CHAPTER 7.9

DESIGN PRINCIPLES OF A NEUROMOTOR PROSTHETIC DEVICE

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Neuromotor prostheses are a type of brain-machine interface (BMI) that seek to extract signals from the central or peripheral nervous system and deliver them to control devices. A brain-machine interface is necessary to detect activity that can be voluntarily modulated for use as a motor control signal. It is generally accepted that electrical potentials are the most valuable sources of information. Neural commands for voluntary movement are essentially issued as electrical signals produced by the spiking (action potentials) and synaptic input of individual neurons; both can be recorded with varying degrees of fidelity and difficulty. The goal is to be able to detect signals that have the largest amount of information about movement and that change about as rapidly as movement commands themselves change. Clearly, recording at the source of the motor commands most readily fulfills these requirements, but indirect recordings of surrogate signals can provide an alternative or supplemental source, if one can learn to make indirect signals mimic motor commands. The decoding methods for use in neuromotor prostheses are the culmination of many years of basic research on the motor system. Whereas recovering movement dynamics and kinematics from neural activity alone comprises a feat of basic science, their use as a control signal marks a shift to applied neuroprosthetics. In this chapter we review mathematical algorithms that have been tested in prototypes of intracortical neuromotor prostheses. 'Closed-loop' refers to the situation wherein the subject is provided access to recovered movement information, and is required to use this prediction signal in a behaviorally useful manner. This access may be afforded visually (neurally derived cursor trajectories), mechanically (as in stimulation of muscles via implanted electrodes), or any number of output devices. We will consider several features that are unique to the closed-loop context of online control, including those specific to use in paralyzed human patients. We consider here the advantages and disadvantages of field potentials and spikes; in the final section of the chapter, we argue that a principled combination of all available information channels, processed by a multiplicity of decoding algorithms, will result in the most effective neuromotor prosthesis.

1. Introduction

Neural prostheses that can restore or augment human functions are now appearing as the result of rapid engineering and biomedical advances in the emerging field of neurotechnology. Devices to restore hearing already are available, while those to reinstate sight and movement are advancing rapidly. While sensory devices have as their goal to inject signals into nervous system (typically the brain), motor prostheses seek to extract signals from the central or peripheral nervous system and deliver them to control devices. It is often forgotten that all voluntary output of the nervous system, whether it is cognitive or a low level reflex, must be produced by a signal from the central nervous system (CNS) to the muscles. This includes a wide range of functions as speech, walking, emotive expression, as well as bowel, bladder and sexual function. Thus loss these actions when the pathways are damaged could be reversed by extracting control signals from the CNS and using them to drive output devices, including physical systems such as computers or robotic devices, other parts of the nervous system, or the muscles themselves.

In a fundamental sense, paralysis restricts the ability of the individual to interact with their environment. In many motor disorders, such as ALS, muscular dystrophy, or spinal cord injury, the individual can be cognitively normal and fully able to generate detailed movement plans using higher motor control structures. Neuromotor prostheses (NMPs) may either re-create the actual lost function or to provide a useful surrogate action to return the ability for the individual to interact with their environment.

Three overarching components are necessary for any NMP (Fig. 1). First, an interface with the nervous system must be developed. This brain machine interface (BMI) must provide a means to detect or inject signals, be safe, last for long periods of time. The interface may contain only passive components, but active signal processing may be required for weak or noisy electrical signals. For devices that are implanted into the body, both the interface and attached processing units must be biocompatible, immune to tissue damage, and sufficiently compact to fit into or onto the body. The second essential design component is signal decoding. Once signals are acquired, subsequent instrumentation must further process signals into a form appropriate for mathematically-based decoding algorithms. The output of the second processing stage is in a form that can be used by physical or biological devices that produce intended actions. In a sense this component is a decoder that translates brain language into machine language. The third component required for an NMP are devices that make effective use of the neural control signals. This includes not only the identification of devices that serve practical purposes, but also the engineering of interfaces that can allow safe, meaningful use of the control signals. Such devices include computer point-and-click type interfaces, the person's own muscles, robotic arms, or even semiautonomous robots. In this review we will consider the design principles to accomplish each of these three major steps necessary to produce an effective NMP. These principles are established on the basis of the current state of knowledge of NMPs from the literature and from our own laboratory, both of which will be reviewed here.

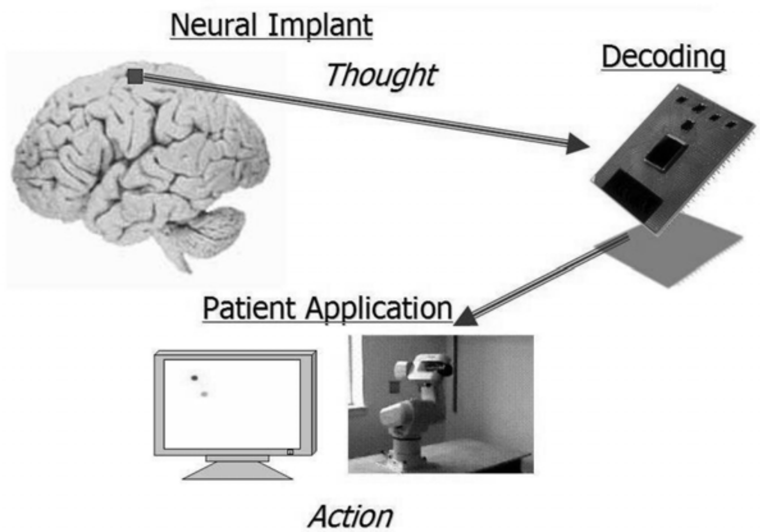

Fig. 1. The three major components of a neuromotor prosthetic. The physical brain-machine interface comprises a neural implant which chronically records the activity of neurons in the brain. These recorded signals are sent to hardware and software which decode that neural activity into intended movement signals. These signals in turn drive the third part of the neuromotor prosthetic, an output device for use by the patient whose neural activity is being decoded. This chapter discusses the range of choices for each of these components.

2. Control Signals

A BMI is necessary to detect activity that can be voluntarily modulated for use as a motor control signal. It is generally accepted that electrical potentials are the most valuable sources of information. Such BMIs are therefore specialized recording electrodes. Other signals such as chemical, metabolic, or blood flow changes are potential sources of information. While BMIs that incorporate these alternative information sources should not be dismissed, they are considered beyond the scope of the current review. Only electrical potentials are discussed below

A major design constraint on BMI interfaces is deciding which type of electrical signal is desired. The nervous system emanates a variety of signals in different frequency bands, with different information content and differing ability to be brought under voluntary control. Neural commands for voluntary movement are essentially issued as electrical signals produced by the spiking (action potentials) and synaptic input of individual neurons; both can be recorded with varying degrees of fidelity and difficulty. The goal is to be able to detect signals that have the largest amount of information about movement and that change about as rapidly as movement commands themselves change. Clearly, recording at the source of the motor commands most readily fulfills these requirements, but indirect recordings of surrogate signals can provide an alternative or supplemental source, if one can learn to make indirect signals mimic motor commands. Nearly all parts of the nervous system are in some way engaged in planning or performing a movement (consider the visual, auditory, proprioceptive and muscle signals issued in relation to reaching for a ringing alarm clock), and each of these areas might be evaluated as a source for control signals. Signals related more directly to limb motion are present in a more limited, but still diverse, set of structures, including the cerebral cortex, thalamus, cerebellum and spinal cord. The cerebral cortex is a particularly suitable site for BMIs. By being close to the surface, it allows ready access to electrical information via a number of recording technologies without penetrating deep into the brain.

From the cortex, one can attempt to detect the spiking of neurons, which are fast events (~ 1 ms, modulating from zero to a few hundred Hertz) reflecting the output of individual cells, or field potentials which carry information that is related to synaptic inputs and local processing and other forms of time locked massed activity (e.g., a fiber volley). As will be discussed below, the basic tradeoffs between spiking and field potential signals are speed, degree of control, and difficulty in recording. Slow potentials are easier to record and are available non-invasively from the scalp surface, or less invasively without penetrating neural tissue. However, slow potentials modulate more slowly than spikes and carry significantly less information about the details of intended movement[22,76,104]. By contrast spikes are difficult to record and require invasive methods, but they carry considerable movement information that modulates on the time scale with movement. We consider here the advantages and disadvantages of field potentials and spikes; in the final section of the chapter, we argue that a principled combination of all available information channels, processed by a multiplicity of decoding algorithms, will result in the most effective neuromotor prosthesis.

2.1. Field potentials

Field potentials (FPs) reflect the summed currents of a volume of tissue and are hence indirect measures of neural processing. As such, FPs can be detected by large electrodes placed on the skin or on or in the cortex. Because they volume average, they are relatively insensitive to the exact placement of electrodes, which is a marked advantage; but for the same reason they also contain severely reduced information about underlying neural processing. Nevertheless, neural prostheses based on these signals have received considerable attention. We will only briefly review the current use of these signals for neural prostheses because this has been comprehensively covered elsewhere[111].

The electroencephalogram (EEG) is the easiest to record reflection of brain electrical activity. With only a few surface electrodes and inexpensive signal processing equipment, surface voltages can be detected at the scalp. Consequently, the EEG and other surface potentials initially received the greatest attention as a possible control signal source for a neuromotor prosthetic device, and devices based on this type of signal have been implemented with some success[61]. However, there are three major disadvantages to the use of the surface EEG as control signals: 1) they are slow to engage or modulate (over 1 second) so that control signals derived from EEG cannot mimic natural actions, 2) they require mental concentration to the exclusion of other activities, and 3) continuous control beyond 1 dimension is difficult to achieve.

