Prediction of Muscle Activity 1 1 from Cortical Signals to Restore Hand Grasp in Subjects with Spinal Cord Injury

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11.1 INTRODUCTION

In the United States, Spinal cord injury (SCI) paralyzes approximately 11,000 individuals every year. SCI leaves patients partially or entirely unable to activate muscles that are innervated by nerves below the level of injury. Roughly half of SCIs occur above the sixth cervical vertebra, thereby affecting all four limbs and leaving the individuals unable to grasp objects effectively with their hands. Injuries as high as C2 also affect the muscles of respiration, requiring that these patients be artificially ventilated.

Although there are important changes to both the muscles and the brain that occur as a result of either the injury or subsequent disuse, the essential problem is that motor commands, still formulated in the brain, can no longer reach the muscles. Toward the end of the eighteenth century, Luigi Galvani demonstrated that muscles are electrically excitable and can be made to contract by the application of appropriate electrical current (Galvani, 1791; Piccolino, 1998). Following this basic principle, functional electrical stimulation (FES) has been used for nearly five decades in an attempt to restore some level of motor function to paralyzed individuals through electrical stimulation of muscles (Liberson et al., 1961; Peckham and Knutson, 2005). FES has successfully been applied to provide appropriately timed dorsiflexion for patients suffering foot drop as a result of SCI or stroke (Vodovnik et al., 1978; Weber et al., 2004), and other systems provide some support for stance or walking (Popovic et al., 1989; Solomonow et al., 1997; Graupe and Kohn, 1998). Stimulation of the phrenic nerve has been used in the case of high-level injuries to replace or augment the use of an external ventilator (Creasey et al., 1996), and systems have been devised to provide bowel and bladder control (Johnston et al., 2005).

Most patients with injuries at the C5 and C6 levels report that, more than any other function, regaining the ability to grasp objects would provide them with the greatest benefit (Anderson, 2004). For this reason, considerable effort has also been devoted to the development of FES systems to restore voluntary grasp. Probably the most clinically successful of these has been the Freehand prosthesis, which has been implanted in several hundred patients since 1986 (Keith et al., 1989). An earlier version was tested in 1980 (Peckham et al., 1980).

One of the primary limitations of the Freehand and related grasp prostheses is the very limited means of control available to patients. Even if it were possible to provide fully articulated and forceful muscle activation, dexterous voluntary control would not be possible through the existing control channels. The problem becomes even more severe for patients with higher-level injuries, who have greater needs for replaced function, with less available control. Fortunately, the advent and rapid development in this decade of the brainmachine interface (BMI) provide an exciting new means by which a prosthesis with more degrees of freedom might be controlled.

Currently, virtually all BMI applications extract kinematic information from the brain. The approach typically involves recording a training data set including both neural discharge and limb position as a monkey makes a series of normal movements. These data are used to compute a mapping between the neural data and hand position that can be used to transform subsequent neural recordings to produce "predictions" of movement intent. If these predictions are made in real time, they can be used to allow an experimental subject voluntary control of an external device.

However, there is considerable evidence that M1 also encodes information about the forces and dynamics of movement (Hepp-Reymond et al., 1978; Thach, 1978; Cheney and Fetz, 1980; Kalaska and Hyde, 1985; Georgopoulos et al., 1992; Riehle and Requin, 1995; Sergio et al., 2005). A small number of groups have begun to pursue the possibility of using this dynamics information as a real-time control signal, through the prediction of grip force (Carmena et al., 2003), joint torque (Fagg et al., 2009), and muscle activity (Pohlmeyer et al., 2007b). We have also shown preliminary evidence that monkeys can easily learn to modulate the magnitude of isometric wrist flexion torque produced through cortically controlled FES following peripheral nerve block (Pohlmeyer et al., 2007a, 2009). Similar results have been reported by another group that operantly conditioned monkeys to modulate the activity of individual neurons that directly controlled the FES (Moritz et al., 2008).

In this chapter we describe our continuing work on developing a neuroprosthesis that uses real-time predictions from an ensemble of recorded neurons to provide voluntary control of hand use following peripheral nerve block.

11.2 BACKGROUND

Several systems have been developed to provide rudimentary hand grasp through FES. Most of these rely on surface stimulation, and all require that the stimulus waveforms be preprogrammed to accommodate the very limited range of voluntary control available to a patient with a mid-cervical lesion. Clearly, even an unimpaired individual is unlikely to be able to modulate independently the large number of muscles needed to form a natural grasp through any but the normal means. Fortunately, a fairly wide range of grasping behaviors can be represented by a much lower-dimensional coordinate system. One study used principal component analysis to determine the dimensionality of hand shape as subjects grasped a series of objects having different size and shape (Santello et al., 1998). Only two components were needed to reconstruct 80% of the variance in hand shape. It should be noted that a later study found that two to three times as many components, or "movement synergies," were required to reconstruct more complex movements (Todorov and Ghahramani, 2004). These results suggest that at least simple functional grasps may be accomplished with a low-dimensional controller.

The current Freehand consists of an implanted stimulator and electrodes implanted in 12 muscles of the forearm and hand (Figure 11.1). The stimulator communicates via a short-range RF link to an external controller that delivers preprogrammed stimulus waveforms to the full set of muscles. These patterns are customized for each patient in a series of sessions with an occupational therapist, who determines the threshold level of stimulation necessary to produce force in each muscle and the maximal stimulation that avoids "spillover" to adjacent muscles with different mechanical actions. Having determined this mapping from stimulus intensity to muscle force, the therapist determines the pattern of stimulation necessary to produce either a power grasp or a lateral grasp. This process accomplishes a mapping from the high-order space of hand muscles to a single control variable.

Control of the FreeHand requires discrete signals for switching between grasp patterns and a continuous signal for controlling hand opening and



FIGURE 11.1

Freehand® neuroprosthesis developed to provide functional grasp to patients with C5/C6 tetraplegia due to spinal cord injury. Implanted stimulation electrodes cause the paralyzed muscles to contract in preprogrammed patterns, using signals sent from an external controller. The patient controls the system through residual proximal limb movement or muscle activity.

Source: Used with the permission of the Cleveland FES Center.

closing within a specific grasp (Scott et al., 1996; Hart et al., 1998). A number of discrete control signals have been used that depend on the user's abilities and preferences. These include switches mounted on the wheel chair or elsewhere, EMGs from one or more muscles, and voluntary movements such as those from a joystick mounted on the contralateral shoulder. Once a specific grasp is selected, continuous control of hand opening and closing is determined by a single degree-of-freedom (DOF) signal directly under the patient's control. Common sources of continuous control signals include external sensors that detect residual motion of the shoulder or wrist and implanted electrodes that sense EMG in muscles remaining under voluntary control. When the desired force level is achieved, the patient can use the discrete command signal to lock stimulation, thereby maintaining the grasp without additional conscious effort. He can then move his hand and the grasped object.

In a multi-center study to evaluate the safety, efficacy, and clinical impact of the FreeHand on fifty patients with spinal cord injuries (Peckham et al., 2001), it was found that the neuroprosthesis produced increased pinch force in every patient. Additionally, in a test of grasp and release ability (Wuolle et al., 1994), 49 of the 50 participants moved at least one more object with the neuroprosthesis than they could without it. More than 90% were satisfied with the neuroprosthesis, and most used it regularly.

