

Chapter 63

Development of neuromotor prostheses for humans†

John P. Donoghue^{a*}, Arto Nurmikko^b, Gerhard Friehs^c and Michael Black^d

^a *Department of Neuroscience, Brown Medical School and The Brain Science Program, Brown University, Providence, Rhode Island 02912 (USA)*

^b *Division of Engineering, Brown Medical School and The Brain Science Program, Brown University, Providence, Rhode Island 02912 (USA)*

^c *Department of Clinical Neuroscience, Brown Medical School and The Brain Science Program, Brown University, Providence, Rhode Island 02912 (USA)*

^d *Department of Computer Science, Brown Medical School and The Brain Science Program, Brown University, Providence, Rhode Island 02912 (USA)*

1. Introduction

Medicine is entering a new period of Neurotechnology development in which devices that can diagnose and treat neurological disorders and restore lost function will become increasingly available. The advent of devices such as deep brain stimulators (DBS), which have been implanted in thousands of people, represent significant early CNS technology (Benabid et al., 2003). The remarkable symptomatic relief for Parkinson's disease and other movement disorders, is increasing the acceptance of devices that require a direct brain interface, despite the need for an intracranial procedure. In this same vein,

* *Correspondence to:* John P. Donoghue, Department of Neuroscience, Brown Medical School and The Brain Science Program, Brown University, Providence, Rhode Island 02912, USA.

Tel: 401 863 1054; Fax: 401 863 1074;

E-mail: John_Donoghue@brown.edu

† Financial Disclosure: Gerhard Friehs and John Donoghue are founders and shareholders in Cyberkinetics, Inc, a medical device company that produces and sells technology described in this chapter.

cochlear implants, vagal nerve stimulators, and various drug pumps are examples of successful neurotechnologies that couple with the peripheral nervous system. Neurotechnology resembles the adoption and development path of cardiac pacemakers, which began as crude stimulating devices and are now widely accepted as a sophisticated human-machine interface (Jeffrey and Parsonnet, 1998).

By contrast, neurotechnology is at a very early stage: systems now in use rely on rather gross levels of electrical stimulation, placement is relatively imprecise, and control parameters are empirically derived, often because the mechanism of their effect is unclear and the nature of the system is vastly more complex than, for example, the heart. Current neurotechnology operates in an open loop fashion. That is, devices are not modulated by feedback sensed by the system. They are always running and are not adaptive to changes in the patients state. Instead, they require subjective human intervention for calibration. Interestingly, these early neurotechnologies often work well, even with vague knowledge of their mechanisms of effect. For

Author: Figures 4 and 5 are not cited in the text – please indicate position

example, the dramatic relief produced by DBS has been postulated to occur through excitation, suppression or modulation of neural activity (Lozano et al., 2002). Nevertheless, the available multichannel, fully implantable stimulators now available represent a major technological step towards more sophisticated and beneficial devices. Neurotechnologies that record, or sense, electrical activity of the nervous system are much less developed, in part because they require more complex neural interfaces and signal processing. Neural activity sensors have the potential to form the basis for devices to diagnose aberrant brain activity patterns, as in epilepsy, or to serve as a replacement pathway for a missing neural output such as a central motor output pathway or peripheral nerve. Neuro Motor Prostheses (NMPs) are devices for the CNS that can couple motor areas to effectors, and ultimately return feedback as a closed loop system. NMPs are now being developed to provide a replacement output for lost functions, such as hand or leg movement or speech. In essence, they represent a physical repair where biological ones are inadequate or unavailable. The newness of this concept is reflected in the multitude of names for these devices: brain-computer interfaces (BCI), Brain Machine Interfaces

(BMI) and neural prostheses all appear in the literature (see e.g. Nicolelis, 2001; 2003; Donoghue, 2002; Wolpaw et al., 2002 for reviews). The term NMP is used here to refer to devices designed to detect that actual motor plan in the cerebral cortex and convert it into a useful output signal for paralyzed humans.

NMPs have the potential to restore movement when central motor control structures remain intact, but their access to the periphery is blocked. Any traumatic injury or disease that disrupts the cortico-spinal pathway, the alpha motor neurons, their connections or their axons, or the muscles themselves can disrupt voluntary movement. Paralysis produced by spinal cord injury, muscular dystrophy, or locked-in syndrome (pontine stroke) leaves the brain cognitively intact and able to generate movement plans. Together, this group of neuromuscular and movement disorders affects hundreds of thousands of Americans. In these individuals, movement intentions cannot be translated into desired actions because the effectors or the pathways to them do not function properly. Thus, an ideal NMP would be able to provide a new output either directly to devices or to the paralyzed muscles (Wolpaw et al., 2002; Serruya and Donoghue, 2003). Figure 1 provides a

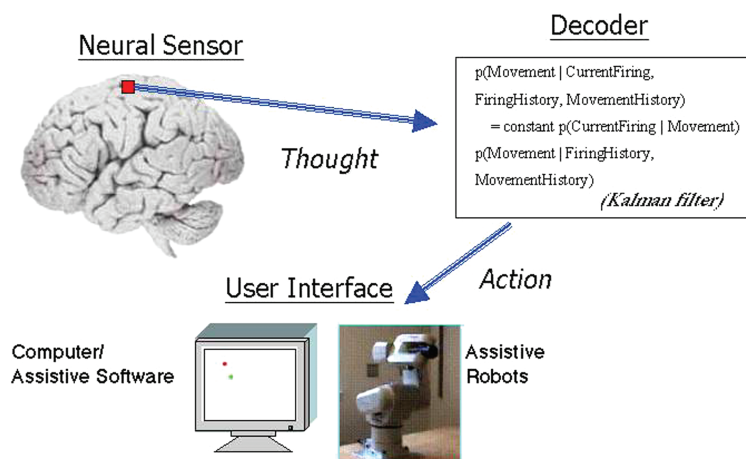


Fig. 1. Basic features of a Neuromotor Prosthesis. Signals must be detected by a neural sensor, which provides an interface between the physical and biological systems. The motor intent (thought) is decoded by mathematical algorithms that translates the signal into an output capable of driving real world devices. Here we give an example of a filter based in a probabilistic framework. This output signal is connected to various user interfaces, such as a computer or a robotic arm that can provide assistive actions for paralyzed patients.

view of the essential steps to create such a system. The NMP must have the ability to sense neural activity related to motor plans or actions, transform or decode this activity into an output signal and then couple that output to assistive devices or to the muscles as quickly and accurately, as the intact nervous system. The idea that such an NMP could be produced still seems to be at the realm of science fiction. However, recent advances of neuroscience, computer science, engineering and mathematics, as well as the emergence of functional neurosurgery are combining rapidly enough to make it likely that human trials of NMPs will begin within the next few years. Below we will review the specific events that allow us to make such a strong statement and discuss the implications for the treatment of human neurological disorders. We will discuss our own advances in developing an NMP and relate these advances to other work in NMPs.