Wolpaw et al.[111,112] observe that the maximum output rates of EEG based signals only achieves 5–25 bit/minute, but true operation rates are typically much lower. Despite these limitations, humans are able to acquire voluntary control over the amplitude or duration of EEG signals in certain frequency bands. Subjects require some form of auditory, visual, or other biofeedback during the training phase in order to develop control. One common technique is known as 'alpha-suppression' in which the 8–10 Hz frequency band amplitude is voluntarily suppressed. In this biofeedback based scenario, EEG signals are only used to trigger events, rather than provide continuous control. Spurious detections can be minimized by requiring the power to be suppressed for a certain amount of time, or by requiring multiple threshold crossings.

Such control has been used for human systems. For example, Lauer et al.[64] have coupled a beta-suppression based EEG system to an implanted electrical stimulation neuromuscular hand-grasp system: C5 quadriplegic patients successfully used this EEG-based signal to open and close their hands via implanted stimulating electrodes. Birbaumer et al.[9] and Kaiser et al.[53] implemented an EEG-biofeedback system to provide low-dimensional control to functionally locked-in patients (see Chap. 7.8). Muller-Gerking et al.[75] demonstrated two types of EEG activity over primary motor cortex during visually guided movement: a rapid burst in activity induced by the visual cue (300 ms long event) and movement related desynchronization (or synchronization) at movement preparation and initiation (1.5 s event), suggesting that different signals types may be obtained from the EEG. These could be exploited for different types of control. Note that these signals are not related to movement kinematics or dynamics (i.e., forces) but are reflections of desired actions.

2.2. Event related potentials

Event-related potentials (ERPs), which occur in response to an 'event' such as a flash of light, a sound, or internally generated intent to move, can be also be used as control signals. One useful evoked potential, available at the scalp surface, is the positive waveform occurring approximately 300–450 ms (P300) after an infrequent task-relevant stimulus appears or is initiated[21]. A visual ERP, for example, can distinguish which of several LEDs or colored targets a subject was regarding[7]. These systems appear to be able to register relatively fast changes, on the order of 50–300 ms, although sensory evoked ERPs require fixed gaze and attention of the participant[7,21]. Thus, for all the surface recording strategies, the range of discrete states that can be easily achieved is small, and signal modulation is very slow, largely precluding the use of EEG-based signals for complex continuous movement control.

2.3. Cortical surface recordings

Cortical surface recordings, obtained by placing electrodes in contact with the meninges to approximate the cortical surface, are used to decrease signal to noise problems introduced by the strong filtering and signal attenuation that occurs with scalp recordings. In addition, areas of the brain inaccessible by external recordings are available, such as the mesial surface of the temporal lobe. These signals are often termed the electrocorticogram (ECoG) or the intracranial EEG (iEEG), although they are sometimes called local field potentials (LFPs), primarily in the experimental animal literature. This nomenclature creates confusion with the LFPs that may be recorded by intracortically placed electrodes, which are a similar signal but can be more local depending on the nature of the recording electrode. In both cases the signal is a slow wave (<100 Hz), not containing spike activity (but see [67]).

The greater focality of the ECoG seems to provide a more useful signal to identify major states related to an intended movement because it may be able to detect local processing that is either topographically more discrete (arm vs. leg) or has greater resolution of movement intent. Consistent with this conclusion, Levine et al.[66] found that the speed and accuracy of motor-related ERP classification is better when performed on ECoG rather than surface EEG signals.

Electrodes placed at different cortical surface locations can be used to classify task parameters, such as voluntary movement frequency, the internal or external nature of the movement cue, the imagined or attempted degree of volition, and the stage of learning (novel task or overlearned). In this regard, Kunieda et al.[62] found that while movement-related potentials were recorded from electrodes over primary sensorimotor cortices during both rapid (2 Hz) and slow (0.2 Hz) finger movements, only slow movements produced such potentials over the supplementary motor cortex (SMA).

This detail of control may be useful at the muscle level. Marsden et al.[70] examined the coherence between EMG of selected muscles and neural activity recorded at pairs of ECoG electrodes on a subdural grid. They found that 50 to 70 ms periods of coherence between ECoG pairs and EMG occurred in different frequency bands (ranging from 5 to 100 Hz) occurred at different locations, and that areas of cortex several centimeters apart could show coherence with certain muscles despite intervening cortex not showing such coherence. Furthermore the intervening cortex could show coherence with the muscles during other tasks. Toro et al.[104] further found that the amplitude and direction of hand movement in humans influenced the magnitude, duration, and extent of the spatial distribution of ECoG power changes in the 8–12 Hz band.

Taken together, these findings suggest that the tens of surface electrodes used in subdural grids could provide enough information to be able to distinguish among a number of intended movement conditions. Whether the ECoG is sufficient to extract the details of a hand motion, in particular a continuous hand motion, appears limited, but this has not been ruled out experimentally.

2.4. Intracortical recordings

The nature of signals available is again different when electrodes are placed into the cortex; it is at this level that electrodes can record either field potentials or spiking. Low-pass filtering (<100 Hz) of intracortical activity yields a local field potential (LFP) signal thought to embody the collective synaptic input of local neuronal clusters[36]. How this signal reflects the neural output is not established. In visual areas the LFP appears to be a coarser representation of the underlying spiking activity or perhaps cognitive variables[32]. However, this does not hold for primary motor cortex (MI) where LFPs are an unreliable correlate of neural activity[5,22,76]. Donoghue et al.[22] compared LFP and extracellular multi-unit activity recorded at particular electrodes and found that: 1) LFP suppression with motor action was ubiquitous across primary motor cortex even if neurons at that site began to fire with motion, and 2) fast LFP oscillations appear quickly upon transition from quiet sitting to resumption of task performance even when neurons are not briskly modulating. The results of combined LFP and neural discharge recordings indicate that LFP oscillations reflect a global process involved in motor planning and preparation, but in MI they do not necessarily capture the details of the motor action[5,22,76]. Thus in MI, the LFP seems to be a useful signal to identify the intention to move, but not more. By contrast LFP signals recorded in the parietal cortex suggests that LFPs contain sufficient information to predict one of eight discrete directions with 100% accuracy, as well as task state, although these seem to obtain from higher frequency bands that are less evident in MI[73,83]. These studies suggest that intracortical LFP recordings may be able to provide discrete motor signals potentially with greater information than that available from the scalp or cortical surface.

2.5. Extracellular unit activity

The firing of neurons in motor cortical areas provides the richest set of movement related signals. Neuron spiking carries specific aspects of the actual motor signal, and such neurons with motor information are broadly available in cortex. Particularly relevant to neuromotor prostheses, neurons rate modulate on a time scale suitable to generate movements as fast as they occur naturally. For voluntary arm movements in primates, which have been most extensively studied, spiking correlates with force, muscle activity, joint angle, movement direction, and the significance of a cue[25,30,51,55,103]. Direction coding of hand motion in reaching tasks has been the most extensively studied of all coding. Neurons located throughout frontal and parietal cortex modulate their firing in a cosine tuned manner that reflects the direction of an intended reach[34,93]. Across areas, neurons vary in the mixture of movement signals they carry; information is generally overlapping between areas. Some of these carry force information; others may be coupled with other movements such as gaze direction[4,13].

The firing rate of individual neurons varies on a short time scale, certainly less than 50 ms and possibly within few milliseconds, so that it could be used as a dynamic control signal. The spiking of individual neurons is a somewhat noisy representation of one or more underlying motor parameters, approximating an inhomogeneous Poisson process. Under the assumption that noise is independent, averaging has been used to show that pooling small numbers of neurons (<100) results in very accurate predictions of reach direction[42]. Simultaneous recordings of multple neurons show that noise is not independent. Consideration of the interactions of neurons, such as their broad firing rate correlations, yields additional movement information[71,79]. Most studies have attempted to reconstruct a discrete parameter, such as the final direction of a movement; however, spiking can also be used to reconstruct continuous movements[82,96,98]. These studies in non-human primates indicate that spike processes of neurons are a rich source of signals to provide a real time, discrete or continuous control for a motor prosthesis for humans. The need to average across cells and the potential for extracting information through interactions, demand that multiple neurons be recorded simultaneously to use spiking for motor prostheses.

By contrast with these marked advantages of spiking, single neuron recordings present a formidable technical challenge to use for a prosthetic device. In order to record spiking, a small recording surface (a cone of 8–30 μm height that tapers from a base of 4–20 μm to a tip of 1–2 μm) must be brought close to the cell body of a neuron[47]. Electrode tips must be placed ~100 μm or less from a cell body of <50 μm in diameter (median pyramidal cell diameter for cortex is ~ 20 μm [72]). Optimal electrodes appear to have a geometry such that the recording surface tapers to a point, although successful recordings can be obtained by some using flat surfaces on the side of an electrode or at the cut end of a small diameter (~ 50 μm) wire[3,100]. The tolerances of these measures are determined by the shape and size of the neuron as well as the type and shape of the recording electrode and other complex factors; for the most part they have been empirically derived.

Stable recordings are rather intolerant of even small motions of the electrode (ca. 50 μm) which can change the signal to noise ratio and dramatically alter the shape of the recorded waveform, including a complete reversal of polarity[40]. Because neurons are noisy encoders or because information is spread across a population of cells, derivation of a control signal requires simultaneous recordings from many cells at once, an even more daunting technical challenge which will be discussed in the next section. Further, use of neuron spiking requires that signals be digitized at much higher rates (ca. 40 kHz/channel) than LFP or EEG signals (<2 Khz/Channel) which are inherently lower frequency signals. Finally, extraction of signals that are based on identified single neurons requires computationally intensive processing to sort spike waveforms from background noise. Together these results suggest that each type of signal has a potential value for prosthetic devices, although spiking is the both the richest source of information and the most difficult to obtain.

