

17 Human Single Unit Activity for Reach and Grasp Motor Prostheses

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There are over 5 million patients suffering from paralysis in the United States alone due to traumatic accidents and diseases (Christopher & Dana Reeve Paralysis Foundation). Paralysis due to spinal cord injury, amyotrophic lateral sclerosis (ALS), or stroke sometimes leads to patients becoming “locked-in,” wherein the patient is cognitively intact but is unable to move or communicate with the outside world (Bauby, 1998). To restore some degree of movement control and communication ability, motor prostheses systems have attempted to tap into intact brain signals and decipher locked-in patients’ intentions (see figure 17.1). Although early prostheses used noninvasive approaches such as electroencephalography (EEG), the signal-to-noise ratios of these approaches have been somewhat limited (but see Birbaumer, 2006) compared to that of using single unit activity (SUA) recorded from many neurons. Even though the extraction of SUA requires an invasive procedure, the successful use of invasive electrodes in cochlear implants and deep brain stimulation (DBS) electrodes to help cure deafness and Parkinson’s disease, respectively, suggested that invasive approaches could hold promise in helping cure paralysis (Donoghue, 2008; Hatsopoulos & Donoghue, 2009). In fact, recent clinical trials have had positive results in enabling paralyzed patients to control computer cursors and robotic arms with SUAs recorded from multielectrode arrays placed in the motor cortices of paralyzed individuals. Two noteworthy efforts are the BrainGate clinical trials at Brown University (Hochberg et al., 2006; Hochberg et al., 2012) and a separate clinical trial at the University of Pittsburgh (Collinger et al., 2012). In parallel, researchers are also working on lower limb prostheses for restoring walking (He et al., 2008; Harkema et al., 2011) including electrochemical options (van den Brand et al., 2012) although this latter research has not reached clinical trial stage yet. A market research study has suggested that motor prostheses that achieve paraplegic functionality for quadriplegic patients, and thereby give them greater independence from caregivers, for at least seven consecutive years can be economically viable for insurance companies (Bansal et al., 2005). Here, we review the progress toward the development of reach and grasp prostheses that may one day achieve this goal.

Monkey electrophysiology has helped guide the understanding of the neural code underlying reach and grasp movement generation as well as helped quantify the amount of information extractable from various signals. With the recent advances in brain–machine interfaces (BMIs)

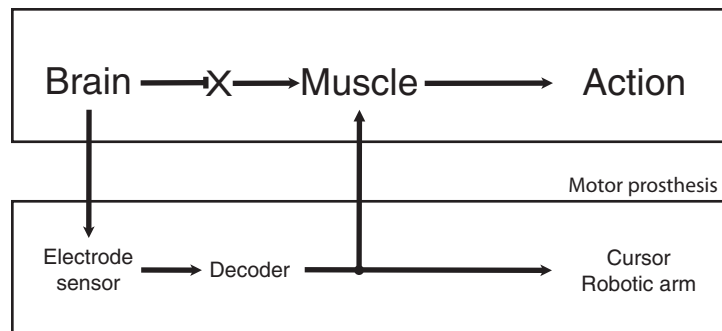


Figure 17.1

Conceptualization of a motor prosthesis or brain–machine interface (adapted from figure 1 in Donoghue, 2008). In a paralyzed subject the normal connection between brain and muscles is severed due to disease or injury. A motor prosthesis records the brain activity using electrode sensors and decodes this activity to infer the subject’s motor intentions. The decoded activity is used to drive the subject’s muscles using functional electrical stimulation or to control a cursor or robotic arm.

to restore motor control in paralyzed human patients (specifically the BrainGate and Pittsburgh clinical trials mentioned earlier) there is tremendous opportunity to not just apply the motor coding theories built on monkey experiments but also to compare and contrast these with human motor cortical control. These studies will help humans with paralysis and simultaneously advance our understanding of human motor neurophysiology (Donoghue, 2008; Mukamel & Fried, 2012).

This chapter is divided into three sections. In the first section, we will review the neurophysiology of motor coding based primarily on single unit recordings in monkeys and humans and its applications toward reach and grasp prostheses. In the second section, we will describe the technical considerations of researchers when building motor prostheses systems. Finally, we end with future directions.

