact 4 x 4 mm device that communicates with external electronics via an ~ 13 cm cable and a percutaneous Ti pedestal. Long-term preclinical studies in Dr. Donoghue's laboratory showed that the array is sufficiently stable to provide long-term recording of neuronal spikes suitable for NMP use.[3] The implant testing and design was submitted to the FDA for a proposed pilot clinical trial in 2004.

Figure 2. Implatable cortical micosystem overview

Microsystem with an active implantable unit in soft encapsulation; transdermal IR telemetry; inductively or IR coupled powered delivery clock

Implantable microsystem connected to subcutaneous high speed fiber optic link; IR power delivery and telemetry through subcutaneous fiber coupled to obdominal/chest cavity unit.

This illustrates two adaptations of the same basic microsystem design for high-fidelity transcutaneous neural signal extraction at high data rates.

2. Signal acquisition and processing by specialized microelectronic device technology. A complete system is produced by Cyberkinetics, and miniaturized versions are being developed by our group to make the devices fully implantable, automated and portable.

3. Decoding based upon a principled mathematical framework has been developed by Drs. Black and Donoghue and their colleagues. Decoding efforts attempt to extract the maximum amount of information related to movement intentions from the sample of neurons detected using the implant. The signal is used for real-time control. Computational methods for signal processing are used to improve the quality of control. These methods attempt to achieve the speed and accuracy of an able-bodied human using a computer mouse to operate a standard PC.

4. Implementation of decoded signals as a control source. Once a brain derived control signal has been created, it can be used to operate a wide range of devices that improve independence, mobility and communication for those with limited movement abilities. Control signals can be used to run a computer and assistive technologies. In addition, control signals have been used to direct robotic arms. The signals are also potentially useful to reanimate limbs by driving electrical stimulators in paralyzed but otherwise operational muscles or actuators in advanced prosthetic limbs.

Decoding the Human Brain

Decoding is the task of transforming complex neural patterns into a meaningful control signal that can drive physical or biological devices. This involves two key parts: First, we must understand how the brain adapts to control new devices and how we can best train the brain to control a new motor system. Second, we must mathematically model the way neural signals encode information about movement, and then exploit these models to develop a real-time "translator" between the neural signals and the inputs needed to control new devices.

We have made substantial progress in this task. Using mathematical algorithms, we can convert motor cortex spiking activity into a continuous reconstruction of hand position, and classify patterns of motor cortex activity into discrete choices.[4-7] Recently we have developed "multi-state" methods that enable the decoding of continuous cursor trajectories and discrete "click" activities from the same population of cells.[8] Unique to this endeavor is the need to develop training methods parallel to new decoding algorithms; in designing algorithms one must take into account how the brain learns and how best to train it.

Accurate decoding can create a richer repertoire than current, fairly simple, scenarios in which the decoding of hand motion is either in one of a fixed number of directions or is a continuous reconstruction of two-dimensional hand trajectory. Our principled mathematical approach provides the foundation to enable the control of physical devices such as wheelchairs, prosthetic arms and dexterous robot hands. In particular, tasks such as manipulating, grasping, pushing, and gesturing involve the composition of more primitive motions. For example, even a simple action such as picking up a block may be composed of a preparation phase, a ballistic hand transport motion, manipulator positioning using visual servoing, and, finally, a grasping motion. Ultimately, the challenge is to develop a prosthetic device under neural control that is capable of executing all such compositional actions. Achieving this high-dimensional control will require basic scientific and engineering advances to determine the full extent of information available from neural spike trains.

Challenges remain, however. For example, decoders in use day to day by patients will need to function adaptively to deal with changes in the system that can arise from instabilities in the sensors or in the biological system. In addition, available neurons may change over time as sensors move even slightly in the tissue. For development purposes, we simulate more complex actions on a computer screen, where we can readily control the properties of a wide range of devices. This knowledge will set the stage for the development of actual devices that can serve real world interactions, such as navigation in complex environments or control of multidimensional manipulators requiring dexterous finger, hand, and arm movements of an artificial device.

RESEARCH TOWARDS WIRELESS FULLY IMPLANTABLE NEURAL INTERFACES

The overall goal of this project is to develop a fully implantable wireless multineuron sensor for broad research, neural prosthetic, and human neurodiagnostic applications. The implantable microsystem is based on the sensor electrode platform which has been extensively evaluated in preclinical animal studies, and now in four tetraplegic humans who are part of Cyberkinetics' BrainGate pilot clinical trials. Related work aims to achieve multi-site stimulation to serve as an input interface for human and animal research applications.