3. Recording Devices

3.1. Surface and subdural recording

The type of recording devices and their availability and safety constrain the solutions that can be applied to the creation of NMPs. Surface EEG confers the major advantage of being non-invasive, and easy to record and process with reliable, commercially available products. With only a few surface electrodes and inexpensive signal processing equipment, surface voltages can be recorded and sent into computers to be transformed into a control signal. Electrocorticograms use the same technology as EEG, but the electrodes are embedded in a thin plastic pad which is placed directly over cortex, beneath the dura mater. Commercially produced, these FDA approved subdural grids are currently widely used in humans to locate seizure foci that cannot be found with less invasive methods. These grids remain percutaneous for a few weeks but it is not clear whether they could remain safely to chronically record a motor signal. In addition, the output leads are currently percutaneous which tether the patient to a large recording system. Most subdural grids consist of 20 to 128 electrodes and cover between 5 to 40 cm^2 of cortex, so that relatively few cover a particular topographic motor area, such as the arm area of MI. Placement of electrodes with high precision is not practical, but it is also not a major concern, because of the number of recorded sites and the summed, volume conducted nature of the signal.

3.2. Intracortical recording

Recording intracortical signals, either spiking or LFP, requires the insertion of electrodes into the cortex. The invasiveness of this insertion procedure raises the threshold for use because of potential risk of mechanical damage to the brain during implantation or postoperative problems, such as infection. However, it should be noted that devices such as surface EEG grids, ventricular shunts, deep brain stimulators, and drug pumps are routinely surgically placed in the nervous system. Small intracortical devices should present less risk of damage than these devices; and infection risk is roughly the same for any intraoperative procedure done in a modern facility. For devices, skin infections are the more common source of problem[10,84], rather than within the CNS itself. Thus intracortical implants do not demand skills that are wholly unfamiliar to surgeons or present undue risks for debilitating neurological problems.

Intracortical devices can provide two types of signals: LFP and neuron spiking activity. Both high (spikes) and low (LFP) frequency activity may be recorded simultaneously on the same electrode, if impedances and tip designs are appropriate. LFPs may be recorded with larger tipped (hence, typically lower impedance) electrodes; spiking of individual neurons requires smaller tips to obtain useful signal to noise ratios. Multiport electrodes[3], microwire bundles[74], cone electrodes[56], and electrode arrays comprise the main intracortical recording tools available to collect multiple single neurons.

Multiport electrodes made with recording patches arranged along a silicon shank are useful for LFP recordings but have been less widely used for single neuron recording devices[3,40]. Multiport electrodes have been designed as single probes and as multiprobe arrays with the intention for use as a chronically implantable device for humans. They have the marked advantage of being very flexible in design because they utilize semiconductor manufacturing process, but being thin they can be difficult to insert and stabilize in the cortex for long term implantation. These electrodes have been developed and distributed for a number of years by the Michigan group.

Microwire bundles, comprised of a group of ~ 50 µm insulted metal wires are successful at recording neurons and can be implanted for long periods of time. However, these devices are fabricated by hand and their recording characteristics are difficult to control. The wires are typically cut off by hand upon insertion making tip properties highly variable and they can cause tissue compression during insertion because they have a blunt surface. Typically wires are fixed with respect to the skull so they can cause considerable damage due to relative motion between the skull and brain, which is on the order of 2 mm in humans. Further, the reliability of wires to provide signals in which single neurons can be recovered is now more of an art form than a science. Nevertheless, both Nicolelis[110] and Schwartz et al.[92] have been highly successful in obtaining chronic cortical recordings in non-human primates with custom fabricated wire bundles.

Cone electrodes, created by Philip Kennedy, consist of a glass pipette filled with a trophic factor to induce in growth of neurites[56]. The cones are inserted into the cortex where neural processes grow in to establish contact with recording wires. It is not known which cells types respond to the damage of the insertion or the presence of the growth factor, so the source of signals obtained are not known. The wires are attached to an implantable signal processing and telemetry system which is simple and reliable, though presently limited in the number of channels transmitted. Unlike any other device up to this time, this technology has been successfully implanted in human motor cortex, where recordings have been obtained and sustained for years. Humans have used these signals to control devices; this achievement provides an important demonstration that neural signals can be usefully employed once they are detected[57,58].

Microelectrode arrays form another class of intracortical recording devices (Fig. 2). Arrays are fundamentally a lattice arrangement of a group of microelectrodes, each one typically designed along the lines of a standard recording microelectrode. Sharpened metal rods insulated except at the tip have been the mainstay of electrophysiology for half a century because they produce high quality signals, which motivates their use for prosthetic devices. The "Utah" array, designed by Richard Normann and colleagues consists of 100 such microelectrodes[52,72], but they are fabricated from silicon. Metal arrays are being developed by others; these include the system developed by deCharms et al.[20] and the MIT/Brown array[14,31].

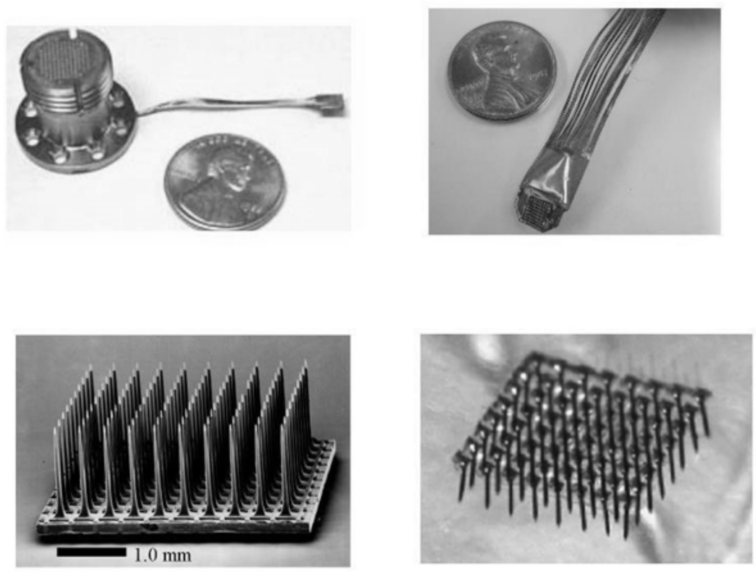

Fig. 2. Two examples of multi-electrode array technology. The left-hand column shows the Utah array developed by Dick Normann at the University of Utah and subsequently commercialized by Bionic Technologies (now part of Cyberkinetics, Inc). The upper left photo shows the array and the percutaneous connector. The right-hand column shows a metal array developed in a collaboration between Brown University and MIT.

Silicon electrodes have been used successfully to record single neurons for years in non-human primates. They have significant advantages over other technologies in that they can be fabricated under precise control in a variety of patterns, shapes and configurations. In addition, arrays are allowed to float on the cortical surface, so that relative motion of the skull and electrode tethering through the connection cable is less of a concern. Observations from our laboratory based on data from twenty eight arrays indicate that useful signals can be derived from ~ 30–40% of the active electrodes.

All these invasive devices raise the concern of long term biocompatibility and stability. Useful neural signals can be obtained with cone, wire, and array electrodes, and early histological evaluation suggests that tissue reaction is acceptable; indicating that suitable long term interfaces can be achieved. In support of the long term acceptance of devices in the brain, electrodes implanted in the ventrolateral thalamic and subthalamic nuclei of humans to treat the motor impairment symptoms associated with Parkinson's disease and essential tremor have functioned for several years[84].

3.3. Physical constraints of an NMP interface

All recording devices have packaging size, bandwidth, and power consumption issues that must be considered in their design. These are significant when considering implanted devices because they must survive in a hostile environment for long times. The implanted hardware can be viewed as having three separate parts: (1) recording electrodes; (2) signal conditioning, typically with pre-amplification and filtering to extract the desired signals (e.g., spike, LFP); and (3) a processor to transform signals into a useful control signal. In addition, there must exist a means to transmit the signal between recording, conditioning and processing devices.

The first component can be considered a passive one, while the others are active because they have circuits with power demands. Currently, for implantable systems being developed in primates[43,56,60,72,89] the active components (2, 3) are outside the subjects' body and signals are passively conveyed to signal processing devices, although Kennedy's system conditions four channels and transmits them. In the future, miniaturized signal conditioning and processing systems and telemetry will be necessary. Low-power, high channel telemetry systems for dozens to hundreds of channels are now at or beyond the edge of current technology.

The materials of the implanted device as well as the circuitry and wiring must be biocompatible. This is a two direction challenge. The package must be made of materials that will prevent its degradation from biological reactions and the materials must not damage to surrounding tissue either mechanically or though tissue reaction (e.g., inflammation or gliosis). These are formidable problems that cannot be considered as a stationary process. As the tissue reacts to the implant, the environment may change; thus materials suitable for short term implantation may not be adequate over the long term[3,38,71,89,106]. FDA approved biocompatible epoxies and thermoplastic polymers such as parylene remain the most likely materials to coat and encapsulate the implanted neural interfaces because they have the longest history of testing. Other significant issues relate to the nature of cabling from electrodes to other connectors or processing devices, high density percutaneous connectors, and telemetry devices. These will only be considered briefly here because they are discussed in greater detail elsewhere[45].