In addition to the Freehand, a number of other grasping FES systems are in use or have been tested (Popovic et al., 2002; Popovic, 2003; Peckham and Knutson, 2005). Although these systems share many underlying principles, they vary in several respects. Many of them rely on surface stimulation rather than implanted electrodes. This approach has the advantage that it can be adopted relatively soon after the injury. The Bionic Glove is designed simply to amplify the passive finger flexion movements caused by active wrist movements (tenodesis grip) for those patients with injuries at the C6 level. It uses surface stimulation to cause the fingers to flex when sensors in the glove detect wrist extension and to extend when it detects wrist flexion (Prochazka et al., 1997; Popovic et al., 1999). The Handmaster is another orthosis that uses surface stimulation (Snoek et al., 2000; Alon and McBride, 2003). However, it is intended for C5 spinal injuries in which there is limited or no voluntary control of the wrist. The patient pushes buttons to trigger preprogrammed stimulation patterns.

At least two systems have been designed in an effort to provide limited reaching functionality as well as grasping for patients with C4-level injuries. The Belgrade Grasping-Reaching System allows control of hand opening and closing simply by the push of a button. A goniometer is used to measure shoulder motion so triceps muscle stimulation can be modulated appropriately during reaching motions (Popovic et al., 2002; Popovic, 2003). The NEC FES-Mate, a multi-channel FES system that uses percutaneous electrodes, is also intended to control reaching as well as grasping. It uses amplitude modulation to control contractile force, modeled on averaged EMG signals recorded from able-bodied individuals. The predetermined stimulation patterns are triggered through a combination of voice control, head switches, sip-puff, and shoulder movement (Handa and Hoshimiya, 1987; Hoshimiya et al., 1989).

To provide an alternative control signal for severely paralyzed patients, several attempts have been made to employ electroencephalic (EEG) signals recorded noninvasively from the scalp. In one case, a patient using the Free-hand device learned to modulate the amplitude of beta-band activity in order to control the rate of change in stimulus-driven grip force (Lauer et al., 1999). Modulation above one threshold caused gradually increasing flexion force, while extension was provided when the signal dropped below a minimum level. Achieving adequate control of EEG modulation required 20 sessions of practice over a period of several months. Subsequently, another group used

bursts of beta-range signals generated by imagined foot movements to control the transition between four distinct phases of stimulation (Pfurtscheller et al., 2003). These phase transitions were quite slow (by design, greater than 5 seconds duration), but they did allow the patient to grasp a cylindrical object using lateral prehension.

Although even this 1-DOF control significantly improves a range of functional activities for most patients who have used it, it is clearly desirable to remove the requirement that grasp patterns be preprogrammed. This might allow the patient to grasp an irregularly shaped object more reliably, or to orient the hand through motion at the wrist rather than the shoulder or the entire trunk. The ability to predict the activity of individual muscles in real time provides a possible means by which this preprogramming stage might be completely avoided.

11.2.1 BMIs as a Potential Control Solution

The earliest demonstration of BMI technology actually used recordings from a human patient with amyotrophic lateral sclerosis who was nearly completely "locked in," retaining only the ability to move her eyes (Kennedy and Bakay, 1998). The patient could modulate the discharge of neurons recorded from the primary motor cortex (M1) adequately to control a simple binary switch. Several subsequent patients learned to move a cursor up or down and to slowly spell out words using a progressive menu selection system. The most successful patient eventually learned to communicate at a rate of approximately three letters per minute.

Research approaches to the study of BMIs can be divided into two major categories that we will call open-loop and closed-loop. Open-loop approaches refer to the prediction of a control signal based on recordings from the brain while the subject makes a series of normal limb movements. This signal may or may not be used to affect movement. The important point is that the subject remains unaware of the signal, such that it cannot affect subsequent movement commands. In many cases these predictions are made only offline using previously recorded data.

In contrast, closed-loop approaches use the predicted control signal to effect movement of a device. Information about that movement is fed back to the subject within tens of milliseconds (in nearly all cases through natural vision), so that it becomes possible for him to correct errors and guide the movement in something of a normal manner. Under these conditions, it is not necessary for the subject to move his own limb, and in many cases he does not.

Any useful control must be closed-loop, but the advantages of the openloop approach to development include its relative simplicity and the fact that many different "decoding" algorithms can be tested and compared using a single data set. Quantitative comparisons of different approaches can be made by computing an error metric (e.g., the coefficient of determination, or mean square error) between the actual and the predicted movements. Such comparisons are not meaningful in the closed-loop state because the subject's natural limb movements (assuming they are made at all) may be influenced by the predictions.

In a sense, single-electrode recordings from the time of Evarts (1968) represent the open-loop approach to understanding how individual neurons in motor areas of the brain encode limb movement. The dichotomy between "muscle" and "movement" control has been explored in this manner for several decades (Evarts, 1968; Phillips, 1975; Georgopoulos et al., 1982; Scott and Kalaska, 1997). In 1970, Humphrey and his colleagues used multiple electrodes to record simultaneously from several neurons, thereby increasing the accuracy with which force- and movement-related signals could be predicted during wrist movements (Humphrey et al., 1970). In 1969, in what is often credited as the first closed-loop BMI, Fetz and Finocchio trained several monkeys to modulate the discharge of single neurons in M1 using auditory or visual feedback (Fetz and Finocchio, 1975).

In 2000, Nicolelis and colleagues chronically implanted large numbers of electrodes in several different motor areas of two owl monkeys (Wessberg et al., 2000). They used both a linear filter model and a nonlinear neural network model to fit ten minutes of data recorded from 100 neurons to single components of hand trajectory during a three-dimensional reaching task. The result was an R^2 as high as 0.5 or 0.6 between the actual and predicted trajectories of test data sets, with little difference between the linear and nonlinear approaches. Two years later, another group used similar linear filter methods to allow several monkeys to control the movement of a cursor viewed on a computer screen (Serruya et al., 2002). Although the movements were considerably slower than normal, the animals were able to make purposeful movements and detect and correct errors. The open-loop predictions in this experiment were similar to those achieved by Wessberg et al. (2000).

Rather than compute filters between input and output, Georgopoulos and his group used an approach based on the concept of neural preferred directions (the direction of hand movement yielding the greatest discharge) (Georgopoulos et al., 1982). They proposed the computation of a population vector that could be used to compute the mean direction of hand movement. Each neuron was characterized in terms of its preferred direction, and the preferred direction vectors were summed, weighted by the magnitude of discharge of the corresponding neuron during a movement. With this

approach, several monkeys learned to control the movement of a cursor in three dimensions using a virtual reality display (Taylor et al., 2002).

As in the studies just described, the most prevalent BMI approach has been decoding of the entire movement trajectory, generally using recordings made in the primary motor cortex. An alternative approach, taken by several groups, has been to decode the final location of the monkey's intended reach. One study compared these two approaches using recordings made in either M1 or the dorsal premotor cortex (PMd). They concluded that the M1 recordings provided more trajectory-related information but that PMd was a better and earlier source of information about the intended movement target (Hatsopoulos et al., 2004).