Motor Coding

A motor prosthesis can strive to replicate various parameters of a reach and grasp movement such as the arm’s or digit’s end-point position, direction and velocity of movement, force, trajectory, or higher-level goals.¹ Through the work of monkey neurophysiologists over the last century, we now have a better understanding of the encoding of these parameters in neuronal populations across motor cortical areas. Feedback and plasticity also play a crucial role in shaping movements on shorter and longer timescales, respectively.

The first detailed account of motor cortical organization in monkeys (that were lightly anesthetized) came from stimulation, lesion, and cooling experiments by Leyton and Sherrington (1917). They identified several sites anterior to the central sulcus (see figure 17.2, plate 16, for a simplified schematic of cortical regions and connected pathways involved in motor

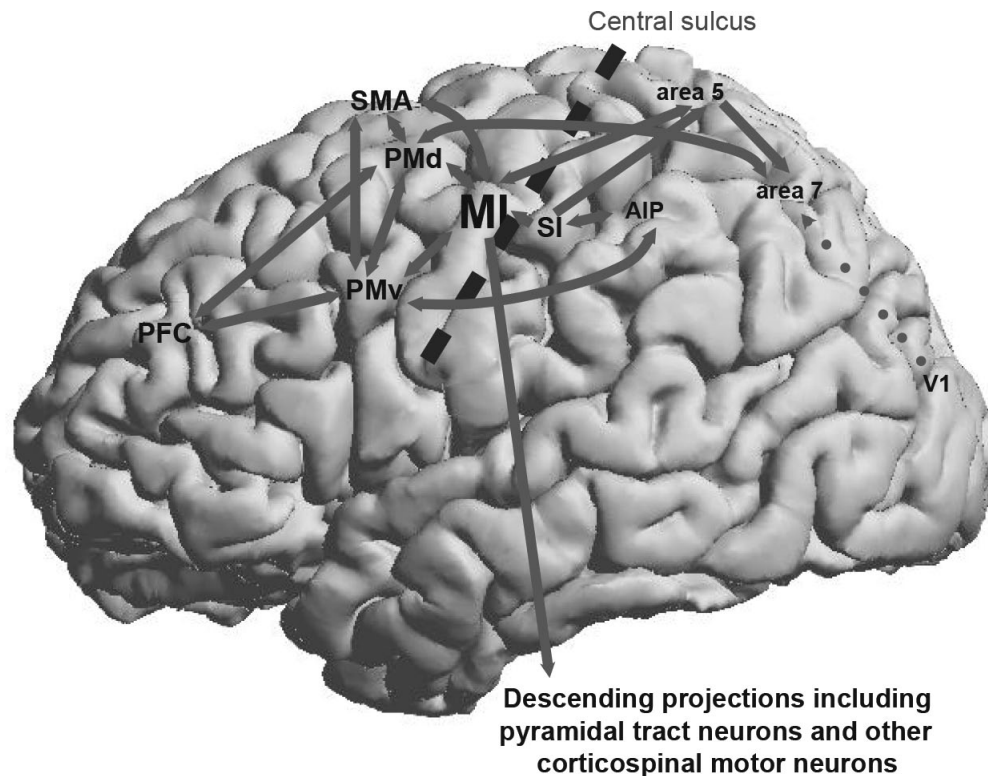


Figure 17.2 (plate 16)

A simplified schematic of cortical regions and connected pathways involved in control of reaching and grasping actions; see text. SMA, supplementary motor area; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; MI, primary motor cortex; SI, primary somatosensory cortex; AIP, anterior intraparietal region; PFC, prefrontal cortex; V1 primary visual cortex. Adapted from figures in Martin (2003), and Scott (2004), and from connectivity results in monkeys from Vogt and Pandya (1978), Matelli et al. (1986), Pandya and Yeterian (1996), and Dum and Strick (2005).

control), which, when stimulated, resulted in relatively stereotyped muscle movements of particular parts of the body such as fingers, arms, neck, hip, and so forth. Such movements were not elicited by stimulating sites posterior to the central sulcus. Penfield and Boldrey (1937) reported that within primary motor cortex (MI; see figure 17.2, plate 16) there is somatotopy in the organization of neurons, with nearby neurons generally coding for the movement of nearby muscles on the body. Subsequent work related the firing rates and patterns of motor cortical neurons to kinematic parameters such as position and velocity, and dynamic parameters such as force and the rate of change of force, but found no single parameter that was best controlled by these neurons (Evars, 1968; Humphrey et al., 1970). A key concept in our understanding of motor coding and its application in human motor prostheses is that of “directional tuning” of motor cortical cells.