2. Neuroscience advances

Fundamental findings in neuroscience are at the root of a successful NMP. We are beginning to understand where sensors should be placed, what signals they should detect and how to detect them. Functional localization provides a guide to finding motor commands. In one sense, the cortex contains a large number of functionally different areas related to sensation, movement, perception, or cognition. However, it is also evident that multiple, overlapping areas are engaged in any sensory, motor or higher level function. Movement control engages a group of areas in frontal and parietal cortex, with the primary motor cortex (MI) a major source of voluntary movement signals and of the corticospinal pathway, which delivers cortical output to the spinal (and brainstem) systems engaged in movement. Electrical stimulation studies beginning in the 19th century emphasized the importance of MI as a voluntary motor area because it had the lowest stimulation thresholds for movement (for a review, see articles by Sanes and Donoghue, 1997, 2000; Sanes and Scheiber, 2001). Connectional, recording and lesion studies all reinforce this role. MI is subdivided into

distinct regions for control of the leg, arm and face. However, contrary to popular textbook images, control of each of these body parts appears to be highly distributed within a somatic region. Thus, for example, the arm MI area appears to be a distributed network; like a network, information about arm motion is widely available from the neurons in that area. These findings point to MI as an ideal target site for a NMP sensor. The distributed nature of representation in MI means that sensors for arm motion commands need not be placed very precisely within the MI arm region in order to retrieve movement information. The other parietal and frontal areas that contain information about arm motion remain to be evaluated as potential sources of a movement output signal (Cheney et al., 2000).

A second important neuroscientific finding is that the number of action potentials or spikes in a small time interval is a fundamental unit of information in the nervous system. Neuron spiking in the arm area of MI carries considerable information about the motion of the hand through space, including its direction, speed, position as well as forces generated at the hand (Evarts, 1966; Humphrey et al., 1978; Georgopoulos, 1982; Kalaska et al., 1997; Kakei et al., 1999). Neurons also encode information about finger movements, but these are less well understood (Sanes and Scheiber, 2001). Thus, an NMP able to sense spiking should be able to derive a rich movement output signal. A third important finding is that information is carried by groups or populations of neurons and their interactions (Georgopoulos et al., 1982; Maynard et al., 1999); single neurons provide information that is limited because part of their spiking appears to be undecipherable noise. However, one can extract, or decode, the intended trajectory of an arm reach by mathematically combining the spiking of a number of neurons (Paninski et al., 1999, 2003; Wessberg et al., 2000; Serruya et al., 2002; Taylor et al., 2002). The size of the neuronal group required to provide a useful signal is surprisingly small – rudimentary movement information is available from as few as a half dozen neurons (Serruya et al., 2002), although larger populations are likely to improve signal fidelity and

provide information about more complex actions of the arm beyond hand motion. Thus, optimal NMP sensors would be able to detect multiple neurons both to generate the optimal output signal and to provide some redundancy should some electrodes fail to record over time.

3. Advances from engineering, computer science and mathematics

The requirement to sense and process multiple neurons into an output signal provides a formidable challenge to combine skills from a number of fields. Engineering advances are required for multineuron sensors and signal processors and computer science and mathematical skills are necessary to understand optimal ways of rapidly extracting the maximum amount of information from samples of neural activity. There have been a number of recent advances in sensor development and decoding that are essential for a human NMP. Advances by our group are reviewed below and compared in the sections below to progress in other groups.

3.1. Sensor development

For the foreseeable future, spikes detection will require sensors comprised of microelectrodes that are placed very near the neurons cell body. No non-invasive means are currently available to detect spiking with sufficient speed and resolution. The consequence of this requirement is that NMP sensors must be placed intracortically, if they are to retrieve the signals that carry voluntary movement intent. Dozens of laboratories have been working on brain computer interfaces that use non-invasive sensors (for a review, see Vaughn et al., 2003). Scalp recorded electrical potentials are comparatively easy to record, but these signals represent a considerably filtered, averaged signal that reflects general brain states, rather than details of motion which are present only in the spiking of neurons of motor related cortical areas. Systems using non-movement based signals have been termed *Indirect* NMPs (Donoghue, 2002). Scalp EEG sensors are also cumbersome and time consuming to apply, prone to

disruption by distraction, and need frequent recalibration. An invasive sensor appears to be the only way to create a direct NMP that provides readout of actual neural movement or its intent and that could restore the movement capabilities present in intact humans. Readers should see Serruya and Donoghue (2003) for a comparison of various technologies.

Creation of an appropriate sensor is challenging because a rich movement output signal depends on recordings from many cells simultaneously, which therefore requires many microelectrodes. Reliable multineuron sensors have been technically difficult to produce, but a number are now in development. Handcrafted bundles of small wires have been used in animals as multineuron sensors for basic research, but their design and manufacturing makes them unsuitable to be a human medical device, at least in their present form. However, multiple sensor probes produced under controlled manufacturing processes suitable for human testing are becoming available. The Utah microelectrode array was designed by Richard Normann at the University of Utah (Jones et al., 1992; Maynard et al., 1997) and later developed through Bionic Technologies, Ltd. We have collaborated with the group at Utah to further develop and test the 'Bionic array' as a chronically implantable device in primates (Figs 2 and 3). The array is now being developed by Cyberkinetics, Inc. (a medical devices company that merged with Bionic Technologies) for human trials (Serruya et al., 2003). This array is micromachined from a monolithic block of silicon into a platform with 100 individual microelectrodes arranged in regularly spaced 10×10 lattice. Each electrode is separated by $400 \mu\text{m}$. The recording tips of these electrodes, when inserted, sit $\sim 1\text{--}1.5$ mm below the pial surface. During insertion, the strength of the silicon allows the sensors to pass easily through the pia-arachnoid, which is a formidable barrier to more flexible electrodes. Our experience in monkey MI indicates that similar human systems could detect dozens of neurons simultaneously (Fig. 3A, B). Monkey systems have functioned for years, suggesting that they can provide signals for long times in humans as well. It is important to note that sensors must be both

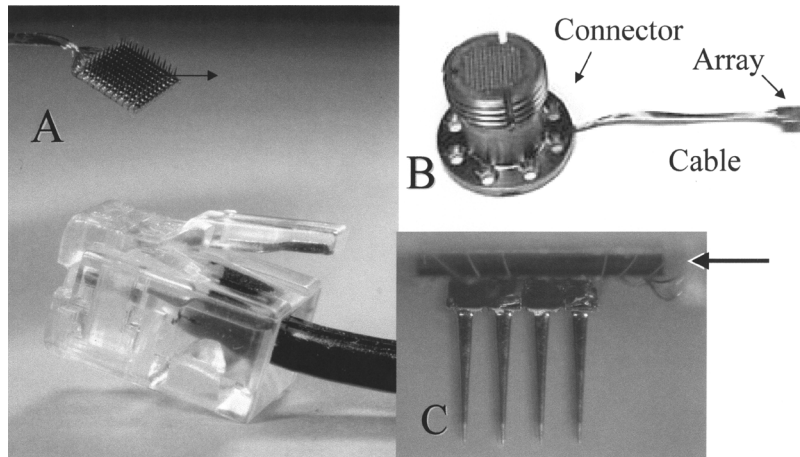


Fig. 2. Sensor technology. A. The Bionic sensor array (arrow) compared to a phone jack. The sensor has an array of 100 electrodes (here pointing upward), each 1 mm long, that emerge from a 4×4 mm platform. B. Implant system. The array is attached to a percutaneous connector via a cable of 100 fine wires. C. Prototype of a sensor with integrated electronics. The platform (arrow) on the back of the array contains a functioning, microminiature 16 channel amplifier system that is fully implantable (developed by A. Nurmikko, Brown University). For scale, electrodes tips are separated by $400 \mu\text{m}$.