EEG and LFPs have signal power in the 1–200 Hz range, so that amplifiers and A/D design is well within the bandwidth and signal processing power that is currently available. Small packaging is perhaps not yet satisfactory if ~ 100 channels are desired. A signal of 20 kHz aggregate rate (200 x 100 channels) is easily processed by modern circuitry, especially if this is done on a standard PC board without miniaturization. By contrast, the demand for large numbers of single neurons is substantial by present standards. Individual action potentials last ~ 1 ms. Effective transmission of the extracellular potential waveforms should have a sampling rate 40 kHz or higher. Neural data from 100 electrodes at a sampling rate of only 10 kHz with a resolution of 10 bits, requires a baud rate of 2 gigabits/s. This is not easily achievable by current technology, especially if it is designed to be small enough for subcutaneous implantation. Another concern is that beyond a radio frequency of 300 MHz, signal energy (as locally dissipated heat) may damage tissue.

Such implanted NMPs must also have sufficient power to continuously amplify and stream high bandwidth data from multiple parallel channels and yet not produce excessive heat that would alter or damage tissue. Amplification of the 10 to 300 μV neurally generated signals is discussed in Section II of this book. It is not clear that battery technology is sufficient to power completely self contained multiple single neuron NMPs, while a surface system with external (percutaneous) connections is possible to fabricate using available technology. Implantable neuromuscular stimulators[41,69] employ inductive techniques to transcutaneously power implanted electronics; a similar strategy might be used to power recording processors.

4. Decoding Algorithms: Principles

The decoding methods for use in neuromotor prostheses are the culmination of many years of basic research on the motor system. Whereas recovering movement dynamics and kinematics from neural activity alone comprises a feat of basic science, their use as a control signal marks a shift to applied neuroprosthetics. In this section we review mathematical algorithms that have been tested in prototypes of intracortical neuromotor prostheses. We define ‘open-loop’ to signify recovery of movement information that takes place without the subject being aware in any way of this recovered information. Such open-loop processing usually occurs offline as recorded experimental data is analyzed, but may also happen in real time as the experiment progresses and the investigator observes ongoing predictions, though the subject remains unaware of them. ‘Closed-loop’ refers to the situation wherein the subject is provided access to recovered movement information, and is required to use this prediction signal in a behaviorally useful manner. This access may be afforded visually (neurally derived cursor trajectories), mechanically (as in stimulation of muscles via implanted electrodes), or any number of output devices. We will consider several features that are unique to the closed-loop context of online control, including those specific to use in paralyzed human patients.

4.1. Two learning machines

In seeking a control signal we are confronted with two general approaches: do we have the computer learn the relationship between neural signals and some external parameter ('computer learns subject') or do we have the subject learn how to drive his own cortical activity that is arbitrarily assigned to an external signal ('subject learns computer')? These two coupled learning systems could fail to converge (which would be tantamount to 'chasing the noise', Mumford, 2001, personal communication), thus preventing the genesis of a useful control signal. In theory, a perfect mathematical prediction of a subject's intended movement would require no effort or learning to use, whereas a randomly varying weighting of a subject's neural activity would be impossible to learn.

In practice, an optimal system will most likely occupy a ground in between completely accurate decoding and fully mastered biofeedback control; both learning systems will be engaged. The question for the neuroprosthetic designer becomes: how can I best have the computer 'learn the subject' so that it provides a control signal that the subject can *most easily and rapidly* improve her control? How can we transform a neural signal, either spiking or field potential, into a regime wherein a subject can efficiently master voluntary control?

Most systems based on EEG biofeedback fall into the 'subject learns computer' category; subjects are required to learn to control their own neural signals in the form that the computer presents them. While these systems do perform signal processing on the EEG signal, they do not attempt to link into specific motor commands a priori to biofeedback training. The reason for this is self-evident — they are based on signals that are not the natural movement signal, but are rather a surrogate for it.

The laboratories using spiking signals have focused on the 'computer learns subject' category; by having the subject play a calibration game, the computer is provided with enough neural and kinematic data to construct a mathematical model. The model is then implemented in realtime to decode future neural activity into the kinematic prediction. This prediction can then be used to substitute for actual hand movement in driving an output device, such as a computer cursor. Accurate models will be easy to control; from the subject's point of view it will be no different than the original motion (or imagined motion) they performed during calibration. Inaccuracies in the decoding will require more effort on the part of the subject to compensate. Of course, one challenge for a fully paralyzed individual is that the natural movement will not be possible. Trial and error calibration will be required.

4.2. Discrete and continuous signals

There are two classes of signals which may be reconstructed from neural activity: discrete cardinal states, and continuous ordinal variables. Discrete states may comprise distinct movement categories (such as one of eight possible intended directions of arm movement, or the contraction state of a muscle) or states that modify the parameters of the decoding algorithm itself. Discrete states of the latter class include patient awareness levels, or commands that route the timing or destination of movement signals. Continuous signals embody absolute characterization of a movement parameter, such as the three dimensional position of the hand in Cartesian space, and have the ability to vary smoothly in time and space. While discrete motor outputs can be concatenated to emulate continuous control, and while continuous signals could be discretized into separate states, extracting each class requires different calibration and decoding steps.

Surface EEG, subdural ECoG, and LFP signals have been used in discrete classifier strategies, the most simple being discrimination between two neural activity states to create a single Boolean switch[9,61,66]. Investigators have relied on elaborate uses of this single switch (such as hierarchies of menus, see Kyberd and Chappell [26,63]) to control assistive devices, but here we concentrate on extracting a richer array of discrete intended movements. The functional utility of discrete commands will increase considerably when sensibly combined with continuous movement signals.

Whether an algorithm will yield a discrete or continuous signal depends upon the manner in which the kinematic variables are originally represented, both in terms of the behavioral task and the data structure. Discrete tasks usually comprise simple movements (such as a ballistic reach), and the action states must be labeled (such as 'reach in direction of 45 degrees'. The fine kinematic details within an action state are thus ignored. To build continuous models, however, calibration tasks often require more complex or wide-ranging movements, and all kinematic details must be captured. The exact strategy to build a particular encoding model will depend on assumptions made about the encoding process itself. Thus, a Gaussian position model could be built from a few samples (to determine mean and variance), if the Gaussian properties are very reliable and stable. Data to date are not sufficient to make such assumptions unequivocally[82].

In the generation of discrete signals, laboratories have employed variations on the center-out task developed by Georgopoulos et al.[34]. In this task, the subject moves the cursor from a center "hold" target to one of several peripherally positioned targets. The task enables investigators to determine the directional tuning properties of recorded neurons. The standard procedure is to average the firing rate immediately after the "go cue" or immediately preceding the start of movement, across all trials in a given direction. The resulting direction-conditional firing rates comprise an empirical distribution representing the neuron's directional tuning properties. It is also possible to integrate information about the magnitude of the movement to derive profiles based on velocity, position, acceleration and force.

Unlike discrete decoders, in which all possible predicted outputs must be sampled at least once for model calibration, continuous decoders do not attempt to sample every possible instance of a kinematic variable, but rather explore the space sufficiently that the model can capture the essential mapping to extrapolate reconstructed kinematics, including instances that were never previously visited. Efficient sampling of this kinematic space is of greater importance in the neuroprosthetic context than in basic science, where lengthy data sets may be carefully analyzed offline after the experiment.

For paralyzed patients, lengthy or complex calibration routines will be unfeasible, especially if they must be repeated. Efficient sampling has been attempted by observing naturalistic behaviors or by carefully controlling the statistics of the stimuli. Wessberg et al.[110] employed the former by monitoring the three dimensional hand position of a monkey freely retrieving food from spatially arranged trays. Such self-paced untrained movements rely on the intrinsic variability of repeated movements to supply the decoding model with sufficient sampling. Paninski et al.[81] envisioned the problem as one of supplying the motor system with white noise, in the form of a randomly moving target for the subject to track, to build a transfer function. Not only does such a strategy ensure a wide range of kinematic features are exercised, it allows detailed control of the statistics of this sampling that can be used later to improve the encoding and decoding models. Taylor et al.[102] employed an elaborate iterative procedure whereby neurons acquired tuning properties over several weeks to facilitate better control. Serruya et al.[98] used data acquired while the subject acquired randomly positioned, uniformly distributed stationary targets.

4.3. Mapped variables

In constructing algorithms that are to extract movement control signals from neural activity, investigators must choose what features of the neural and kinematic data they seek to model. Neural activity can be divided not only into different frequency ranges, but further parsed into data structures thought to indicate distinct features of underlying computation. Local field potentials are thought to reflect local input into the recorded area, and many investigators have converted such signals from the temporal to the frequency domain. Pesaran et al.[83] employs multi-tapered spectrograms to isolate features robust to nonstationarities in the signal, whereas Marsden et al.[70] convert surface potentials to the frequency domain in order to measure coherence between recording sites. Isolated action potentials can also be considered in terms of their timing relative to LFP oscillations, or relative to other spikes[22]. Taylor et al.[102] and Vargas et al.[108] have used the fine temporal structure of spike trains (such as the presence of synchronous spikes within narrow windows) as input into population vector or spike metric algorithms, respectively.

Numerous groups have been able to extract a wide range of movement parameters from multi-neuron recordings[30,103]. In addition to position, velocity and acceleration, investigators have been able to predict from neural activity joint torques[87], generated force[95], task stage in a sequence[15], and contraction state of multiple muscles independently[8,35]. As investigators explore new output devices as end effectors in neuromotor prostheses, other classes of kinematic variables may be introduced relevant to those particular devices, such as robotic arm servo positions.