One of the most successful examples of target prediction was demonstrated recently by Shenoy's group, which employed maximum likelihood methods using either Gaussian or Poisson models of the spiking statistics of neurons recorded from PMd to classify the intended reach target (Santhanam et al., 2006). While selecting among 8 or 16 targets, one monkey achieved information transfer rates above 6 bits per second (roughly equivalent to typing 15 words per minute) using signals recorded from 96 chronically implanted electrodes. Most groups use 500 to 1000 ms of spiking history to make continuous predictions of movement trajectory. However, to achieve such a high transfer rate in this experiment, the classifier was based on only 60 to 130 ms of spike data, making the result even more remarkable.

Recordings from the posterior parietal cortex have also been used to classify the intended reach target. The parietal reach region (PRR) is an area within the medial wall of the intraparietal sulcus and the dorsal aspect of the parietooccipital area that is thought to represent the goal of a reaching movement in visual coordinates (Batista et al., 1999). Discrimination accuracy among eight targets of about 65% was achieved using a relatively small number of neurons (Musallam et al., 2004). Interestingly, it was also possible to decode information about the monkeys' expectation of the likelihood or magnitude of the anticipated reward from the same signals. It is worth noting that PRR and, to a lesser extent, PMd, may undergo fewer functional changes following spinal cord injury than M1. For this reason, it may be a particularly attractive cortical site for clinical consideration.

11.2.2 BMIs for Control of Dynamics

A virtual device (a cursor for example) can simply be instantaneously repositioned based on the predicted endpoint position. Controlling a robotic limb is more difficult and typically accomplished with a PD (proportionalderivative) controller, which compares the intended state variables (position and/or velocity) to the current state of the limb. The PD controller drives the production of appropriate torques to reduce measured limb state errors. Its parameters typically are adjusted to optimize performance under particular dynamical situations. Consequently, if the mass of the plant changes significantly, as when the subject must grasp and apply force to an object in order to push it, the change in system dynamics can result in the controller behaving suboptimally. For the most part, this problem has not yet been faced in current BMI applications, which have been limited to a single dynamical condition. The purely kinematic BMI faces further limitations if the subject must apply controlled forces, as when grasping and manipulating an object.

There have been very few studies of M1 discharge and force-related variables using large numbers of chronically implanted electrodes. In one of these, monkeys learned to control the force of a gripper together with its position in two dimensions, first using actual hand movements and then using real-time force and endpoint velocity predictions (Carmena et al., 2003). The accuracy of offline prediction of grip force was significantly higher than that of either hand position or velocity. Another group showed that shoulder and elbow torque could be predicted during planar limb movements with an accuracy nearly as high as the corresponding kinematic signals (Fagg et al., 2009).

Likewise, we have shown that EMG signals for both arm and hand muscles can be predicted during reaching and grasping movements with an accuracy as high as or higher than that of most studies of kinematic signals (Pohlmeyer et al., 2007b). This was particularly surprising given the relatively noisy, stochastic nature of the EMG signal. We have since used these predictions as real-time inputs to a four-channel stimulator controlling the level of contraction of four flexor muscles. Two monkeys used the system to control isometric wrist flexion force despite temporary paralysis induced by a peripheral nerve block. One, using input from approximately 80 neurons, achieved sufficient precision to track a target that moved among three different levels (Pohlmeyer et al., 2009).

Fetz and colleagues adopted an approach inspired by his classic work, using the discharge of individual, voluntarily modulated neurons to control FES activation of individual muscles (Moritz et al., 2008). Their monkeys typically learned to control isometric wrist force in either the flexion or the extension direction after practice of only several tens of minutes.

11.3 METHODS

Most current BMIs control movement kinematics: a cursor on a screen or a robotic arm driven by a PD controller. However, signals recorded from the



FIGURE 11.2

Cortically controlled FES for grasp implemented in an experimental monkey. The monkey's forearm muscles were temporarily paralyzed by injections of lidocaine to the motor nerves. Signals recorded from an intra-cortical microelectrode array implanted in primary motor cortex were used to predict the EMG activity during the monkey's attempted movements. These predictions were used to modulate the intensity of stimulation, much as with the Freehand neuroprosthesis in Figure 11.1. Our system allows the monkey voluntary control of the paralyzed muscles.

motor cortex should also be well suited to the control of movement dynamics, including the activity of muscles. We have begun experiments designed to harness the body's natural control signals as a means to control paralyzed muscles through FES. As a simple model of some of the deficits resulting from spinal cord injury, we temporarily paralyzed the forearm musculature with lidocaine injections (Figure 11.2). We recorded from the hand area of the primary motor cortex using chronically implanted 100-electrode arrays. We also implanted epimysial electrodes on a variety of muscles of the arm and hand that were used both to record EMG signals and to stimulate the muscles electrically. We used real-time predictions of EMG activity to control the input to a multi-channel FES stimulator that caused contractions of the paralyzed muscles. (All animal care, surgical, and research procedures were consistent with the Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Northwestern University.)

11.3.1 Isometric Wrist Torque Tasks

The monkeys were initially trained to sit in a primate chair that faced a computer monitor. All of the behavioral tasks required them to interpret force feedback information that was represented by a moving cursor displayed on the monitor. Once the monkeys learned this basic association, they were trained on several specific tasks that were used for the FES experiments. One was an isometric wrist task in which the monkey was required to move the cursor from a central target at zero force to a peripheral target using various combinations of force generated along the flexion/extension and radial/ulnar deviation axes. The monkey's upper arm was restrained by a custom-fitted cast that maintained his elbow at a 90-degree angle. Force was measured by a 2-axis strain gauge mounted between casts on the monkey's hand and forearm. Cursor movement distance was proportional to the measured torque along each axis.

After holding in the center for 0.5 second, an outer target appeared. The monkey was required to move the cursor to the target within 5 seconds and to maintain that torque for 0.5 second in order to receive a juice reward. In some cases, cursor movement was constrained to the horizontal (flexion/ extension) axis. In other cases, the monkey was required to control torque along both axes. In the one-dimensional version of the task, as many as five targets were presented along the flexion/extension axis. The most distant targets required torques of approximately 35–50% of the monkey's maximum voluntary contraction (MVC). In the two-dimensional task, eight targets, separated by 45 degrees, were presented on the circumference of a circle, analogous to the center-out movement task adopted by many groups since its introduction (Georgopoulos et al., 1982). These tasks allowed us considerable control over the time course and direction of the torque exerted by the monkey.

11.3.2 Hand Grasp Tasks

Although the isometric task was well controlled and stereotyped, other tasks we studied were based on more functional movements. In the least constrained of these, the monkey was required to pick up a ball from a small tray and place it in a tube with a 60-mm opening. The balls were of a variety of diameters and weights: 40-mm, 130 g; 40-mm, 95 g; and 24-mm, 60 g. The monkey started each trial by placing his hand on a touchpad for 0.2 second. A "go" tone indicated the beginning of a 5-second reach time period during which the monkey attempted to pick up the ball from the tray. An infrared sensor in the device tray detected the monkey's initial grasping attempts. Removing the ball from the tray began another 5-second interval during which the monkey was required to place the ball in the tube. A successful ball return earned the monkey a juice reward. The next trial was initiated when the monkey returned his hand to the touchpad.