biocompatible and biostable – the materials must not induce a tissue reaction that will block recording and they must not be degraded by tissue response to the foreign body (Turner et al., 1999). This is not as much a function of the base substrate of the sensor but of the coating materials that come in contact with the tissue. The coating materials of the ‘Bionic array’, including parylene (Schmidt et al., 1988), silicone, and platinum, have properties appropriate

for humans. Animal tests show that Bionic arrays appear to be both biostable, as evidenced by their longevity, and biocompatible, based on years of tests in monkeys (Fig. 3). Further, they can be safely removed and a new array inserted in the same tissue will provide useful neural signals (Fig. 3A). Thus, this technology seems to pass major hurdles necessary for a human NMP sensor. However, this silicon array technology is limited to the exposed surface of

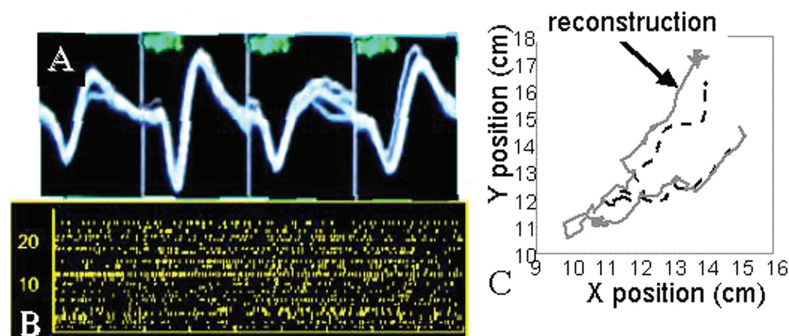


Fig. 3. Recording and decoding. A. Electrophysiological recording showing superimposed traces for each of four simultaneously recorded neurons, demonstrating signal quality. B. Spiking patterns of 24 neurons over a 4 s period. Each tick in a row represents the spike from one neuron. Each row represents a different neuron. C. Results of decoding. Dashed line shows the path of a monkey’s hand across a tablet. Solid line represents the reconstruction of the predicted hand path based upon the decoded multiple neuron activity, using a linear regression method. Note the close resemblance between the neural path and the actual hand path.

the cortex. Reaching deeper cortical areas and subcortical structures is very difficult with these materials and the manufacturing process. Titanium and other metal-based arrays, being explored in our group, can be electromachined into a variety of shapes and lengths (Fofonoff et al., 2002) which may address some of these issues.

Other electrode arrays in development include those with multiple recording ports on individual shanks, which can not be achieved with the Bionic array. Multiport electrodes allow a recording from larger number of neurons across each of the 4 cellular layers of MI. It is not clear which of the layers would be optimal for NMPs, but this could be resolved experimentally with this technology. Silicon electrodes developed at the University of Michigan are fabricated using semiconductor manufacturing (planar photolithography) processes which gives them a very wide flexibility in design (Bai and Wise, 2001; Csicsvari et al., 2003). Recording patches can be arranged in complex patterns in many locations along a thin film electrode shank which can be arranged singly or in an array of electrodes. Michigan electrodes arrays have not yet been tested for long term stability in primates, but various designs are in wide use in animals for acute recording and these can function chronically in rats (Kipke et al., 2003). New polyamide and ceramic electrode arrays, which provide flexibility using a biocompatible material, are also in development (Moxon, 1999; Rousche et al., 2001). These electrodes can conform to different shaped surfaces, but flexibility can make them difficult to insert. Trophic factors are being developed to attract neurites to the electrodes in order to integrate brain and sensor into a stable, long-lasting unit. Each of these sensor systems may provide better or longer lasting signals, but as human products, they are still in the early stages of development. One important exception is the 'cone electrode' developed by Kennedy et al. (1989) (Kennedy and Bakay, 1998; Neural Signals, Inc.). This electrode, which consists of a glass pipette tip-electrode filled with growth factors, has been inserted into human cortex of paralyzed patients. Cone electrodes are capable of providing

neural signals for prolonged periods through the ingrowth of neuritic processes, but gaining population recordings may require a very large number of individual cone insertions, which has not been tried. Further, it remains to be seen whether such integration is necessary or even desirable, if the ability to remove these sensors for medical reasons or to upgrade technology is an important design feature.

All currently used arrays are entirely passive, so that they require bulky electronics outside the body to amplify and process large numbers of signals as well as ways to route this information via cabling and connectors from the sensor to the outside. The first human NMPs are likely to have this form. An implant based upon the Bionic array is shown in Fig. 2. The sensor is wired to a percutaneous connector that passes signals from the brain to signal processors and decoding computers. The percutaneous connector is complex because it must carry signals from each of the 100 electrodes in the array through a package compact enough to fit relatively unobtrusively on the head. Similar connectors have been used in cochlear implants and related devices (Downing et al., 1997).

Not only will NMP sensors have to process information, but processing must occur quickly if systems are to mimic the intact nervous system's operation. The processing required for 100 channels of neural data now requires multiple, PC-scale devices as well as signal amplification and processing hardware. This type of technology will tether patients to bulky, relatively immobile equipment. Success in early human pilot trials will likely drive microminaturization of the external components so that they can be fully implanted and the system can be portable; such devices for NMPs are already in development. Miniaturized, even implantable electronics seem possible because fast, cheap, microscale components are rapidly being developed for many purposes, such as cell phones and computers. Microelectronics sufficiently small to mount on the back of these arrays is feasible and is already in early stages of testing. Those with a silicon base (i.e. Michigan electrodes) can have electronics directly integrated directly into the electrode (Bai

a or b?

and Wise, 2001). It is more challenging to attach electronics for other sensors; electrically mating two dissimilar components on a very precise (micrometer) scales is a challenging engineering problem. Recently the Brown group has successfully attached a microscale, fully operational 16 channel amplifier and signal multiplexing integrated circuit directly onto a Utah array (Patterson et al., 2003). This silicon microelectronic chip reduces what is currently about the size of a DVD player to a fingernail thick platform about 5×5 mm across (Fig. 2c). Scaling this system to 100 channels is readily possible, with only a few leads required for the serialized data transmission and the powering of the chip. The design of such microelectronic chips takes concepts from current ultralow power microelectronic, such as encountered in cellular phones, to provide a technologically sophisticated microelectronic interface to the sensor array. Fully digital, serialized broadband data acquisition capability being developed as the next step towards eventual integration of all the functional components of the data acquisition system onto the sensor array (currently occupying an instrument rack).