4.4. Control and meta-control

Decoding algorithms can generate two levels of command signals. We can define control signals as those which actively control some feature of the movement of an output device, for example the three dimensional endpoint of a robotic arm. Meta-control signals are those which modify the way in which control signals are implemented, such as their timing or destination. Signals in the latter category include those which instruct the neuromotor prosthesis to initiate a control cascade at a particular time, or select a particular effector out of several choices. Meta-control signals provide patients the ability, for example, to decide whether neural activity will drive the wheelchair or functional electrical stimulation, or both. Certain physiological phenomena lend themselves to being used as meta-control signals; the pre-movement depression in the intracortical local field potential[22] offers itself as an ideal 'go-cue' to trigger initiation of previously or concurrently generated movement commands. Incorporation of multiple signals will likely be useful for both standard and meta-control.

4.5. Human calibration

Beyond implementing algorithms that can reliably and accurately provide useful control signals, neuromotor prosthetics must address features unique to human use. Hambrecht[39] noted that to be accepted by patients and clinicians, neuroprosthetic devices must satisfy the following criteria: 1) the benefit of using the device must outweigh the cost, in which the benefit is measured in terms of functional gain, and the costs are mental, emotional, physical (including cosmesis), and financial; 2) use of the remaining CNS must be maximized while learning required to use the device is minimized; and, 3) the neural prosthetic must be simple to use and not require significant mental concentration. Tedious repetitive operations ought be automated, especially for patients who are frail or those who want to achieve multiple forms of control. These needs can be addressed by a principled choice of neural and kinematics parameters, supervision of how decoding algorithms outputs are used, and automation of certain tasks. In terms of the balance of two learning machines, it is worth noting that highly accurate decoders provide the most natural control; they should be as natural and easy as moving one's limbs is for mobile individuals.

Most of the decoding algorithms rely on a calibration session during which a set of both neural and kinematic data are accumulated in order to build the parameters of the predictive model. Paralyzed humans will be unable to provide such kinematics, hence proxy variables must be developed. The most obvious choice will be to relate neural activity to the visual stimuli that instruct attempted movement. Auditory cues could also be implemented to instruct patients to attempt certain movements. Imaging studies by

Humphrey et al.[48] and Shoham et al. [99] show that paralyzed patients can activate motor cortices many years after injury. Most importantly, Kennedy et al.[57,58] has established proof of concept with locked-in patients who have achieved control, however limited, of a computer cursor with neural activity directly recorded from motor cortex. These preliminary findings imply that the neural activity in the brains of paralyzed individuals should be capable of generating a useful control signal.

Findings of two recent studies demonstrate that hand motions used to build decoding algorithms are not required to implement them. Taylor et al.[102] have shown that neural control of a computer cursor is possible despite absence of original hand movement by restraining the arms of macaque subjects during an online neural control task. Serruya et al.[98] found that a macaque subject ceased moving a manipulandum without instruction. These findings reinforce the view that sufficient information can be obtained without gross movement. In both these cases, however, it is impossible to rule out that some instance of clandestine movement provided the source of control. More important is that the goal of neuromotor prosthetics is not to forcibly dissociate cortical activity from external movement in healthy macaques, but to assess whether accurate, reliable control signals can be derived directly from cortical activity, and these two studies are evidence that this is the case.

In patients who do retain some movement in some muscles, but are paralyzed in others, the issue of dissociation may take on clinical significance in that control of the neuromotor prosthesis should not compromise already intact movement. In this case, the functional anatomy of neocortex should be considered; arrays should be implanted either in regions sufficiently distant from motor cortex retaining functional axonal output to the periphery, or in brain regions whose activation does not always require gross movement, such as premotor and supplementary motor areas, as well as other frontal or parietal regions.

The choice of recording device location relates to another issue of neuromotor prosthetic control humans: the conscious percept associated with achieving certain patterns of neural activity. Control signals based on neural activity recorded in parietal areas — which contain many neurons that encode movement in retinal coordinates — may lead to the confound of prosthetic control being distorted or superceded by eye movements. As non-invasive eye tracker systems to control cursors already exist as an alternative for eye-position based control, and as patients may not want motor effectors to move everywhere their eyes are directed, such a confound could be prohibitive in using certain cortical areas as the origin of the control signal. In a given brain region, the precise location of the recording device and the types of neurons recorded may also affect control. Kennedy et al.[57 2000] demonstrated that locked-in patients could indeed activate neurons which grew into a neurotrophic cone electrode; however, initial attempts at control were described by patients as effortful to the point of exhaustion. While the reasons for this effort are unknown, it is possible that the small number of neurons and their origin as part of systems related to effort played in a role in this effect. Investigators may want to implant multiple recording devices in multiple regions to ensure recording from a sufficient number of sites whose neural activity is based on easy-to-activate conscious percepts. In the meantime, initial development of NMPs must rely on existing knowledge about functional neuroanatomy.

4.6. Error measures

Various measures can be used to assess prediction accuracy for reconstructed trajectories. Correlation coefficient, fraction of total squared error (r^2), and Euclidean distance between actual and predicted movement have been used[81,82,110]. While such mathematical measures are useful for initial evaluation of an algorithm in extraction of control signals, more significant for prosthetic applications are functional error measures based on the device's use by paralyzed people. Consider that a large mean squared error could occur in a trial in which a neurally controlled computer cursor nevertheless reaches its goal as quickly as if the hand were controlling it. Extensive processing to reduce trajectory error below some threshold might be both time consuming for the user and potentially even beyond the capability of the system. Kilgore et al.[59] evaluated the utility of functional electrical stimulation systems by considering the level of functional independence achieved with device use. Serruya et al.[98] used a functional measure of time between target appearance and acquisition when controlled by either the hand or neural activity. Ultimately for patients, the measure that achieves the patient's qualitative view of success that will matter most.

5. Decoding Algorithms: Examples

For decoding that depends on spike activity, stability issues dictate that decoding doesn't depend on particular cells with exceptional tuning. The broadly overlapping representation of features by single neurons within a representational zone (i.e., the MI arm area) help with this problem. For illustrative purposes and critical evaluation, several examples of decoding algorithms that have been used to extract kinematic information from small neural populations area are now presented.

5.1. Population vector

Georgopoulos et al.[34] found that neurons recorded from in primary motor cortex could be described as having preferred directions, namely directions of movement outward from a central position that drove their firing most effectively. Furthermore, the change in activity from preferred to non-preferred directions could be stated as a cosine tuning function: $|\mathbf{B}|\ |\mathbf{M}| \cos\theta$, where $\mathbf{M}$ is the unit vector in the movement direction, $\mathbf{B}$

comprises the regression coefficients for each dimension of that vector (up to three), and θ is defined as the angle between the preferred and actual directions of movement.

While any given neuron provides incomplete information about the actual velocity of movement, when the population of vectors generated from these cosine tuned functions are summed, accurate predictions of actual movement are possible[34]. Cosine tuning can be considered an encoding assumption.

In an extension of this method, Taylor et al.[102] derived three dimensional tuning functions for simultaneously recorded neurons in monkey primary motor cortex and subsequently used velocity predictions based on firing rate to drive the position of a spherical cursor. Monkeys were successfully trained to use these prediction-based cursors as a substitute for actual hand motion[102]. Schwartz et al.[93] described an elaboration of their model in which a neuron was assigned to one of three different cosine tuning functions per neuron depending on its firing rate range. Velocity-based models raise the concern of accumulating a position error upon integration; such drift errors affect accuracy and may require a method to automatically reset the cursor to an initial position should it move out of the workspace.

Schwartz et al.[93] note that if cells are truly cosine tuned, and preferred directions are uniformly distributed, then the population vector is equivalent to a maximum likelihood estimation under uniform variance conditions. These assumptions can be questioned on the basis of recent findings of other tunings[2] and non-uniform distributions[37]. In the case that such criteria are not met, a variety of procedures to weight the contribution of a given neuron to the population vector based on both its firing rate and its fit to a cosine function can be implemented to improve velocity prediction so that this approach can still provide a viable control signal option[93].

5.2. Principle component analysis

Principle components, based on the uncorrelated eigenvalues of the covariance matrix, can be considered as parameters which extract recurring patterns of covariance of ensemble neural activity. Principle component analysis (PCA) differentially weights each neuron's contribution to population average according to its correlation with other neurons and has been used by both Wessberg et al.[110] as a pre-processing step and Isaacs et al.[49] as the central decoder in online neuroprosthetic decoding algorithms. The ability to parameterize the high dimensional space spanned by the complex spatiotemporal patterns of neural activity is both the strength and weakness of techniques such as PCA. While essential features of neural activity can be captured, loss of fine temporal or spatial structure may preclude generation of a detailed motor control signal.

5.3. Maximum likelihood estimation: discrete control

Bayes' rule provides a means to calculate the *a posteriori* conditional probability distributions of particular states. For example, by examining the firing rates in neurons in a defined time period around a cue to initiate movement, we can choose the maximum likelihood estimation of which way the monkey went. To build a model of this process, the probability of going a certain direction within the context of the experiment [P(dir)], the probability of a given cell firing a certain number of spikes after the go cue [$P(r^i_n)$], and the conditional probability of firing at a certain rate given the monkey is moving in a direction [$P(r^i_n|dir)$] are calculated. Using 15 cells, it was possible to guess the direction correctly over 60% of the time (five times chance) in an eight direction task. If the prior probabilities of P(dir) and $P(r^i_n)$ are not used, then the Bayesian formula reduces to a simple non-normalized maximum likelihood calculation. Maynard et al.[71] was able to correctly predict direction (out of eight) in 90% of tested trials using the firing rates of 16 cells in a 600 ms window centered on movement onset. Hatsopoulos et al.[42] used 8 neurons and found 100% correct classification of two directions, using a 200 ms window placed immediately before movement onset. In both cases different permutations of cells were used and the results averaged. In an early demonstration of device control, Serruya et al.[6,97] implemented a Bayesian decoder to drive a robotic arm to one of eight possible directions.