11.3.3 Surgical Methods

Following several months of training, when the monkeys reached a suitable behavioral criterion, a sequence of two surgical procedures was performed to

implant the necessary recording and stimulation electrodes. (All surgery was conducted under aseptic conditions using Isoflurane inhalational anesthesia. Antibiotics (Amoxicillin or Cephazolin) and Dexamethasone were given preand postoperatively. Analgesics (Buprenex and Meloxicam) were also given postoperatively.)

11.3.3.1 Electrode Array Implantation Surgery

A single array composed of 100 silicon microelectrodes in a 10×10 grid (Blackrock Microimplantable Systems, Inc.) was chronically implanted in the hand area of the primary motor cortex (M1). A craniotomy was performed above M1, and the dura was incised and reflected. The electrode array was positioned on the crown of the right precentral gyrus, approximately in line with the superior ramus (medial edge) of the arcuate sulcus. In most cases, we used interoperative stimulation of the exposed cortical surface to determine the optimal implant site. A piece of artificial pericardium was applied above the array, the dura was closed using 4.0 Nurolon sutures, and another piece of pericardium was applied over it. The excised bone flap was replaced, and the skin was closed.

11.3.3.2 Limb Implants

In a separate procedure, electrodes (either epimysial or intramuscular) were implanted on a variety of muscles in the forearm and hand. The electrode leads were routed subcutaneously to a back connector using published methods (Miller et al., 1993). The electrodes were used for both bipolar recordings and monopolar stimulation. The full list of muscles included

- Those responsible for motion of the wrist: the extensor and flexor carpi ulnaris, the extensor and flexor carpi radialis (ECU, FCU, ECR, and FCR), and the palmaris longus (Pal).
- The common digit muscles: the extensor digitorum communis (EDC), the flexor digitorum superficialis (FDS), and the flexor digitorum profundus (FDP).
- The intrinsic hand muscles: the flexor pollicis brevis (FPB) and the first dorsal interosseous (1DI).

Both FDS and FDP were implanted with electrodes located in both the ulnar and radial compartments.

In the same procedure, custom-made nerve cuffs were implanted around the median, ulnar, and radial nerves at sites just proximal to the elbow. The cuffs were connected via cannulae to subdermal injection ports (Mentor Injection Domes) implanted in the upper arm. In this way, a block of all three nerves

at the elbow caused paralysis of the wrist and hand muscles. To achieve the nerve block, we injected lidocaine or other local anesthetics into each port, providing a temporary means to paralyze the limb and mimic some of the effects of a C5-C6 spinal cord injury. The EMG activity was negligible after 5 to 20 minutes. (The details of this method have been published (Pohlmeyer et al., 2009)).

11.3.4 Data Collection

Data were simultaneously recorded from the EMG electrodes and the intracortical array while the monkey performed one or more of the motor tasks described earlier. A torque signal was also recorded during the isometric wrist task. The data were recorded using a 128-channel Cerebus system (Blackrock Microsystems, Inc.). Action potential waveforms and their corresponding timestamps were saved for later offline spike discrimination using Offline Sorter (Plexon Neurotechnology Research Systems, Inc.) or streamed to separate computers for real-time analysis and control. These methods are described in greater detail later.

The EMG signals were amplified, band-pass-filtered (4-pole, 50-500 Hz), and sampled at 2000 Hz. Subsequently, EMG was digitally rectified, low-pass-filtered (4-pole, 10-Hz Butterworth), and subsampled to 20 Hz. Subsequent analysis was carried out primarily using MATLAB (The Mathworks, Inc.) and is described in greater detail in a later section.

11.3.5 Linear Systems Identification

We used a linear decoder to predict EMG activity in each muscle using the set of available neural recordings. The selection of a linear decoder was based on previous studies demonstrating only small improvements in performance with more complex decoding algorithms for estimating both EMG signals (Pohlmeyer et al., 2007b) and limb kinematics (Gao et al., 2003; Lebedev and Nicolelis, 2006). The selection was also based on our motivating rationale that the use of a muscle-based decoder would further simplify the decoding of motor cortical recordings. It should be noted that most BMI applications, including ours, span a relatively small portion of the animal's natural motor behavior. As this range is expanded, nonlinear decoders are likely to become more important (Shoham et al., 2005).

The implemented decoder assumed that the EMG in each muscle could be described by Eq. (11.1), in which $x_k(t)$ is the *N*-point vector of neural recordings from electrode k; $h_k(t)$ is the *M*-point finite impulse response function (FIRF) relating $x_k(t)$ to the muscle EMG z(t). w(t) is a random process accounting for measurement noise, nonlinearities, and contributions

from unmeasured inputs.

$$z(t) = \sum_{k=1}^{N} \sum_{\tau=0}^{M-1} h_k(\tau) x_k(t-\tau) + w(t)$$
(11.1)

The linear filters relating cortical recordings (input) to muscle activity (output) were efficiently estimated according to Eq. (11.2), in which $\hat{\vec{h}}$ is the vector of estimated FIRFs relating each input to the output; Φ_{XX} is the matrix of correlation functions between all inputs; and $\vec{\Phi}_{Xz}$ is the vector of cross-correlations between each input and the output. Further details on the structure of these matrices can be found in Westwick et al. (2006).

$$\hat{\vec{h}} = \Phi_{XX}^{-1} \vec{\Phi}_{Xz} \tag{11.2}$$

This identification process was repeated separately for each muscle in which EMG was recorded. We previously assessed the influence of FIRF length on EMG prediction accuracy (Pohlmeyer et al., 2007b) and found that 500-ms filters produced reliable and consistent predictions. That is the filter length that was used throughout this study. The FIRFs were estimated using 10–20 minutes of training data. When these numbers of data are available, we have found, Eq. (11.2) can be used directly and all available inputs can be incorporated into the identification. When fewer data are available, the identification process can be made more robust by restricting it to an optimal set of inputs (Sanchez et al., 2004; Westwick et al., 2006; Pohlmeyer et al., 2007b) and by using robust techniques to perform the matrix inversion required in Eq. (11.2) (Westwick et al., 2006).

One problem with using linear filters to predict EMG is the difficulty of accurately estimating periods of muscle quiescence. Low levels of noise in the estimates may substantially reduce the precision of control. This is true for both kinematic and EMG-based BMIs. However, it is a particularly important problem when using EMG predictions to drive FES because even low levels of continuous stimulation can increase the rate of muscle fatigue. We have demonstrated that nonlinear cascade models consisting of the linear FIRFs described earlier, followed by a static nonlinearity with characteristics similar to those of a threshold function, can enhance prediction of periods of muscle quiescence (Pohlmeyer et al., 2007b). Such models can be estimated from experimental data using published techniques (Bussgang et al., 1974; Hunter and Korenberg, 1986). In a closed-loop system as described in this chapter, the problem can be solved as well by employing a simple threshold function between the predicted muscle activations and the muscle stimulation

commands. Such a threshold is commonly incorporated into FES systems to prevent small changes in the command signal to each muscle from triggering the onset of stimulation. Because our FES system incorporated such a threshold, we found it unnecessary to incorporate an additional static nonlinearity in our identification process; the use of two similar nonlinearities would have been redundant and would have led to unnecessary system complexity. The process of setting this threshold for FES stimulation is described below.