Sensors will also require implantable power sources and telemetry to eliminate the need for percutaneous leads (Heetderks, 1988; Martel et al., 2001). These, too, are complex technologies for human devices, because the sensors require considerable power and high bandwidth that are at the cutting edge of current technology and they must be sealed from external fluids, ideally in a way that lasts for decades. While there is a growing effort being directed towards microscale neurotechnology, considerable development is necessary to achieve a fully implantable system that can provide reliable output with fully implantable sensors, electronics, and communication/telemetry systems. We are developing optically based connections which permit bidirectional communication with an implanted chip using only a single fiber thinner than a hair. The tremendous bandwidth of optical fibers coupled with the ability to provide on chip power through optical connections are potentially significant engineering feats that will allow future technology to be very

ultracompact and to be easily coupled to larger components placed in more accessible areas of the body, as is now done for cardiac pacemaker leads and their supporting power and control package. The fiber optical approach, in particular, is an intriguing and attractive concept to create a future "information neural superhighway" from/to the living brain.

3.2. Decoding

In addition to being able to sense neural signals, NMPs must be able to decode them. Decoding is a process by which neural signals are translated into an output that can serve as a useful control signal for real-world assistive devices for patients. In essence, decoding is a mathematical mapping between the activity patterns of neural populations and movement. Almost simultaneously, three labs recently demonstrated that ongoing hand motion can be accurately reconstructed from multineuron recordings in monkey MI (Paninski, 1999; Wessberg et al., 2000; Serruya, 2002; Taylor et al., 2002). These studies identified mathematical approaches to decode neural spiking patterns into a signal that reflects hand motion. Decoding could be performed within a few hundred millisecond using fairly standard computer hardware.

Decoding is a problem of classification of spike activity. Typically, spike count from small time bins (~ 50 ms) across many neurons are first compared to a desired or real output (e.g. path of hand motion) and then a function is created to relate the pattern of spike counts across the population of cells to that output. This function can then be used to decode future spiking observations into a hand motion or other outputs such as the selection of a switch. Linear filters, maximum likelihood discrete classifiers and neural networks have all been successful in decoding neural activity into reasonable estimates of hand motion (see Serruya et al., 2003 for overview and references). Which algorithms will be best is an area of active inquiry.

Advances in decoding require a principled mathematical approach so that algorithms can be rigorously evaluated and implemented. To that end we have adopted a statistical, probabilistic approach.

We view the problem of decoding as one of inference over time from sparse, ambiguous, and uncertain data – the intended movement based upon a complex pattern of the activity of many neurons. We have developed our approach from the large literature on control theory and probabilistic inference that addresses just this problem. This approach can be explained as follows: At a given instant in time we desire an estimate of the intended movement given the history of neural activity up to that time, the history of previous movements, and any contextual information we may know about the task. If we are trying to reconstruct movement, we can use the information we know about how the system performs naturally to help estimate the desired output. For example, if the past predictions of arm motion say that the arm is moving smoothly to the left, a decoded sample that predicts that arm should quickly be at a distant location on the right is highly suspect. Such improbable estimates could be eliminated until we gather more ‘evidence’ about what the neuron output is specifying. The probabilistic approach provides a clear framework to deal with these kinds of situations. Specifically, Bayes’ rule is used to invert what we know to what we predict: given that we can measure the probability of an observed firing pattern when we know the hand is moving left (written $p(\text{CurrentFiring}|\text{Movement})$), we can now predict how a firing pattern predicts a particular movement.

The problem can be formulated as one of modeling the probability of movement in terms of the observations and history:

$$p(\text{Movement}|\text{CurrentFiring}, \text{FiringHistory}, \text{MovementHistory}) \\ = \text{constant } p(\text{CurrentFiring}|\text{Movement}) \\ p(\text{Movement}|\text{FiringHistory}, \text{MovementHistory})$$

where we have exploited Bayes’ rule (and a first-order Markov assumption) to re-write the a posteriori probability on the left hand side in terms of two simpler probabilities. The first term, $p(\text{CurrentFiring}|\text{Movement})$, represents the encoding model of motor cortical activity. This quantifies the “likelihood” of observing a particular pattern of neural activity given a particular movement. The

second term on the right hand side represents the a priori probability of the movement. Hand motion, for example, has continuity and physical limits that are represented by this “prior”. This prior also defines how the history of previous measurements is incorporated into the current estimate of the movement.

We take movement to be represented by the position, velocity, and acceleration of the hand. It has been shown that these properties are roughly linearly related to the firing rates of MI cells (e.g. Georgopoulos et al., 1982; see also Serruya et al., 2003). We further assume that the observed firing rates are corrupted by Gaussian noise. This leads to an approximation of the likelihood as a simple linear Gaussian model, which is a simple way to model a noise process. We further assume that the hand

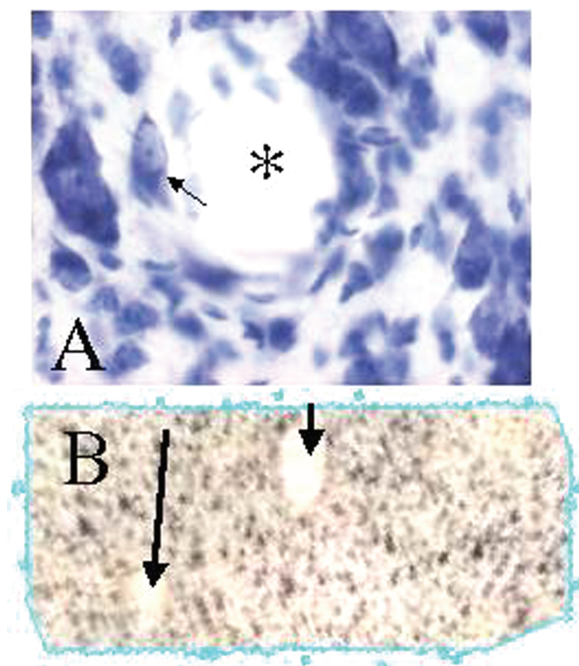


Fig. 4. Histological appearance of tissue after array implantation. A. photomicrograph showing normal appearing, Nissl-stained neurons near electrode tip (*), one month after array implantation. B. Lower power picture showing two electrode tracks (arrows), near layer V of motor cortex 2 years after implant. Tissue shows little sign of gliotic response, consistent with biocompatibility of the array.

motion at one time instant is linearly related to the motion at the previous time instant and is also corrupted by Gaussian noise. When these assumptions are met, the a posteriori probability is also linear and Gaussian and it can be optimally estimated using a Kalman filter which is a well understood and widely used method for real-time inference from noisy data. Despite the simplifying assumptions, we have found this Bayesian decoding method to be more accurate than the more common population vector or linear filter methods (Gao et al., 2002; Wu et al., 2003a, b).

The Bayesian formulation makes the modeling assumptions explicit. Without changing the basic framework, these assumptions can be relaxed and refined in principled ways. For example, we have been developing non-linear and non-Gaussian encoding models that may capture some of the additional complexity of neural activity (Gao et al., 2003). These necessitate new decoding algorithms

but the overall framework remains the same. As they develop, NMPs will be able to leverage current computer science research in probabilistic modeling and machine learning to develop new decoding algorithms.