5.4. Linear filters

Linear filters may be constructed by building a response matrix containing the firing rate history of each neuron for the last t seconds, and regressing this matrix onto the columns of kinematic absolute positions using a psuedoinverse technique. Linear filters comprise a closed-form solution of the least-squares formulation:

$$\mathbf{u} = \mathbf{R} \bullet \mathbf{f} = \mathbf{R}(\mathbf{R}^T\mathbf{R})^{-1}\mathbf{R}^T\mathbf{k}$$

where **R** is the response matrix, **f** is the linear filter, **k** comprises the kinematic values (absolute position), and **u** is the reconstruction. The response matrix may be built in the format outlined by Warland et al. [109].

This method has been adapted for to be used for reconstructing movement by Paninski et al.[81,82] (Fig. 3). Filters can be generated to estimate kinematic values based on neural activity preceding or subsequent to the time instance being evaluated. Serruya et al.[96,98] restricted analysis to 'causal' (predictive) filters such that, for a given kinematic point at time *t*, the 30th bin (for each neuron) contained the rate at time *t* with the previous bins containing the firing rates earlier in time. Unlike the maximum likelihood model (which assumes a Gaussian probability distribution), or the population vector algorithm (which assumes a cosine tuned relationship between firing rate and movement direction), the linear filter model makes no assumptions about underlying distributions of the neural representation of a kinematic variable; it simply solves for the least-squared-error linear solution. While the construction of confidence intervals, computing mutual information, and other theories built around linear regression assume Gaussian noise, the least mean squares equation doesn't depend on normality anywhere (Paninski, personal communication, 2001). This lack of constraint should take advantage of the full richness of the neural tuning functions available without the assumptions of potentially inaccurate parametric models (see also ref. [90]).

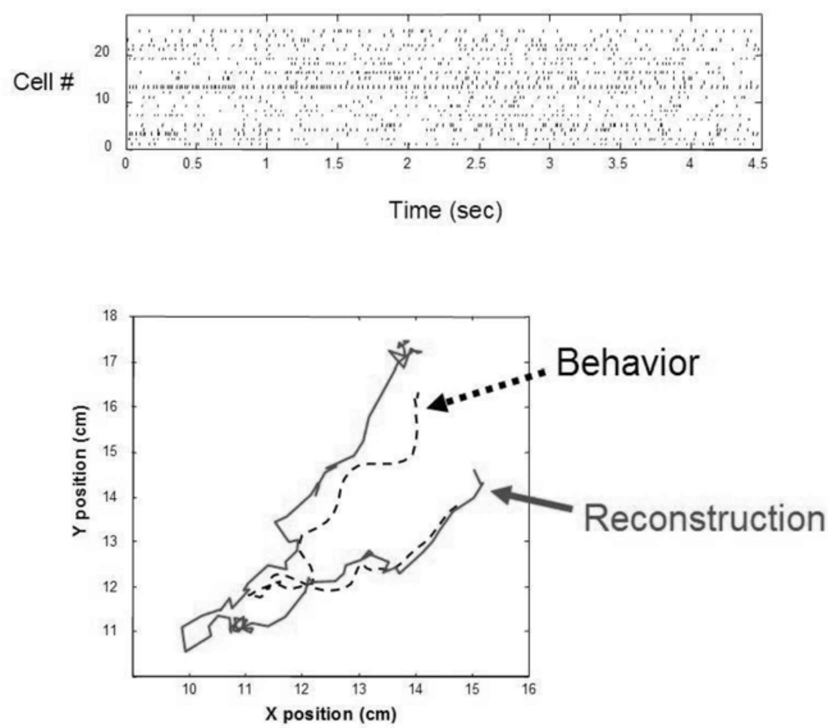

Fig. 3. Linear filter reconstruction of intended movement. This is an example of reconstructing 4.5 seconds of continuous movement using a linear filter model which takes the activity of 24 neurons recorded in motor cortex as input. The black dotted line represents the actual trajectory taken by the macaque's hand, while the red line shows the reconstruction. In this particular example, the reconstruction took place offline after the experiment. From [81].

Serruya et al. [96,98] showed that the Paninski et al. [81] approach provides a quick and accurate neural control signal in monkeys. Neural control signals derived from linear filters based only on a few minutes of initial calibration were sufficient to allow accurate neural control of a computer cursor. That is, the decoded neural signal substituted for hand motion in a task that required movement of the cursor from one target to another randomly appearing target. This decoding functioned immediately upon filter application, without any additional training; that is, this signal decoded accurately enough that it was a reasonable substitute for the hand motions originally used to perform the pointing task. The pronounced, immediate success of the linear-regression method compared with other approaches may be due to the lack of strong assumptions about neuronal firing, to the robustness of the linear-regression method, or to the type or number of cells used for decoding.

5.5. Adaptive neural networks

There exist a wide range of neural network algorithms which may be used to reconstruct movement from neural activity. Schwartz et al.[93] describes the use of a self-organizing feature map (SOFM) which consists of a single layer of nodes, each initialized with random vector n weights, where n is the dimensionality of the input. The SOFM is tuned by comparing an input vector to a weight vector for each node. Different learning rules may be employed to build associations into the neural network, including a winner takes all strategy, by which the weight vector closest to the input gets modified slightly closer to the input over a training session. Schwartz et al.[93] found that this method could construct arm trajectories from neural data, and that the SOFM included the benefit that its representation of parameter space is topology preserving. The disadvantage of using this class of neural networks lies in the fact that resulting clusters must be manually labeled.

Wessberg et al.[110] tested a more complex adaptive neural network to reconstruct trajectory in real time, but in an open-looped context, meaning that the subject (an owl monkey) was unaware of the prediction output. The ANN included a single hidden layer which was updated by a gradient descent backpropagation function offline before real time use. Wessberg et al.[110] reported that such ANNs yielded slightly better performance than linear filter techniques in the open-loop context. However, Gao et al.[33] found that neural network based algorithms in fact performed worse than linear filters. Given the wide range of possible neural network architectures and updating learning rules, certain ANNs may yet prove to be useful in an online closed-loop context, but it will be worthwhile to understand the nature of the variability in the results.

ANNs have the distinct disadvantage over the previously described methods in that the means they by which they solve the decoding problem are not readily apparent. Unlike the algorithms discussed previously, the resulting weights present within a neural network do not lend themselves to intuitions about how neurons may be representing kinematic variables in a time-varying manner. Linear filter coefficients, for example, reveal not only which neurons are most strongly involved in a representation, but identify the optimal delay between firing rate modulation and kinematic estimation (Black MJ, Bienenstock E, Gao Y, personal communication).

5.6. Feedback-driven models

Fetz and Baker [28] and Schmidt et al.[91] [1978] found that macaques could be operantly conditioned to rapidly change the firing rate of one or more cortical neurons by visual cues. Such biofeedback-driven control schemes could be usurped to control a prosthetic device. Biofeedback, based on data from non-invasive systems, can be powerfully incorporated into neural prosthetic devices. Feedback may be in the form of external signals, such as visual or auditory cues, or via internally injected signals, such as electrical stimulation to substitute for lost sensory channels. Recent studies suggest that meaningful percepts can be generated through electrical stimulation[88,101] as discussed below.

Feedback-driven methods clearly fall more in the domain of 'subject learns computer.' Taylor et al.[102] attempted to combine a feedback-driven calibration stage with decoding models based on assumptions of cosine tuning. They concluded that feedback enabled macaques to directionally-tune otherwise poorly tuned firing patterns, increase the dynamic range of these patterns, and evenly distribute preferred directions. In addition to the increased time and effort required to master feedback-driven control schemes, the open-ended nature of algorithms focused on 'subject learns computer' may make standardized, automated calibration routines difficult to implement. However, the principled use of feedback-driven features in combination with other decoding algorithms may prove a valuable addition to a supervisor algorithm organizing the control structure of a neuromotor prosthesis.

5.7. Number of cells

In extracting kinematic control information from neural ensembles, the number of neurons recorded becomes an issue of great concern. Nicolelis [77] predicted that hundreds to thousands of neurons would be necessary to provide sufficient information for neuromotor prosthetic use. Two recent studies by Serruya et al.[98] and Taylor et al.[102] prove that this is not the case. Both studies found that using less than 20 neurons, macaque subjects could achieve accurate control of a computer cursor in two or three dimensions. Such findings are significant in that they show a rich control signal can be provided from a small number of neurons; however they do not preclude the possibility that even more detailed and robust signals could be generated from a higher number of neurons.

Fellows et al.[27,82] performed a neuron-dropping analysis to assess linear filter prediction performance relative to number of neurons used. Their basic conclusion was that prediction accuracy depended less on total number of neurons than on the particular features of individual neurons, i.e., some sets of neurons were more informative than others. Obviously a recording system that can access a wider range of neurons will have a better chance of picking up more informative neurons; however such benefits must be weighed against the additional costs incurred by implanting larger or more complex devices into the brain.

5.8. Summary of decoding algorithms

The studies discussed here indicate that useful motor control signals can be extracted from the nervous system. The richness of this signal, even from a limited number of recorded neurons or sites, has been demonstrated in non-human primates. The ability of such a wide range of algorithms to extract kinematic information directly from neural activity may imply an intrinsically linear or redundant encoding within cortex, but in any case paves the way for further studies in humans. The limiting factors of generating useful control signals may thus stem less from the power of available mathematical techniques, and more from the bioengineering and neurosurgical aspects of the design and implantation of the recording device.