11.3.6 Nerve Block Effectiveness

It was important to assess the level of nerve block in these experiments, but compensating for changes in the monkey's level of motivation complicates an accurate assessment. However, we took advantage of our ability to predict the level of EMG activity to improve our estimates. We recorded 30-second segments of EMG activity together with the corresponding M1 discharge at frequent intervals throughout the experiment, both before and after nerve block. Since in most cases, the monkey was unable to complete the task under block, he was rewarded simply for attempting to do so. We computed the ratio between the predicted and the actual EMG activity as a measure of nerve block effectiveness. The percent block was expressed simply as

Percent Block =
$$100 \left(1 - \frac{EMG_{Actual}}{EMG_{Pr\,ed}} \right)$$
 (11.3)

11.3.7 Stimulation

In order to use cortical recordings to control an FES system in real time, the basic EMG predictions need to be mapped into appropriate stimulator commands to cause the desired muscle activation. Our typical closed-loop FES experiments involved the stimulation and control of four to six muscles using a 16-channel stimulator with a common return electrode (FNS16, CWE). The stimulator output consisted of pulse width-modulated trains of biphasic pulses of fixed current and frequency. Stimulus frequency was common to all channels, typically 25 or 30 Hz, which was high enough to achieve nearly complete fusion of muscle twitches yet low enough to minimize fatigue effects. In a separate set of experiments for each monkey, we determined the current (typically 2–10 mA) necessary for each muscle such that pulse widths in the 50–100-us range provided near-maximal muscle force. Using this stimulus frequency and current, we determined the threshold pulse width necessary to produce detectable force, as well as the pulse width at which significant nonlinear "spillover" effects were noted in the relation between pulse width and force. In any given session, we mapped the point at which the EMG

prediction exceeded the noise floor by approximately two standard deviations to the stimulus threshold, and the peak EMG prediction to the spillover point or 200 µs, whichever was smaller.

Exceptions to these rules occurred when, during a closed-loop experiment, muscle fatigue significantly affected task performance. To compensate for the decreasing stimulation-evoked muscle force, we often increased the stimulation frequency to 30 Hz and, if needed, increased the currents by 25% or 50%.

11.3.8 Real-Time Control

Online sorting was performed to discriminate action potential waveforms based on the waveform clustering in principal component feature space. We made some effort to identify waveforms that appeared to result from single neurons, based on standard criteria: well-defined waveform clusters and a minimum inter-spike interval greater than 1.5 ms. However, the overlapping activity of well-modulated multiple units recorded from a single electrode were also included in our neural signal population despite failing the requirements for single-unit classification.

As soon as an action potential was discriminated, the Cerebus sent a UDP packet with the timestamp and neuron identification data encoded. A process running on a real-time Linux system received the packets and sorted the timestamps into different circular buffers for each neuron. The circular buffers were converted into the binned firing rates and passed to the linear filter that generates the predicted EMG activation. The EMG predictions were mapped to stimulus pulse width commands, as described above, and sent to the stimulator over a serial connection. The stimulator used these new values to update the stimulus pulses delivered on subsequent clock cycles.

11.4 RESULTS

The following subsections describe the results we achieved in our FES experiments.

11.4.1 Offline Signal Prediction

The data for our experiments were collected from two monkeys. One (EO) was trained to do both the 1D isometric wrist task and the ball grasp task. The other (OR) was trained to do the isometric wrist task under both 1D and 2D conditions. EMG predictions for the 1D task were based on seven sessions from monkey EO and 5 from monkey OR. EMG predictions for the 2D wrist

task were based on five sessions with monkey OR. Grasp task results were from 17 sessions with monkey EO.

11.4.1.1 Isometric Wrist Tasks

Torque during the isometric wrist task was generated primarily by the flexor and extensor carpi radialis and ulnaris muscles. These muscles each pull roughly in the directions suggested by their names. *Radialis* and *ulnaris* refer to the radius and ulna bones of the forearm, situated on the thumb and little finger sides, respectively. These muscles were differentially modulated during the torques to the different targets. Both the neural signals and the EMG activity were well modulated during the 1D isometric wrist task, as can be seen by comparison with the torque signal (Figure 11.3). We were able



FIGURE 11.3

EMG predictions for four wrist muscles that generate isometric wrist torque. Predictions were based on the activity of 74 neurons. The discharge rate of each neuron was normalized to its maximum firing rate within this period. The corresponding flexion/extension torque signal is overlaid. Please see this figure in color at the companion web site: www.elsevierdirect.com/companions/9780123750273

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EMG prediction accuracy for each of the implanted muscles during the 1D wrist task. Bars show mean +/-1SD (one standard deviation) of the multi-fold, cross-validation predictions calculated across 14 data sets.

to use information from the neural signals and simple linear filter models to predict the modulation of each muscle quite accurately. In this example, we used approximately 10 minutes of activity recorded from 77 neural signals to compute the filters. The predicted EMG signals shown here were computed from test data that were not used for generation of the decoder models. We quantified the accuracy of the predicted signals by computing the R^2 value between the actual and predicted EMG signals across the seven data sets collected from monkey EO. With a single exception (FCU), the average multifold cross-validation R^2 values for the task-relevant muscles were at or above 0.80 (Figure 11.4).

In a similar fashion, we used information from more than 100 neural signals recorded from monkey OR to predict EMG activity that occurred during the 2D task. In this task, the spatial patterns of muscle activity necessary to reach each of the targets were more varied than were those for the simple 1D task. The different combinations of EMG activity corresponding to the eight targets can be readily appreciated from Figure 11.5. In this example, prediction accuracy of the ulnaris muscles was somewhat lower than that of the examples shown



FIGURE 11.5

Predicted EMG activity for the 2D center-out isometric wrist task computed from more than 100 neural signals. Large arrows at the bottom of the figure indicate the direction of the target presented to the monkey during the period indicated by the gray shaded regions. Please see this figure in color at the companion web site: www.elsevierdirect.com/ companions/9780123750273

for the 1D task. However, this did not appear to be a function of the higher dimensionality of the task. The predicted EMG signals were somewhat less accurate for both versions of the wrist task for data from monkey OR compared to monkey EO. There were, however, no consistent differences between the tasks for monkey OR (Figure 11.6).

11.4.1.2 Grasp Task

The grasp task differed from the isometric wrist task in several respects. It involved more complex muscle activation patterns, including co-activation, rather than reciprocal activation of antagonistic muscles of the wrist and fingers. A mix of brief, phasic bursts and longer tonic patterns of EMG activity typically appeared in a rapid sequence, making this task much less stereotypic than the isometric wrist task from trial to trial. Figure 11.7 is an example from



FIGURE 11.6

EMG prediction accuracy during the 2D wrist task for a single, representative day. There was no systematic difference in prediction accuracy between the 1D and 2D tasks.

monkey EO of three EMG signals recorded from finger and wrist flexors and their corresponding activity predicted from 106 neural signals. Flexor digitorum profundus (FDP), the main flexor muscle of the digits, was characterized by a relatively simple, several-hundred-ms burst that occurred during the time the ball was being grasped ("pick up"). The accuracy of this predicted signal was similar to that of the best signals during the isometric task. Flexor digitorum superficialis (FDS), on the other hand, was more complex, with briefer bursts that occurred somewhat less predictably, sometimes with repeated bursts within the grasp, and occasionally with short bursts between trials when the monkey was returning his hand to the touchpad. FDS was predicted with considerably lower accuracy than during the isometric task (Figure 11.3), but with values that were still close to those typically reported elsewhere for kinematic reaching signals. The wrist flexor FCR had perhaps the most complex pattern of activity and yet, in this example, it was predicted with an accuracy between that of FDP and FDS.