Not only can motor cortex signals be decoded, this neural signal can substitute for actual hand motion in a visuomotor task, as Serruya et al. (2002) first demonstrated. Monkeys chased a target using a brain controlled cursor nearly as well as this task was performed with a hand controlled cursor (via a computer mouse). Cursor motion was implemented by decoding the output of multiple neurons with a linear filter; this decoded signals provided the x and y commands to drive the computer's cursor. Surprisingly, cursor control could occur without making hand tracking motions, which has implications for using MI activity for prosthetic devices in paralyzed humans. Taylor et al. (2002) had very similar findings contemporaneous with those of

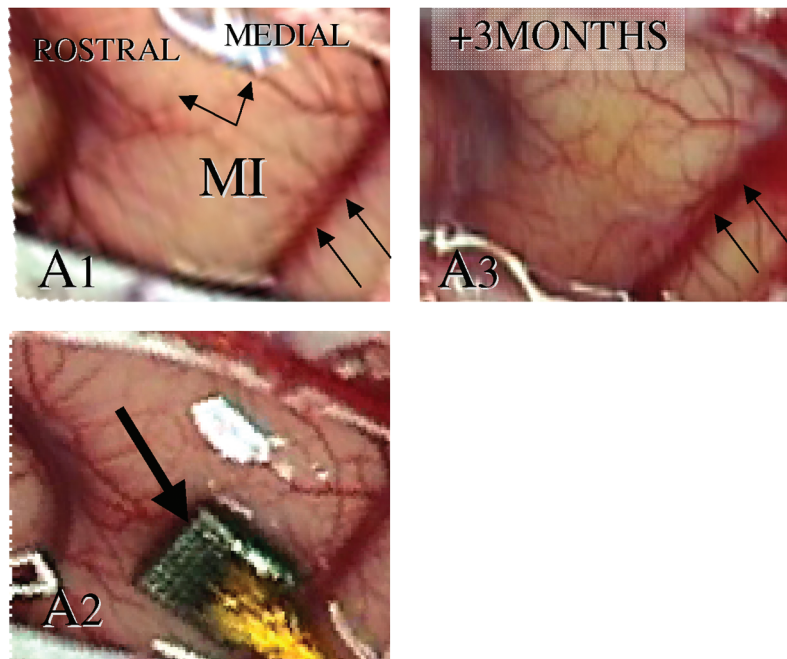


Fig. 5. Array implantation and removal. A1. Photograph of the motor cortex surface in a monkey prior to array implantation. A2. Immediately after array insertion. A3. Cortical surface from same animal in which array was removed 2 months earlier. Note the tissue appearance and surface vascular shows little change as a consequence of prior array implant, suggesting that these types of surface arrays can be safely removed.

Date
req.

Serruya et al. (2002) and further showed that this real-time control could be achieved in three dimensions, even when the hand motion was prevented. Whether additional coding dimensions can be extracted is unknown, but this will be essential if control is to be extended to more complex effectors that might incorporate arm, hand and finger motion. We anticipate that the probabilistic approaches we have adopted will guide and enhance our abilities to add this additional control.

4. Can NMPs be used in humans?

The recent accomplishments in recording and decoding and the base of animal data from multiple laboratories suggest that the approach is feasible in humans. However, important issues remain for human use. Decoding algorithms in animal research have been generated by first observing the relationship between hand motion and neural activity, as described in the previous section. The encoding model provides the basis to then build a mathematical *decoder* that turns this relationship around – so that movement can be predicted from neural activity. However, hand motion is not possible in paralyzed patients. It is not self-evident how to build an encoding model under these circumstances. Patients could imagine moving the hand to generate the necessary training data. Functional MRI (fMRI) studies demonstrate that humans activate the hand area of MI when they imagine moving (Humphrey et al., 2000; Shoham et al., 2001, Turner et al., 2001; Sabbah et al., 2002), but the fMRI method, being an indirect measure of neural activity, cannot demonstrate population that activity is sufficiently ‘normal’ to construct useful decoders. This will require direct human testing. However, a critical study by Kennedy et al. demonstrated that a paralyzed human can activate MI cells by imagining movement. The patient, JR, implanted with cone electrodes, was able to drive a computer cursor. (Kennedy and Bakay, 1998; Kennedy et al., 2000). With this small number of neurons, he was able to select at a rate of about 3 letters per minute, which is slower than desirable for practical NMPs. Nevertheless, this is a landmark

demonstration of the ability to couple brains to computers using neural signals in MI and further supports the conclusion that NMPs can be effective sources of new output signals in paralyzed humans.

5. Uses for Neuromotor prostheses

NMPs create an output signal to replace one that is aberrant or lost. To be valuable to movement-impaired patients, this output must connect to effectors that achieve some or all of the lost functions. Computers represent one of the simplest devices for a human to control because they are so highly developed to be a human friendly technology, and they are empowering because they have such far-ranging uses. Many of us spend large amounts of time communicating, learning, creating, and being entertained by pointing, clicking and typing on a computer. Many movement disorders restrict or eliminate the ability to use a computer. Mass production and relative simplicity in programming and interfacing with other devices has made it relatively easy to develop PC-based assistive products. Modern PC operating systems already come with control options to help those with functional limitations in vision or movement that could be sufficient for patients with NMPs. More versatile assistive software is also readily available (e.g. EZKEYS Words+Lancaster CA). These products are often designed around a simple switch or choice, which usually provides only very slow selection rate. For this ‘scanning’ software, the computer scans the cursor over the screen and a switch press is used to make a choice when the cursor moves over the desired target. With this technology, rates for typing, for example, are typically so slow as to barely be worth the effort to use, unless no other effectors are available. The current animal experiments have indicated that it is possible to achieve point and click with the cursor motion under direct brain control, which is sufficiently fast to navigate most computers near the speed of actual hand motion (Serruya et al., 2002). However, skill level, as well as learning abilities, for paralyzed humans awaits human trials. With a simple, but fast point and click ability it is

possible to type, web surf, and even drive a variety of external functions. Inexpensive commercially produced 'X10' modules can operate through simple computer commands to turn lights off and on, adjust room temperature and perform other such functions of daily living that are very challenging to those with compromised motor function. An effective NMP would mimic the hands' capabilities on a PC as well. Finger motion signals appear to be embedded in the spiking activity that gives rise to hand signals (Georgopoulos et al., 1999), a reflection of the multiplexed network organization of MI, although no one has found a means to decode this activity into finger-like control. Thus, it is plausible that a sufficiently large population could achieve further complexity of control, perhaps similar to what the arm and hand can achieve. Given the remarkable plasticity of cortex, including motor cortex (Rioult Pedotti et al., 2000; Sanes and Donogue, 2000), it may be possible for humans to learn very complex functions. These can be readily explored through a computer interface that simulates real-world applications; it is likely that there will be a vast amount learned about human NMP use with the first clinical pilot trials.

6. Future devices: what is needed?

NMPs are in an embryonic stage. Widespread adoption of this and related neurotechnology would continue to drive the quest for effective non-invasive sensors. Getting access to useful signals without an intracranial implant is a considerably more challenging task. There are a variety of imaging systems, like MRI or MEG machines, but these both give rise to filtered, indirect or more global signals and in current form are very large and expensive. Strategies to capture neural spiking could include amplifying and recording spikes through less invasive means. For example, if one could pass harmless molecular level tags to a subset of neurons, and these could amplify electrical signals and convert them to light of an appropriate tissue transparent wavelength, an external sensor might be able to detect spiking.