6. Output Devices

Once an accurate and reliable control signal can be generated from neural activity, NMP designers must next consider what type of motor effector is most suitable for paralyzed individuals. In this section we will discuss the output devices which have received the most attention for use in NMPs, and then review the role of semi-autonomous circuits within the output devices and the use of sensory feedback.

Output devices promise to restore functional independence to paralyzed patients by enabling them to navigate in powered wheelchairs, maneuver robotic limbs, activate electrical stimulation of intact muscles, and engage in a variety of computer programs, including those related to word processing, e-mail, internet browsing, video games and creative self-expression.

In determining which output device to couple to the neurally-based control signal, the desired function must be considered in practical terms. Arm motion is easier to emulate or use in either robotic limbs or electrically stimulated muscles. While progress is being made on electrical stimulation of trunk and leg muscles to restore standing and walking[105], direct neural control over a wheelchair is a more immediate and practical application of a neural signal to restore independence to a paralyzed individual.

There are two types of movement which neuromotor prosthetics must restore to severely paralyzed patients: those related to communication, and those related to gross physical movement of the body, limbs, or objects to interact with. Clinicians quantify functional independence by an itemizing scheme known as activities of daily living (ADL [59,65]). ADL include such abilities as dressing oneself, feeding oneself, and moving around the room. By restoring control over a variety of output devices, NMPs must allow patients to achieve such activities independently.

6.1. Assistive devices

Before considering how NMP may achieve these goals, a review of current assistive devices reveals what has already been achieved with available technology and serves to motivate thinking about what NMPs may strive to achieve beyond available technology.

Severely paralyzed patients are often able to voluntarily move a very small subset of muscles, such as those of the tongue, a single finger, or to move or blink the eyes. A wide range of assistive devices has been developed to take advantage of the discrete, Boolean signals such movements afford. The most basic communication is for a visitor to ask yes or no questions, in which the patient communicates 'yes' or 'no' with one or two eye blinks, respectively. To spell out a word, visitors may slowly say each letter of the alphabet and the patient will blink when the desired letter is named; or a transparent board with the letters of the alphabet written on it is held before the patient, and the visitor can note the direction of the patient's gaze to discover the intended letter.

Some of these functions have been automated by computer programs, such as EZKeys (Words+, Inc) which automatically highlights various letters or word choices; patients select a letter by briefly closing a discrete switch (through intact movement, such as by the tongue, a finger, or eyebrow) when that letter is lit up. A computerized version of the alphabet board is the scanning board: a matrix of letters and numbers are displayed, and each row sequentially selected. After a row is selected, each column is then cycled through until the desired item is found. Another system uses an infrared eye-tracker in which eye position controls the cursor. Note that these systems coopt available systems and therefore limit their use in other 'natural' activities.

Patients with greater mobility can use more switches to achieve more choices, more quickly. Certain quadriplegics retain movement control in the head and neck and hence can use multi-directional joysticks driven by chin position, or use respiratory control with sip-and-puff devices.

Once input to a computer can be obtained, a wide range of other functions can be achieved through automated or predictive computer programs. In addition to spelling out words to communicate with, disabled users can use one or more switches to control wheelchair movement or turn off and on appliances linked the computer through radiofrequency links (X-10). Finally, in addition to providing simple communication and the ability control wheelchairs and external appliances, computers can be used in and of themselves for such activities as email, internet use, video games for entertainment, programming, or creative expression. NMPs must enable users to achieve all the abilities provided for by existing devices, and do so in a manner that is faster, more reliable, and ultimately with many more degrees of freedom than a few Boolean switches.

6.2. Computer cursors

Preliminary research on closed-loop neural control has focused on moving a computer cursor around a screen or a virtual space[58,98,102]. The first application of cursor control will be communication: Kennedy et al.[58] have shown that a paralyzed patient can achieve half-dimensional control over a computer cursor in order to select icons that communicate information to clinicians and family members. More detailed control will allow for such selection to occur more rapidly and provide a greater number of choices.

Cursor control strategies already tested in existing assistive devices provide useful tests of possible NMP designs. Rao et al.[86] found that given the choice between a position-control and an isometric-force control joystick, patients with cerebral palsy preferred the position based joystick despite its increased instability relative to the force joystick. Evans et al.[24] found that disabled users preferred a head-operated infrared pointer that had the characteristics of a joystick (a discrete, relative pointing device) to those of a mouse (a continuous, absolute pointing device). The ability to toggle between discrete and continuous decoders may be crucial for users attempting to master voluntary control over particular effectors.

6.3. Robotic assistants

Robotic assistants include computerized wheelchairs, robotic assistants, and robotic arms. Powered wheelchairs may be considered robotic when they are able to engage in repetitive or automatic tasks. While sip-and-puff, joystick, and eye-position based controllers can afford considerable mobility to paralyzed wheelchair users, numerous rehabilitation engineering groups are developing more sophisticated wheelchair circuitry[1,29,113]. These systems are termed semi-autonomous because they require some high order human control (such as instructions to move forward, backward, or turn), yet automate low-level tasks such as obstacle avoidance through the use of sensors and reflex circuits. Initial NMP robotic wheelchairs will simply replace the physical input devices (the mechanical or sip-and-puff switches) with decoded neural activity. NMPs, however, could achieve much more sophisticated control as more details of intended movement are conveyed to semi-autonomous robots.

In addition to wheelchairs, investigators have considered using neural activity to control robotic limbs. Robotic arms may be mounted on a wheelchair[12,18,23,85], stationed at a desk[107], or integrated into a prosthetic limb an amputee can wear[11] (see also see links to robotic prosthetic limb sites in reference section). Both discrete and continuous control derived from neural activity has been used on robotic arms in experiments using healthy macaque subjects[17,44,97,110]. Robotic arms may be especially useful for patients in whom functional electrical stimulation is impossible, such as those with ALS or muscular dystrophy.

In addition to wheelchairs and robotic arms, both of which are in close physical contact or proximity to the patient, robotic assistants can be controlled at a distance (telerobots) and may afford a greater range of independence. Semiautonomous telerobots could retrieve objects or perform other tasks for patients for whom wheelchair use is impractical. As with robotic wheelchairs and robotic arms, NMPs would replace mechanical switches with signals based on decoded neural activity (M. Black and H. Christensen, S. Suner and P. Pook, personal communications).

Semi-autonomous systems are appealing end effectors for NMPs because they combine the high order control signals directly from a human user with the low level automated navigational and task automation system of the robot. As with all assistive devices, it will be important to keep the user interface simple enough to be quickly learned and mastered.

6.4. Functional electrical stimulation

For patients in whom the neuromuscular system, despite being cut off from the brain, remains essentially intact, NMPs coupled to Functional electrical stimulation (FES) exist as a strategy to reconnect the brain to the muscles to restore independent movement. Implanted upper-arm and upper-leg neuroprostheses based on FES have already been tested for several years in patients[59,105]. These systems operate by stimulating motor nerves as they enter muscles, causing the latter to contract. By controlling the electrical parameters and temporal order of muscle stimulation, these implanted neuroprostheses have restored basic movements (such as various hand closure grips) to provide patients with increased autonomy.

Quadriplegic patients with spinal cord transection at the level of the fifth cervical vertebra retain shoulder movement, but lose the ability to open and close the hand: by stimulating intrinsic and extrinsic hand muscles, FES-based neuroprostheses have allowed such patients to manipulate objects. These systems are particularly useful because they capitalize on the intact muscles; by enabling patients to pick up and hold a pencil, for example, the FES permits them to use shoulder musculature to ‘play’ the arm such they can sign their names and achieve other complex movement.

Currently, FES systems rely on mechanical or automated control signals. Upper-extremity neuroprostheses developed by the FES laboratories in Cleveland are driven by an externally worn joystick on the contralateral shoulder[41,59]. Joystick angle is translated by the stimulator circuitry into a command to open or close the implanted hand. Lower-extremity implants can be controlled by hitting one or more externally worn buttons that initiate specific stimulation sequences to enable patients to stand or engage walking pattern generators. Lauer et al.[64] has successfully bypassed mechanical switches with one based on EEG biofeedback. In this study, patients were able to suppress beta-band activity recorded by scalp electrodes overlying sensorimotor cortices such that suppression of specified durations triggered opening or closure of the stimulated hand.

Lauer et al. reported that while patients appreciated the restoration of movement by 'thought alone,' they found the EEG monitoring apparatus unwieldy and the conscious energy and attention required to master beta-suppression excessive compared to that needed to use the mechanical joystick.

As FES-developers increase the number of muscles that can be stimulated (including collections of muscles that might be controlled by stimulating key areas of the spinal cord), and therefore the number of degrees of freedom, generating an appropriate control signal gains considerable importance. Cursor control achieved by preliminary studies could be used in the context of robotic arms and FES controllers[58,98,102]. The idea would be that a two or three dimensional position would be fed into circuitry that would solve the inverse kinematics and engage robot servos or FES patterns to move the hand to the desired endpoint. As information is extracted about motions beyond hand position, such as simultaneous movement in multiple digits[8] or the wrist[46,54], NMPs might be able to restore considerably more elaborate control than simply end-point position.

6.5. Appliances and vehicles

Activities of daily living could also be restored by NMPs by direct neural control over appliances (telephones, microwave ovens, televisions) and vehicles. Such control will undoubtedly be through computer interfaces that can rapidly and accurately transform neural activity into the appropriately structured control signal. As with the other assistive devices discussed, direct neural control would first seek to mimic the control already achieved by existing systems (such as mechanical use of a universal remote controller to turn off and on X-10 linked appliances) and then move on to faster, more wide-ranging control.