The results shown in Figure 11.6 are representative of the overall results from the grasp task. Predicted EMG signals typically had R^2 values somewhat lower than those of the isometric wrist task. The average multifold cross-validation R^2 values computed from 17 training data sets ranged



FIGURE 11.7

Grasp-related raw data: (a) the firing rates of 98 neuronal signals and (b) the corresponding actual and predicted EMG activity during a series of three normal grasps. The neuronal signals were strongly correlated with the bursts of muscle activity around the time the monkey began to reach toward ("Go") and grasp the ball ("Pick up"). The R² values calculated between the actual and predicted EMG signals for these muscles are reported on each graph. Please see this figure in color at the companion web site: www.elsevierdirect.com/companions/9780123750273

between 0.40 and 0.76 for six wrist and finger flexor muscles, with an average of 0.53.

11.4.2 Real-Time FES Control

The brain-controlled, real-time FES results from the isometric wrist task were based on seven experimental sessions with monkey EO. For the grasp task, the

prediction results were from 17 model-building sessions with EO, and those for real-time FES control were from 20 experiments.

11.4.2.1 Isometric Wrist Task

As described above, the primary muscles involved in the isometric wrist task are the wrist flexors FCU and FCR and the extensors ECU and ECR. Because of the relatively weak forces generated by electrical stimulation and the substantial problem of fatigue (described later), we also stimulated the digit flexors FDS and FDP as well as the digit extensor EDC to increase the available force. Figure 11.8 illustrates the amount of wrist torque that could be generated by the monkey under blocked conditions and with BMI-controlled FES in the flexion and extension directions. While flexion torque reached 75% of normal, extension torque was limited to about 50%. However, the decreased magnitude of wrist torque was not the only control limitation imposed by FES activation. The stability of the torque was also less than normal, for at least two reasons.

For one, even with a stimulus frequency of 30 Hz, the muscle contractions were typically not completely fused since FES causes synchronous activation of motor units. This created a small ripple in the muscle force. In addition, there were lower-frequency fluctuations in the applied force, which may have



FIGURE 11.8

Maximum voluntary contraction (MVC) wrist torque under nerve block and FES conditions as a percentage of normal. The nerve blocks resulted in greatly diminished wrist strength. Cortically controlled FES allowed both monkeys to generate much greater torque voluntarily during the block.

been due to inadequacies in the predictive models of EMG or perhaps due to the loss of normal proprioceptive feedback that would also have been caused by the nerve block.

Furthermore, as noted later (Figure 11.10), FES-generated force was rather quickly reduced through fatigue—a consequence of abnormal motor unit recruitment, in this case because electrical stimulation preferentially recruited the large, fatigable fibers. Because fatigue was greater in the flexor muscles than in the extensors, the net result was that the practical operating torque range in both directions was limited to about 25% of normal. Consequently, the monkey's ability to reach targets at various levels was fundamentally limited by the precision with which the torque could be controlled and by the maximum torque that could be sustainably generated.

We chose the target size under FES control such that two nonoverlapping flexion targets could be presented within the monkey's assisted range. This target size was approximately twice that used under normal conditions. If the FES force range was divided into three different targets, the monkey was typically unable to control the torque level with sufficient precision. It was rarely possible to use more than one extension target. An example of threetarget, cortically controlled FES performance is shown in Figure 11.9. To reduce the effects of fatigue, we used twice as many low-flexion as high-flexion targets. For all three targets, the monkey was able to generate appropriate torque. As under normal conditions, a successful trial required a 0.5-second hold time. In this one-minute segment of data, all of the FES-assisted trials were successful (light gray targets). However, catch trials were introduced in random trials, in which the stimulators were turned off unexpectedly at the time of the go cue. These trials served to demonstrate that the FES was necessary for the monkey to be able to complete the task. Two of these occurred within this series of trials (dark gray targets). During these trials, the monkey was essentially unable to produce any useful torque. However, although his attempts were unsuccessful, it is important to note that the neural discharge patterns could be used to indicate that he was still trying to complete the task. Note the discharge that occurred at the beginning of the two catch trials in Figure 11.9 at 547 and 573 seconds. Indeed, the activation during the second of the two catch trials was as strong as or stronger than that during any of the other FES trials. Similar results were obtained over the seven experimental sessions with monkey EO. Over these sessions, the monkey was unable to complete a single catch trial in 71 attempts. Under FES conditions, he performed at a 65% success rate compared to 95% under normal conditions.

Muscle fatigue is a serious problem in all FES applications, as electrical stimulation essentially reverses the normal motor unit recruitment order. Much of the force is produced by the activation of the largest, most





Cortically controlled 1D isometric wrist task during paralysis. (a) Firing rate plot of the neural activity that was used to control muscle stimulation. (b) Rectangles indicate the torque targets, including successful (medium gray) and failed (dark gray) trials. The cortically controlled FES system was operating only during the shaded periods. Note that the failures occurred during catch trials when the FES was turned off. However, the firing rate shows that the monkey was trying to do the task during these periods. Please see this figure in color at the companion web site: www.elsevierdirect.com/companions/9780123750273

fatigable muscle fibers. We found that as little as 5-10 minutes of trials under brain-controlled FES caused a significant force reduction. In addition to the direct effects on performance, fatigue also adversely affects the monkey's motivation. We quantified the amount of fatigue that occurred over a typical FES experimental session by stimulating with fixed trains (10 mA, 200 µs for 3 seconds) at the beginning and end of the session. The results for five such sessions are shown in Figure 11.10. The decrease in flexion torque was considerable, dropping to 33% of its initial value. The change in extension torque was much less pronounced, probably because there were fewer extension targets, of lower torque in the course of a typical FES session.

11.4.2.2 Grasp Task

Real-time FES experiments for grasp were carried out under median and ulnar nerve block, with the radial nerve intact. This paralyzed the wrist and finger flexors but left the extensors under the monkey's normal control. Thus, the



FIGURE 11.10

Fatigue resulting from FES at the end of the experimental session. There was a significant decrease in the torque generated by a standard stimulus train between the beginning and end of a typical FES session.

monkey was capable of opening his hand to prepare to grasp the ball or to release the ball without the assistance of the FES, but he needed FES assistance to close his hand to complete the grasp. Each experimental session began with a period of data collection under normal conditions in order to establish baseline performance and muscle activation levels. An example of one such block is shown in Figure 11.11. We injected lidocaine to block the median and ulnar nerves at time 0. After 15 minutes, the block was essentially complete, as determined by the loss of flexor muscle EMG activity (see Section 11.3) and the onset of significant motor deficits. The remainder of the session consisted of a series of 10-minute blocks in which the monkey attempted to complete the grasp task either with or without FES assistance. In most of the blocks, the monkey was not successful in any of the unassisted catch trials. He completed only 4 out of 57 catch trials, primarily by adopting adaptive strategies to scoop the ball in his hand using unblocked muscles and passive forces. In contrast, the average success rate in this session with FES assistance was 80%.