While this sounds fanciful, fluorescent semiconductor quantum dots to image neurons, which fulfill part of the first few requirements are already being tested now by our group (Shapiro et al., 2003). From a current perspective these developments are exciting, but the appearance of non-invasive spike recording systems like the one described here still seem quite far off.

NMPs described above detect and decode signals. Ideally these devices would be coupled to input devices that could provide feedback. Although cursor movement is well-guided by vision, manipulation by a robotic prosthesis or even an anaesthetic limb would be greatly aided with a form of tactile feedback to judge grip force or simply contact with objects (Chapin, 2000). Tactile feedback could be provided by electrical stimulation of the brain. Although electrical stimulation is highly artificial in the way it activates neurons, experiments in monkeys show promising results that stimulation of the sensory cortex can be used about as effectively as actual touch (see Donoghue 2002).

Assistive robots are another device that can potentially be controlled by NMPs and be useful to movement impaired individuals. Along with medical technology, robot capabilities are advancing at a very fast pace. The many autonomous functions of new robots may allow a brain-robot hybrid system in which very simple neural signals can command complex functions in an assistive robot. A test robotic arm that was driven by a neural output is shown in Fig. 1, but current brain controlled robots are only achieving simple actions. Actions that clearly benefit patients will be necessary. A wheelchair, for example, can be considered as a type of assistive robot. An NMP controlled wheelchair could free the 'sip and puff' users of the need to use their mouth for wheelchair movement when they are engaged in conversation, eating or other orofacial actions. Autonomous mobile robots use various sensors (sonar, infra red, laser, and video) to perform tasks such as obstacle avoidance, path planning, map learning and navigation through doorways. Similarly, current robotic arms use various end effectors (grippers or hands) and can exploit visual cues from

a video camera to perform automatic hand-eye coordination for grasping. Current cortical control signals are not yet rich enough or stable enough to achieve precise control for tasks as complex as robotic grasping. Consequently, we envision a hybrid human-robotic control system in which coarse commands are controlled via the NMP and the details are carried out autonomously. Similar problems have been faced for decades in the area of telerobotics and can provide a useful history for making more rapid advances for robotic NMP systems. A great deal more research will be necessary to understand the most natural models for neural control of robots. Even then, the best form of control will likely vary from patient to patient and may even vary over time for an individual.

Another goal of an NMP would be to restore movement to the patient's paralyzed muscles. Great strides have been made in methods to stimulate muscles through fully implanted functional electrical stimulation systems (FES). FES systems being developed at Case Western (Mauritz and Peckham, 1987) and the Bion system (Loeb et al., 2001) represent the two most advanced of these technologies. Current FES systems requires use of available muscle groups to activate a switch to produce muscle contractions. These actions may be poorly controlled or unavailable in paralyzed patients. A cortical control signal could provide a direct and more natural input to the paralyzed muscles and potentially a much richer control signal (Lauer et al., 1999). The success of NMPs in monkeys and the current FES systems suggest that early systems could be developed as soon as a useful FDA approved sensor is available.

The success of NMPs would undoubtedly spawn a new generation of related neurotechnologies with intelligent components and greater capabilities. Among these could be diagnostic aids: sensors that can detect abnormal brain states and report them to patients or their health care professionals. Therapeutic versions could incorporate treatment as well as diagnosis. For example, a sensor that could predict and block a seizure would be of profound medical value. Such devices might also be extended

to the treatment of psychiatric disorders, if brain activity abnormalities could be clearly identified and controlled. These sorts of applications have long development times given the current state of knowledge, but become more plausible with further testing of NMP technology.

7. Demands of NMPs on the medical system

Widespread emergence of neurotechnology will make new demands upon a variety of medical services. Successful NMPS in severely paralyzed patients could lead to their application in other movement disorder patients, including those with ALS, strokes, muscular dystrophy, cerebral palsy, Guillain-Barre Syndrome, among others. Increases in the number of functional neurosurgeons will be necessary if demand expands. The advent of DBS and other FDA approved neurotechnologies is stimulating the growth of this area and is bringing the experience of these individuals into the design and development of human applicable NMPs. Still, there is likely to be a need for additional training programs in this subspecialty. Neurologists will be required to track the function of these devices and to adjust them when necessary; such functions have already emerged for DBS, vagal nerve stimulator, and similar patients who require tuning of their stimulators or pumps. The unique integration of man and machine in an NMP, coupled with the medical needs of patients with movement disorders, is also likely to require specially trained physicians and health care workers. While monkeys have been trained to operate computers through NMPs in remarkable ways, we do not understand how humans will best use these devices to improve their lives. What will be the optimal form of an output signal? How much will abilities to function improve over time. This demand may fall on professionals in physical medicine and rehabilitation who must be able to help patients learn to use an NMP, select the best assistive devices, and use them to restore a productive life. This matching of assistive technology to individual

capabilities will require new training for rehabilitation therapists. Rehabilitation will involve training the human and robotic systems in a coupled fashion. Computer science, robotics, and programming may become essential components in the training of clinicians working with NMP patients. Neurotechnology may also make unusual demands on medical ethicists. As devices like NMPs become better understood and their uses extended into diagnosis and treatment of other CNS disorders, ethical issues may arise. How would we accept the ability to manipulate behavior with devices? It is not unreasonable that neurotechnology could advance to a state where psychiatric disorders could be effectively treated with a small implant that could sense and manipulate aberrant brain activity. What if we could enhance intelligence or control deviant behavior, would this be ethical? Although this may sound like a new challenge, electroconvulsive shock, psychoactive drugs, and psychosurgery have been, or are presently in wide use to alter undesired behaviors and have raised such debates previously (Fins, 2003). Nevertheless, it would be valuable to begin to consider how this new technology may be used in the best interests of human health and well-being before complex ethical challenges emerge.

8. Conclusions

The advent of NMPs and a wide variety of other neurotechnologies will provide a new way for physicians to treat their patients. NMPs will provide a way for humans with a variety of movement disorders to interact more effectively with the world. While these devices will at first be tied by wires to large external systems, their success will undoubtedly promote the development of tiny, implantable systems that are fully portable. These may be coupled to computers or assistive robots. Restoring movement via FES systems also seems very feasible. Such miniaturized sensors and stimulators give rise to a new generation of neurotechnology that can diagnose or treat a broad range of neurological and psychiatric disorders. The development of these

devices will make demands upon the medical system for new skills and for carefully considered ethical policies. However, the opportunities for improved health care and quality of life for many disabled humans is potentially profound.

Acknowledgements

The authors would like to thank the following for support of work described in this paper: NIH/NINDS grant NS25074 and contract RFP 99-03, DARPA BioInfoMicro Program, Keck Foundation.