6.6. Sensory feedback

Sensory feedback from output devices could enhance NMP use by providing users with information both from the effector being used (e.g., artificial propioception of a robotic arm) and about objects being manipulated (e.g., the heat of a cup being grasped via FES). Just as motor commands can be divided into control and meta-control, so too can sensory information be divided into content (continuous tactile sense of a surface being grasped) and meta-content (higher level instructions such as a warning light if wheelchair control is reaching a mechanical tolerance level, or a robotic arm battery is running low).

While visual feedback has been shown to enable considerable control, as it does in ordinary movement[50], non-visual modalities may further enhance neuroprosthetic device control in various contexts. Kilgore et al.[59] discuss how patients benefit from an electrode which provides sensory feedback in proportion to the grasping state of the stimulated hand. While patients with certain types of paralysis may retain their original sensory feedback (locked-in syndrome, muscular dystrophy), patients with other types (spinal cord transection) do not and may thus benefit from direct stimulation of sensory cortex to restore tactile sense. Romo and Salinas [88] report that finely graded sensory discrimination is possible from direct cortical stimulation in monkeys. These studies imply that cortical feedback techniques are feasible. Sensory feedback may include information not only about touch and proprioception, but also temperature, pain (or damage to NMP effectors), linear and angular acceleration. Scinicariello et al.[94] were able to correct for postural disturbances in standing volunteers by galvanic stimulation to the mastoid bone (posterior to the ear) which induces vestibular sensation. Such 'balance prostheses' may be particularly useful in NMPs aimed at restoring upright walking with FES.

Information from sensors on motor effectors need not all be sent to the user; semi-autonomous circuitry can use force and position feedback to engage obstacle avoidance or other automated responses without requiring the user's involvement. Whether to provide such sensory feedback directly back to the patients' brain will be an issue for future empirical investigation. For a more comprehensive review of the use of sensory feedback in the context of neuroprosthetic control see [59,80,101].

7. Integrated Control

Given the plethora of decoding algorithms and output devices, NMPs require some way of integrating control into a unified scheme with an intuitive user interface. In this section we consider several features which NMPs ought to incorporate: a supervisor algorithm, adaptive processing of neural activity input and decoded command output, automated routines, predictive algorithms based on use statistics, and an overall integration framework.

As we do not yet understand the limits of control signals that could be generated by using particular combinations of neural activity classes and decoding algorithms, a pragmatic approach would be to compute multiple predictions of intended movement simultaneously and use the subset that provided the control the user found most beneficial. The decision of which decoded outputs are most useful will be a combination of automated accuracy measures and user feedback. During calibration sessions, supervisor algorithms can compare predicted output with instructed trajectories and automatically select the decoding algorithm which minimizes the error between the two. During daily use, the supervisor can use a variety of strategies: one might be an ongoing comparison between simultaneously generated decoded outputs and an averaging of the three signals with cross-correlation coefficients higher than some preset threshold; another strategy might be to track number of near-misses with obstacles (such as might occur in wheelchair navigation), and cycling to the next decoder after this number exceeds a certain threshold. In the user-feedback context, one or more decoded outputs can be used as meta-control signals, namely selector switches to demultiplex the most favored output to be used to control one or more output devices.

Adaptive processing of neural input includes assessment of the quality of a neural signal at each conditioning and processing stage before it is used to build decoding algorithms. Using channels in which few or no action potentials are recorded, for example, may disrupt maximum likelihood estimation and linear filter models from functioning. If a neuron fires very infrequently or erratically during the calibration session, an maximum likelihood estimation based decoder may excessively weight its contribution when a spike does occur later. Channels with no spikes whatsoever will lead to singular matrices preventing correlation matrix inversion in linear filter generation. Signal processing schemas to remove these channels will be needed. It is important to remember that decoding algorithms are not evaluated on mathematical errors based on extensive offline data ('how well does the algorithm capture the actual movement that occurred in a healthy animal?'), but rather upon functional error measures ('how well does the algorithm allow the paralyzed user to achieve output device control?').

Just as erratic or non-firing single units can affect decoder performance, slow potentials can reflect global processes which can be examined to modify the way in which the decoders operate. EEG traces, for example, are thought to be good descriptors of global attention and arousal levels, wherein fast desynchronized rhythms indicate awake engagement, and slow synchronized rhythms indicate increasingly drowsy and asleep states. Moore (personal communication, 1999) incorporated these awareness states as input to 'smart device drivers,' namely, the principled use of arousal measures to scale the neural-to-kinematic mapping. Moore found that at the beginning of a neural-control session, the cursor moved with such great speed and amplitude that the user was unable to visually track it, and towards the end of a session, the patient became fatigued and could barely move the cursor. By scaling cursor mapping to arousal state, 'smart device drivers' could in theory achieve considerably more uniform control and hence improved efficacy of an NMP.

Automated routines, discussed earlier as part of semi-autonomous control circuitry for robotic devices and FES, improve user independence by taking care of low-level, downstream control issues. Automated features emulate the low-level processing that occurs naturally in the reflexes, central pattern generators, and even motor plant properties of the intact central nervous and peripheral neuromuscular systems. Many of these routines will be conserved from the output device control strategies that have already been developed. Designers of myoelectric prosthetic arms, for example, found that users found it easier to have hand-closure as an involuntary default state, and hand-opening being the state requiring voluntary myoelectric activation. Kilgore et al.[59] noted that users found particular grip settings most useful, and rarely used certain intermediates, suggesting that ability to limit choices (voluntarily decrease the degrees of freedom) may be useful in certain output device control contexts.

NMPs should capitalize on algorithms which make predictions of intended instructions based on previously learned user behavior. Assistive communication aids already use word prediction in automated alphabet scanning programs such as EZKeys. The predictions can be based on the statistics of the language being used (for example, the program can guess the letter ‘e’ after ‘th’ are already selected), or on those particular to the user (such as recognizing the start of an often used proper noun, e.g., guessing ‘Fido’ given ‘fi’ or ‘Dr. Pirandello’ given ‘drp’)[19,26].

Techniques used in visual pattern recognition can also be used: M. Black (personal communication, 1999) proposed that repeated neural or kinematic data related to movement gestures could be recognized, much like personal organizers take advantage of letters written in an instructed ’graffiti’ mode (trademark, Palm, Inc) . King (personal communication, 1999) proposed looking for certain temporal sequences that could be termed neural gestures that represent particular movements. Vargas et al.[108] outlined a more comprehensive strategy by which the fine temporal structure of spike trains could be used to encode a variety of intended movement instructions. Another feature of output device control that NMPs can improve function on is hysteresis; myoelectric controllers engage different prosthetic hand grasps depending on the immediately preceding instructions and states of the prosthesis[16,63,68].

The meta-control motor commands and the meta-content sensory feedback must be integrated to allow the appropriate control commands to be routed to the correct output devices at the right time and in the proper order. Just as automated wheelchair routines and FES sequences can be modeled as finite state machines, so too can the NMP control hierarchy. Reach and grasp movements of an prosthesis or an electrically stimulated limb could be controlled by distinct classifiers. The ballistic reach to a target area might be controlled by a discrete decoder, whereas control could switch to a continuous decoder output once in the target region to move an object or position the hand, and finally a switch to another discrete decoder would close the hand around an object. The decision of when to switch between output signal sources will be based on both meta-control commands derived from neural activity, and feedback based on sensors and automated sequences.

Finally, all these ongoing processes of neural activity filtering, decoding, output accuracy comparison, automated and user-feedback, and multiple device control must be assembled into a unified framework that is intuitive to set up and use for patients, clinicians, and assistants (such as family members, friends, teachers, and therapists). Not only do NMP designers wish to pragmatically take advantage of whatever movement instruction information may be available through recording multiple classes and channels of neural activity, and from the use of decoding algorithms and multiple processing steps, they also strive to build a system which can be scalable and modular as certain inputs and outputs are removed or added, and to allow increasingly adept users to maximize control by allowing them access to more of the inner workings of the integrated NMP.

Nisbet[78] noted that attempts to group control of the numerous assistive devices used by paralyzed patients into one software program did not succeed because they ultimately compromised use of constituent devices. He discovered some principles of assistive device arrangement that we consider here in the context of NMP design:

Appropriate controls: Integrated systems must allow the user to choose the most appropriate and effective decoding algorithm control output for each target device.

Overall control characteristics: Signals generated by neural activity are subject to processing, filtering and transformation en route to the target device. The control characteristics of the overall interface can be matched to the target device, and to the user's physical, cognitive and perceptual abilities.

Distinct output devices: Different skills and controls are needed for each target device (e.g., a power wheelchair vs. a communication aid); integrated systems must therefore be designed to take account of these differences to avoid compromising safety and efficacy.

Considering all the design principles discussed in this chapter, we are forced to recognize that the design of an overall integrated control system will be a complex task akin to designing a computer operating system. The power to engage this daunting task will rely on the continued trust and cooperation between investigators and the paralyzed individuals who seek to become more independent by using neuromotor prostheses.

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Otto Bock 3C100 C-Leg System:
http://www.ottobockus.com/products/op_lower_cleg.htm

Endolite Intelligent Prosthesis Plus: http://www.endolite.com/micro.htm

Utah Arm 2: http://www.utaharm.com/products.htm#u2

Re-flex VSP (not robotic, but incorporate biomechanical modeling:)
http://www.ossur.com/template14.asp?PageID=282

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