The success rates over 20 experimental sessions during normal-condition, closed-loop control and catch trials are summarized in Figure 11.12(a). FES assistance improved the rate by a factor of 7. We also quantified the monkey's performance in terms of the time required to complete a successful trial. We measured the time from the monkey's initial contact with the ball to the successful ball grasp for all three conditions. Under nerve block, the closed-loop FES system significantly improved the speed at which the monkey successfully completed trials (Figure 11.12(b)). It is important to note that the catch trial times represent only the successful trials, achieved mostly through an alternate motor strategy. The great majority of these trials were not successful.



FIGURE 11.11

Summary of grasp task performance during median and ulnar nerve block. (a) Success rate for the seven experimental data sets for both FES trials and randomly inserted catch trials during which the stimulators were turned off. The monkey was essentially unable to pick up the ball during the catch trials, completing only 4 of 57 attempts. (b) Both nerve block effectiveness and stimulus effectiveness for FDPu and FDPr were tested at frequent intervals during the experiment. Please see this figure in color at the companion web site: www.elsevierdirect.com/companions/9780123750273

11.5 DISCUSSION

The following subsections discuss the successful outcomes of our FES experiments as well as the limitations of FES those experiments revealed.

11.5.1 Successful Proof of Concept

Our results demonstrate the feasibility of using a motor cortical BMI to control an FES system for restoring hand and wrist function following paralysis. Specifically, we demonstrated its utility for controlling the wrist in one and potentially two degrees of freedom, and for controlling simple hand grasp.



FIGURE 11.12

Summary of the results of 20 FES experimental sessions. (a) Success rates for normal, FES, and catch trial conditions comprising nearly 6000 trials. The monkey completed 77% of the trials with FES but only 11% when the stimulators were turned off. (b) Speed at which the successful trials were completed was significantly different for all three conditions (p < 0.0001, two-tailed Mann Whitney test). The great majority of catch trials failed as a result of the 5-second time-out.

In contrast to previous BMI studies, ours focused on decoding the intended muscle activation patterns rather than limb kinematics or torques. This greatly simplifies the use of a BMI for FES control, since the goal of an FES system is specifically to control the activation of paralyzed muscles. This approach allows us to harness the computational power of the brain for controlling the dynamics of movements; we do not have to rely on neuromechanical simulations to infer the most appropriate muscle activation patterns from a decoded movement trajectory.

11.5.2 Limitations in the Control of Complex Motor Tasks

The simple linear models used here yielded remarkably accurate EMG signal predictions, accounting for over 80% of the EMG variance during the isometric wrist task. The somewhat lower R^2 values in the ball grasp task may have arisen from the task's greater complexity. However, if this were the case, we would have expected to see a similar drop in the quality of predicted signals in the two-dimensional isometric wrist task compared to that in the one-dimensional task, was not the case.

In earlier work, we showed that decoders developed from training data collected in one task often did not generalize well to muscle activity recorded in a separate task, despite the fact that signals from either task could be accurately predicted independently (Pohlmeyer et al., 2007b). This phenomenon of limited task generalization may also have been at play when we used the cortical recordings to predict muscle activity during real-time control of hand grasp using FES. The EMGs recorded normally during the ball grasp task were transient, occurring only for brief periods associated with the ballistic nature of the movements used when unimpaired monkeys completed this task. However, the M1 and EMG activity used for decoder training data also included considerable sustained muscle activity resulting from the fact that the monkey often gripped a bar on the primate chair between successive ball grasps. The decoders constructed from this sustained activity appeared to have had somewhat poorer predictive power for the transient EMG recorded from FDS during the ball grasp task.

In addition to its dimensionality, the grasp task differs in another important way from the isometric wrist task. The latter was performed under FES control with patterns of predicted EMG that were very similar to patterns of normal EMG (Pohlmeyer et al., 2009). Although success rates were a bit lower and torque rise time a bit slower, behavior under FES was qualitatively normal. This was not the case with the grasp task. Although FES made it possible for the monkey to grasp the ball successfully despite paralysis, the movements were not normal. The overall posture of the hand was affected, and the strategies used differed noticeably from the norm. This was likely due to the fact that only a subset of the paralyzed muscles were activated by FES, requiring the monkey to adapt his motor strategies so that the grasping task could be completed. Hence, the real-time EMG predictions under FES conditions may have essentially involved generalization not unlike that between explicitly different motor tasks.

There are at least two important factors unrelated to the use of FES that may lead to problems with generalization. The first involves the high correlation of muscle activation patterns across many common tasks. Although the primate motor system is highly redundant with respect to the number of muscles available to control the skeletal degrees of freedom, activity within these muscles is highly correlated. These correlations lead to significant challenges when developing a robust neural decoder capable of generalizing to motor tasks other than those of the training data. Cortical neurons that contribute primarily to the activation of one muscle may nonetheless give excellent predictions of the activity of a second muscle, provided that both muscles remain well correlated. However, a decoder generated from such data would fail to generalize to novel tasks in which these two muscles were not used synergistically. This potential problem emphasizes the need for a robust training set that encompasses the range of muscle activation patterns relevant to the functional tasks of interest.

A second issue is that multiple neural pathways contribute to the activity of a given muscle. As one example, consider the role of peripheral feedback, which may alter muscle activity independent of descending commands. Proprioceptive feedback varies substantially with the environment a user interacts with. Unless the properties of this environment are also available as inputs to the decoder, generalization to interactions with different environments are not reliable.

A related challenge is that the role of motor cortical neurons can vary in a task-dependent manner, as demonstrated by Muir and Lemon (1983). These researchers identified motor cortical neurons whose relationship to the activity of their target muscle varied depending on whether a precision grip or a power grip was being performed. Similarly, Tanji and Evarts observed a differential role for motor cortical neurons in feedback control of distal arm muscles depending upon whether precision or ballistic movements were performed (Fromm and Evarts, 1981). Each of these findings illustrates the task-dependent role of the motor cortex in the generation of muscle activation and the corresponding challenges in developing a robust decoder for muscle activity based on recordings from a limited number of motor cortical neurons.

11.5.3 Limitations Related to the Use of FES for Control

There may be advantages to our approach as a result of the dynamical similarity between motor cortical discharge and muscle activity. However, the use of FES presents a number of formidable technical difficulties. Most are related to the efficacy with which muscles can be stimulated electrically and how well that stimulation can be used to replicate natural control.

One of the challenges encountered when using FES is fatigue, which can lead to a changing relationship between motor cortical activity and muscle activation. Electrical stimulation tends to invert the normal recruitment order, activating the fast fatigable fibers before the slow, fatigue-resistant fibers. In many of our experimental sessions, fatigue was evident within 5–10 minutes. Muscle fatigue is a complex process to which multiple mechanisms can contribute (Enoka and Stuart, 1992). These range from changes in the

contractile properties of muscle to changes in descending motor cortical commands. Mechanisms with a peripheral origin, as in this case, alter the relationship between muscle stimulation and force, introducing an error between the intended motor output and that achieved by the FES system. The problem of fatigue may be mitigated somewhat in a chronic application because chronically stimulated muscles develop some level of fatigue resistance (Peckham et al., 1976; Kernell et al., 1987). Also, it may be true that most real-world applications would not require the intensive stimulation within a relatively short period of time that was typical of our experimental sessions.