References

- Bai, Q. and Wise, K.D. Single-unit neural recording with active microelectrode arrays. *IEEE Trans. Biomed. Eng.*, 2001, 48(8): 911–920.
- Benabid, A.L., Vercucil, L., Benazzouz, A., Koudsie, A., Chabardes, S., Minotti, L., Kahane, P., Gentil, M., Lenartz, D., Andressen, C., Krack, P. and Pollak, P. Deep brain stimulation: what does it offer? *Adv. Neurol.*, 2003, 91: 293–302.
- Chapin, J.K. Neural prosthetic devices for quadriplegia. *Curr. Opin. Neurol.*, 2000, 13(6): 671–675, Review.
- Cheney, P.D., Hill-Karrer, J., Belhaj-Saif, A., McKiernan, B.J., Park, M.C. and Marcario, J.K. Cortical motor areas and their properties: implications for neuroprosthetics. *Prog. Brain Res.*, 2000, 128: 135–160, Review.
- Csicsvari, J., Henze, D.A., Jamieson, B., Harris, K.D., Sirota, A., Bartho, P., Wise, K.D. and Buzsaki, G. Massively parallel recording of unit and local field potentials with silicon-based electrodes. *J. Neurophysiol.*, 2003, 90(2): 1314–1323.
- Donoghue, J.P. Connecting cortex to machines: recent advances in brain interfaces. *Nat. Neurosci.*, 2002, 5(Suppl.): 1085–1088, Review.
- Downing, M., Johansson, U., Carlsson, L., Walliker, J.R., Spraggs, P.D., Dodson, H., Hochmair-Desoyer, I.J. and Albrektsson, T. A bone-anchored percutaneous connector system for neural prosthetic applications. *Ear Nose Throat J.*, 1997, 76(5): 328–332.
- Evarts, E.V. Pyramidal tract activity associated with a conditioned hand movement in the monkey. *J. Neurophysiol.*, 1966, 29(6): 1011–1027.
- EZKeys. Words+, Inc. 2002 <http://www.words-plus.com/web-site/products/soft/ezkeys.htm>.
- Fins, J.J. From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of

- neuropsychiatric research. *Neurosurg. Clin. N. Am.*, 2003, 14(2): 303–319, ix-x, Review.
- Fofonoff, T., Wiseman, C., Dyer, R., Malasek, J., Burgert, J., Martel, S., Hunter, I., Hatsopoulos, N. and Donoghue, J. Mechanical assembly of a microelectrode array for use in a wireless intracortical recording device. 2nd Annual International IEEE-EMBS Special Topic Conference on Microtechnologies in Medicine and Biology, Poster no. 153, 2002.
- Gao, Y., Black, M.J., Bienenstock, E., Shoham, S. and Donoghue, J.P. Probabilistic inference of hand motion from neural activity in motor cortex. *Advances in Neural Information Processing Systems*, Vol. 14, The MIT Press. 2002.
- Gao, Y., Black, M.J., Bienenstock, E., Wu, W. and Donoghue, J.P. A quantitative comparison of linear and non-linear models of motor cortical activity for the encoding and decoding of arm motions. In *1st International IEEE/EMBS Conference on Neural Engineering*, March 2003, 189–192.
- Georgopoulos, A.P., Kalaska, J., Caminiti, R. and Massey, J. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J. Neuroscience*, 1982, 8(11): 1527–1537.
- Georgopoulos, A.P., Pellizzer, G., Poliakov, A.V. and Schieber, M.H. Neural coding of finger and wrist movements. *J. Comput. Neurosci.*, 1999, 6(3): 279–288.
- Heetderks, W.J. RF powering of mm- and submm-sized neural prosthetic implants. *IEEE Trans. Biomed. Eng.*, 1988, 35(5): 323–327.
- Humphrey, D.R., Corrie, W.S. and Rietz, R. Properties of the pyramidal tract neuron system within the precentral wrist and hand area of primate motor cortex. *J. Physiol. (Paris)*, 1978, 74(3): 215–226.
- Humphrey, D.R., Mao, H. and Schaeffer, E. Voluntary activation of ineffective cerebral motor areas in short- and long-term paraplegics. *Society for Neuroscience Abstract*, 2000.
- Jeffrey, K. and Parsonnet, V. Cardiac pacing, 1960–1985: a quarter century of medical and industrial innovation. *Circulation*, 1998, 97(19): 1978–1991, Review.
- Jones, K.E., Campbell, P.K. and Normann, R.A. A glass/silicon composite intracortical electrode array. *Ann. Biomed. Eng.*, 1992, 20(4): 423–437.
- Takei, S., Hoffman, D.S. and Strick, P.L. Muscle and movement representations in the primary motor cortex. *Science*, 1999, 285(5436): 2136–2139.
- Kalaska, J.F., Scott, S.H., Cisek, P. and Sergio, L.E. Cortical control of reaching movements. *Curr. Opin. Neurobiol.*, 1997, 7(6): 849–859.
- Kennedy, P.R. The cone electrode: a long-term electrode that records from neurites grown onto its recording surface. *J. Neurosci. Methods*, 1989, 29(3): 181–193.
- Kennedy, P.R. and Bakay, R.A. Restoration of neural output from a paralyzed patient by a direct brain connection. *Neuroreport*, 1998, 9(8): 1707–1711.
- Kennedy, P.R., Bakay, R.A., Moore, M.M., Adams, K. and Goldwithe, J. Direct control of a computer from the human central nervous system. *IEEE Trans. Rehabil. Eng.*, 2000, 8(2): 198–202.
- Kipke, D.R., Vetter, R.J., Williams, J.C. and Hetke, J.F. Silicon-substrate intracortical microelectrode arrays for long-term recording of neuronal spike activity in cerebral cortex. *IEEE Trans. Neural Syst. Rehabil. Eng.*, 2003, 11(2): 151–155.
- Lauer, R.T., Peckham, P.H. and Kilgore, K.L. EEG-based control of a hand grasp neuroprosthesis. *Neuroreport*, 1999, 10(8): 1767–1771.
- Loeb, G.E., Peck, R.A., Moore, W.H. and Hood, K. BION system for distributed neural prosthetic interfaces. *Med. Eng. Phys.*, 2001, 23(1): 9–18.
- Lozano, A.M., Dostrovsky, J., Chen, R. and Ashby, P. Deep brain stimulation for Parkinson's disease: disrupting the disruption. *Lancet Neurol.*, 2002, 1(4): 225–231, Review.
- Martel, S., Hatsopoulos, N., Hunter, I., Donoghue, J., Burgert, J., Malaek, J., Wiseman, C. and Dyer, R. Development of a wireless brain implant: the telemetric electrode array system (TEAS) project. *Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Vol. 4, 2001, 3594–3597, Istanbul, Turkey.
- Mauritz, K.H. and Peckham, H.P. Restoration of grasping functions in quadriplegic patients by Functional Electrical Stimulation (FES). *Int. J. Rehabil. Res.*, 1987, 10(4 Suppl. 5): 57–61. No abstract available.
- Maynard, E.M., Nordhausen, C.T. and Normann, R.A. The Utah intracortical electrode array: a recording structure for potential brain computer interfaces. *Electroencephalogr. Clin. Neurophysiol.*, 1997, 102: 228–239.
- Maynard, E.M., Hatsopoulos, N.G., Ojakangas, C.L., Acuna, B.D., Sanes, J.N., Normann, R.A. and Donoghue, J.P. Neuronal interactions improve cortical population coding of movement direction. *J. Neurosci.*, 1999, 19(18): 8083–8093.
- Moxon, K.A. Multiple-site recording electrodes. In: M.A.L. Nicolelis (Ed.), *Methods for Simultaneous Neuronal Ensemble Recordings*, CRC Press, Boca Raton, FL, 1999a.
- Moxon, K.A. Multichannel electrode design: considerations for different applications. In: M.A.L. Nicolelis (Ed.), *Methods for Neural Ensemble Recordings*, CRC Press, Boca Raton, FL, 1999b, 25.
- Mussa-Ivaldi, F.A. and Miller, L.E. Brain-machine interfaces: computational demands and clinical needs meet basic neuroscience. *Trends Neurosci.*, 2003, 26(6): 329–334, Review.
- Nicolelis, M.A. Actions from thoughts. *Nature*, 2001, 409.
- Nicolelis, M.A. Brain-machine interfaces to restore motor function and probe neural circuits. *Nat. Rev. Neurosci.*, 2003, 4(5): 417–422, Review.
- Paninski, L., Fellows, M.R., Hatsopoulos, N.G. and Donoghue, J.P. Coding dynamic variables in populations of motor cortex neurons. Abstract. *Society for Neuroscience*, 1999.