The miniaturized brain implantable NMP microsystem-on-chip now under development at Brown has unique design features; it is flexible and scalable to allow transmission of increasingly larger amounts of neural information from the cortex to assistive technologies. The microsystem design architecture is also compatible with the longer term prospects of connecting the motor cortex to muscle nerves *intra-corpus* via a fiber optical network within the body, as well as via external prosthetic devices. In the development of the new NMP technology, we will be guided by experience gained from ongoing BrainGate human trials that employ passive microelectrode recording arrays, which are coupled by a percutaneous connector to external electronic modules.

Early prototypes of the implantable microsystems are under way, which incorporate advanced ultra-low power microelectronic circuits and processors with optoelectronic devices as integrated cortical implants, shown schematically in broad overview in Figure 2. This project charts a new pathway to human neuroprosthetics, well beyond the current state-of-the-art, while ultimately endeavoring to create a platform for a new neuro-technology paradigm for "whole-body" prosthetic networking via cortical interfaces. The design of the new implantable NMP microsystems will leverage information acquired from human clinical trials, including the experience gained with the present external cabling system developed by Cyberkinetics. The goal of the microsystem-on-chip is to enable very high data rate wireless transmission of high fidelity neural signals (spikes and LFPs) with transcutaneous powering and signal transmission. We have already achieved an initial prototype 16-channel microsystem which has been tested at the benchtop and initial rat animal studies.

CONCLUSIONS

As they apply to biohybrid limb research, on-going advances in neural interfaces, microelectronic devices and decoding may allow dynamic linkages between the cortex and robotic prostheses through novel systems, such as the NMP system we are developing. Ultimately, these technologies could provide direct brain control of artificial limbs for amputees, or direct control of muscles for those with paralysis, as well as an entirely new means for physical monitoring and repair of the human nervous system.

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Identifying Clinically Meaningful Improvement In Rehabilitation of Lower-Limb Amputees

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THE EFFECTIVENESS OF TISSUE ENGINEERING, and both surgical and prosthetic interventions for lower limb amputees must be assessed rigorously through carefully designed outcome studies. While objective measurements such as faster gait speed and better balance are important ways of evaluating rehabilitation success, they are insufficient without an assessment of the patient's subjective experience of intervention effectiveness. Thus, the outcomes that we use to evaluate our interventions will include physical performance measures as well as measures of the amputee's subjective experience of prosthetic satisfaction, quality of life, and mobility.

For small groups of subjects, the choice of highly reliable and responsive outcomes measures is imperative. The best instruments for use with individual patients and small group studies have superior measurement properties: in particular, reliability, measurement range, and responsiveness. However, not all measurements work with individuals or small groups. Scales with large floor or ceiling effects, or substantial numbers of patients scoring at the bottom or top of the scale, for example, are not appropriate choices for measuring individual-level change. In addition, some instruments may lack the psychometric properties that detect change on the individual level.[1] To assess the effectiveness of interventions in clinical practice and small studies, measures must be responsive to change on an individual level, and research on responsiveness must assist in interpretation of scores.

In the ceiling effect, there is little room for patients to show improvement, because they already score at the high end of the scale.

In large clinical trials, the effectiveness of interventions is assessed statistically, by comparing mean change in outcomes scores between groups of patients. These same comparisons are impossible in clinical practice or trials using very small samples. Thus, common measures of responsiveness—such as effect size,[2] standardized response means,[3] or the responsiveness statistic[4]—summarize test responsiveness and are useful for making relative comparisons between measures, but do not contribute to the interpretation of test results in individual subjects or patients.[5] For interpretability at the individual level, one should be able to answer questions such as, "Does a change in score of 10 points in a certain measure denote an important change for these patients?" and "Is a 5-point change in score the same as a 10-point change in score?"

Data on two properties, **minimum detectable change** (MDC)[6-8] and **minimal clinically important difference** (MCID)[9-10] can assist in interpreting scores for individuals and small groups of patients. Minimum detectable change is a statistical measure of meaningful change, defined as the minimum amount of change that exceeds measurement error.[8] From a statistical perspective, an individual patient is considered to have changed only when the difference between the previous score and the current score exceeds the MDC associated with the measurement.[7] MCIDs, on the other hand, define the threshold at which an individual has experienced a clinically relevant change.[9,10]