FES also is limited in its ability to re-create the dexterity of movement observed in natural control. This limitation arises from the number of muscles that can be implanted in a given subject and the efficacy with which those muscles can be stimulated. At most, we stimulated six muscles in these experiments, which was sufficient to restore a rudimentary form of palmar grasping but much less than what would be needed for more dexterous control. While stimulators with more channels exist, they may not be sufficient to restore natural control because of the many challenges associated with controlling muscle force electrically.

The first of these challenges is associated with the difficulty of fully recruiting the fibers within a given muscle. We used electrodes to activate each of the FES target muscles in our experiments. These have the advantage of being highly selective, at least at low stimulation levels. However, it is difficult to activate an implanted muscle fully, since the high-stimulation currents needed to achieve full activation often spread to neighboring muscles, resulting in "spillover" stimulation that degrades the fidelity of individual muscle control.

Cuff electrodes, placed around the nerves innervating each target muscle, can be used to generate much more complete muscle activation with substantially lower currents. However the recruitment order problem remains. This technique works well for larger muscles, but is not feasible for smaller ones, many which have restricted access to their isolated motor nerves. Furthermore, beyond the multiple heads that are recognized in some muscles, many (in particular the extrinsic digit muscles) have multiple compartments that preferentially affect individual digits.

An alternative is to use multicontact electrodes placed more proximally on peripheral nerves innervating multiple muscles of interest. We have begun to test this approach using both multicontact flat interface nerve electrodes (FINE) (Leventhal and Durand, 2003) and the multi-electrode Utah "slant" array (Branner et al., 2004). These technologies hold the promise of effective, selective activation of muscles or muscle compartments, including the intrinsic hand muscles. However, their utility for dexterous control of the primate hand during functional tasks has yet to be demonstrated.

11.6 FUTURE DIRECTIONS

Although our present results demonstrate the feasibility and promise of a muscle-based decoder for FES-controlled hand grasp, there are a number of areas in which the current system might be expanded or improved. Each presents interesting applications and challenges in the area of signal processing.

11.6.1 Control of Higher-Dimensional Movement Using Natural Muscle Synergies

Control of more complex, higher-dimensional grasping movements through FES will certainly require refinements in our ability to activate many muscles. However, generating the necessary control signals that can be expected to remain robust across a variety of movements will also present considerable challenges. There are at least 30 muscles with insertions distal to the elbow that are involved in the control of hand movements. Despite this fact, the kinematics of even rather complex manipulation tasks can be predicted with only six or seven components (Santello and Soechting, 2000; Todorov and Ghahramani, 2004). A number of studies have reported that several different groups of muscles appear to be activated synergistically across a broad range of movements. This inferred organization is based on spinal cord stimulation as well as recordings from groups of muscles during behavior (Kargo and Giszter, 2000; d'Avella et al., 2003; Ting and Macpherson, 2005; Tresch and Jarc, 2009). The groups appear to act as a basis set for the construction of more complex movements.

This organization also seems to be reflected in the central nervous system, where it has been shown that that individual neurons in M1 nearly always project to more than one muscle (Fetz and Cheney, 1980; Schieber, 1996). It is possible to describe the "muscle space" preferred directions of individual M1 neurons in terms of the muscle or muscles with which a given neuron's activity is correlated. Neurons tend to cluster within restricted regions of this muscle space, in areas that correspond to groups of synergistically activated muscles (Holdefer and Miller, 2002; Morrow et al., 2007). The appeal of these results is that they suggest dimensionality reduction may occur within the nervous system, perhaps at the spinal level, to reduce the complexity of control at the central level.

Although there remains some debate as to the role or even existence of muscle synergies in the control of natural movement, such an approach may provide a useful tool for controlling movements through FES. Importantly, the use of synergies that exploit the natural dynamics of the musculoskeletal

system may be used to simplify control without substantially sacrificing motor performance or flexibility (Berniker et al., 2009). By specifically decoding the activation patterns for groups of muscle synergies rather than individual muscles, it may also be possible to increase the robustness of an FES controller. This increase would arise from the reduced chance of erroneously predicting the activation of an individual muscle, since muscles with a relatively small weighting in a given synergy would have the benefit of being associated with the commands to muscles with a deeper modulation and therefore an increased signal-to-noise ratio. A number of computational techniques have been used to estimate muscle synergies, including principal component analysis, independent component analysis, and non-negative matrix factorization (see the comparison of algorithms in Tresch etal. (2006)). The last has the benefit of restricting muscle activations to non-negative values, which can be directly mapped to muscle stimulation commands.

11.6.2 Adaptation

While we stress the utility of simple linear decoders, it is possible that further performance gains may be made with adaptive decoders. Such decoders are likely to be beneficial for the implementation of practical BMIs, in which training data is generally not available (Hochberg et al., 2006; Kim et al., 2008). Just as the learning of complex motor tasks requires substantial adaptation at the cortical, subcortical, and peripheral levels of the neuromuscular system, it is likely that the challenges just identified will be partially met by a system in which the user has the ability to adapt neural commands as needed to obtain the desired motor output. Indeed, in our experiments we did not find a strong correlation between our ability to predict EMG signals offline and the online, closed-loop performance of the same decoder. This suggests that the monkeys were able to adapt their motor commands to compensate for changes in the relationship between their intended movements and those actually produced by the FES.

A co-adaptive BMI controller that benefited from both motor learning and algorithm adaptation was described several years ago (Taylor et al., 2002). In that case, the decoder was modified after trials containing errors so that the pattern of recorded neural discharge would generate the desired movement. More recently, investigators tested the ability of human subjects to learn to control a two-dimensional cursor using a 19-dimensional digit movement signal recorded from a data glove. They discovered that small changes in the transform between digit movements and cursor movements that only partially corrected errors led to a more rapid increase in performance than did either a fixed decoder or large changes that fully corrected the errors (Danziger et al., 2008). A similar approach applied to higher-dimensional FES control signals that lacks fixed kinematic targets will present new challenges. It may be beneficial to combine this approach with the muscle synergy-based control outlined earlier.

Several more extreme examples of adaptation have been reported, in which monkey subjects were able to learn to adapt even to decoders that had been intentionally scrambled (Jarosiewicz et al., 2008; Ganguly and Carmena, 2009). In one case, monkeys were able to learn, over a number of days, two different decoders and to switch rapidly between them. Their performance on a fixed decoder was actually better after several days than their performance when a decoder was recomputed from new training data at the beginning of each session (Ganguly and Carmena, 2009). The investigators suggested that optimal performance would be achieved by allowing the monkeys simply to learn the properties of a fixed decoder. However, they did not attempt to modify the decoder optimally.

These results, demonstrating the importance of neural adaptation, are in accordance with our general philosophy of using relatively simple decoders and relying on the computational power of the brain to use them to their fullest potential. It remains to be seen if more complex, adaptive decoders will exhibit a substantial improvement in performance during tasks involving more degrees of freedom than those used in the present study. If so, they are likely to require adaptive algorithms tailored to the behavior and learning rates of each subject.

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