**Details
yet?**

- Paninski, L., Fellows, M.R., Hatsopoulos, N.G. and Donoghue, J.P. Temporal tuning properties of motor cortical neurons for hand position and velocity. *J. Neurophysiol.*, 2003, in press.
- Patterson, W.R., Song, Y-K., Bull, C.W., Ozden, I., Deangelis, A., McKay, J.L., Nurmikko, A.V., Donoghue, J.D. and Connors, B.W. A chipscale microelectrode/microelectronic hybrid device for brain implantable neuroprosthetic applications. Submitted to IEEE Transactions on Biomedical Engineering.
- Rioult-Pedotti, M.S., Friedman, D. and Donoghue, J.P. Learning-induced LTP in neocortex. *Science*, 2000, 290(5491): 533–536.
- Rousche, P.J., Pellinen, D.S., Pivin, D.P., Jr., Williams, J.C., Vetter, R.J. and Kipke, D.R. Flexible polyimide-based intracortical electrode arrays with bioactive capability. *IEEE Trans. Biomed. Eng.*, 2001, 48(3): 361–371.
- Sabbah, P., De, S.S., Leveque, C., Gay, S., Pfefer, F., Nioche, C., Sarrazin, J.L., Barouti, H., Tadie, M. and Cordoliani, Y.S. Sensorimotor cortical activity in patients with complete spinal cord injury: a functional magnetic resonance imaging study. *J. Neurotrauma.*, 2002, 19(1): 53–60.
- Sanes, J.N. and Donoghue, J.P. Static and dynamic organization of motor cortex. *Adv. Neurol.*, 1997, 73: 277–296, Review.
- Sanes, J.N. and Donoghue, J.P. Plasticity and primary motor cortex. *Annu. Rev. Neurosci.*, 2000, 23: 393–415, Review.
- Sanes, J.N. and Schieber, M.H. Orderly somatotopy in primary motor cortex: does it exist? *Neuroimage*, 2001, 13(6 Pt. 1): 968–974.
- Schmidt, E.M., McIntosh, J.S. and Bak, M.J. Long-term implants of Parylene-C coated microelectrodes. *Med. Biol. Eng. Comput.*, 1988, 26(1): 96–101.
- Sergio, L.E. and Kalaska, J.F. Systematic changes in directional tuning of motor cortex cell activity with hand location in the workspace during generation of static isometric forces in constant spatial directions. *J. Neurophysiol.*, 1997, 78(2): 1170–1174.
- Serruya, M.D., Hatsopoulos, N.G., Paninski, L., Fellows, M.R. and Donoghue, J.P. Instant neural control of a movement signal. *Nature*, 2002, 416(6877): 141–142.
- Serruya, M.D., Paninski, L., Fellows, M.R., Hatsopoulos, N.G. and Donoghue, J.P. Robustness of neuroprosthetic decoding algorithms. *Biol. Cybern.*, 2003.
- Shapiro, M., Ozden, I., Venkataramani, S., Uribe, H., Nurmikko, A.V., Tsomia, N., Mierke, D. and Connors, B.W. Semiconductor quantum dots with short molecular ligands for neuronal imaging applications. Submitted to *J. Neuroscience*.
- Shoham, S., Halgren, E., Maynard, E.M. and Normann, R.A. Motor-cortical activity in tetraplegics. *Nature*, 2001, 413(6858): 793. No abstract available.
- Taylor, D.M., Tillery, S.I. and Schwartz, A.B. Direct cortical control of 3D neuroprosthetic devices. *Science*, 2002, 296(5574): 1829–1832.
- Turner, J.N., Shain, W., Szarowski, D.H., Andersen, M., Martins, S., Isaacson, M. and Craighead, H. Cerebral astrocyte response to micromachined silicon implants. *Exp. Neurol.*, 1999, 156(1): 33–49.
- Turner, J.A., Lee, J.S., Martinez, O., Medlin, A.L., Schandler, S.L. and Cohen, M.J. Somatotopy of the motor cortex after long-term spinal cord injury or amputation. *IEEE Trans. Neural Syst. Rehabil. Eng.*, 2001, 9(2): 154–160.
- Vaughan, T.M., Heetderks, W.J., Trejo, L.J., Rymer, W.Z., Weinrich, M., Moore, M.M., Kubler, A., Dobkin, B.H., Birbaumer, N., Donchin, E., Wolpaw, E.W. and Wolpaw, J.R. Brain-computer interface technology: a review of the Second International Meeting. *IEEE Trans. Neural Syst. Rehabil. Eng.*, 2003, 11(2): 94–109. .
- Wessberg, J., Stambaugh, C.R., Kralik, J.D., Beck, P.D., Laubach, M., Chapin, J.K., Jim, J., Biggs, S.J., Srinivasan, M.A. and Nicolelis, M.A. Real time prediction of hand trajectory by ensembles of cortical neurons in primates. *Nature*, 2000, 408(16): 361–365.
- Wolpaw, J.R., Birbaumer, N., McFarland, D.J., Pfurtscheller, G. and Vaughan, T.M.. Brain-computer interfaces for communication and control. *Clin. Neurophysiol.*, 2002, 113(6): 767–791.
- Wu, W., Black, M.J., Gao, Y., Bienenstock, E., Serruya, M., Shaikhouni, A. and Donoghue, J.P. Neural decoding of cursor motion using a Kalman filter. In: *Advances in Neural Information Processing Systems 15*, MIT Press, 2003a.
- Wu, W., Black, M.J., Mumford, D., Gao, Y., Bienenstock, E. and Donoghue, J.P. A switching Kalman filter model for the motor cortical coding of hand motion,. In: *Proc. IEEE EMBS*, 2003b.