Visual information about the object to be reached and grasped arrives into the brain from the eyes, and through the lateral geniculate nuclei of the thalamus (LGN), to the primary visual cortex (see figure 17.2, plate 16). The location and shape of the object to be reached and grasped are thought to be extracted via regions in the parietal cortex such as area 7 of the posterior parietal cortex and anterior intraparietal region (AIP). Area 5 estimates the current configuration of the arm, and nearby regions compute the transformations required for the arm and hand to perform the reach and grasp. Parietal regions are also reciprocally connected with premotor regions. AIP is reciprocally connected with ventral premotor cortex (PMv) while area 7 is reciprocally connected with dorsal premotor cortex (PMd). These circuits are thought to be preferentially involved in grasp and reach, respectively (but see Vargas-Irwin, 2010, and Bansal et al., 2012a, for a discussion about reach and grasp in PMv). Premotor regions also receive higher order goal information from the prefrontal cortex. MI is reciprocally connected with premotor cortex, area 5, and receives input from the primary somatosensory cortex. MI computes motor command signals that are transmitted to the spinal cord and brainstem structures via descending projection such as the pyramidal tract neurons and other corticospinal motor neurons. Note that the dotted arrow in figure 17.2 (plate 16) indicates indirect connections, and the dashed line indicates central sulcus. Connectivity is based on anatomical results in monkeys of homologous brain regions and is not meant to be exhaustive. Note that here we do not present other important structures important for motor control such as the basal ganglia, cerebellum, cranial nerves, and the vestibular and oculomotor systems.

Directional Tuning

Individual neurons' firing rates in monkey MI exhibit cosine-shaped tuning to a range of preferred directions of reaching arm movements in two (Georgopoulos et al., 1982) and three (Schwartz et al., 1988) dimensions. This property is analogous to the orientation tuning displayed by cells in primary visual cortex when subjects are presented with stimuli of various orientations. Remarkably, by using the weighted combination of individual neuron responses or "population vector," the direction of the monkey's arm movement was determined (Georgopoulos et al., 1986; Georgopoulos et al., 1988). Thus, each cell did not code for a unique movement, but groups of cells acted together to perform a movement. From Georgopoulos et al. (1999), we write the mathematical expression for the population vector as

$$P_j = \sum_{i=1}^N w_{ij} C_i,$$

where P_j is the population vector for the j th finger or wrist movement, C_i is the preferred direction of the i th cell (N total cells), and w_{ij} is a weighting function:

$$w_{ij} = d_{ij} - \bar{d}_i,$$

where

$$\bar{d}_i = \frac{1}{M} \sum_{j=1}^M d_{ij} .$$

M equals the number of movements, and d_{ij} is the mean firing rate of the i th cell for the j th movement.

In principle, the population vector could then be used to control a motor prosthesis. From the perspective of motor prostheses, it is important to note that these early studies were investigating fundamental questions of motor coding and therefore reconstructed the direction of arm movements *offline*, which means after the experiment when the monkey actually performed the action. More recently, several studies motivated by building motor prostheses showed that monkeys could control a cursor *online* in real time with just their neuronal activity. Moreover, earlier experiments were considered *open loop* since the monkey did not receive any feedback about its decoded intentions, but more recent experiments are termed *closed loop* as the monkey controls an effector with its brain signals and receives sensory (typically visual) feedback during brain control (open-loop robotic arm in 1-D and 3-D, Wessberg et al., 2000; instant cursor control, Serruya et al., 2002; 2-D end point, Musallam et al., 2004; 3-D cursor, Taylor et al., 2002). It is also noteworthy that neuronal tuning properties often change during closed-loop brain-control trials, resulting in improved motor control over time (see the “Plasticity” subsection later in this section). Decoding algorithms that account for changes in tuning are an active area of research (see the “Decoding Algorithm Design” subsection of the “Technical Considerations” section below).

The invasiveness of the microelectrodes required for single neuron recordings have precluded the validation of the monkey physiology results in healthy human MI. Initial work with human ALS patients implanted with neurotrophic² electrodes demonstrated that they could modulate the activity of a single neuron in their MI that drove an on/off switch and controlled a cursor or a speech synthesizer (Kennedy & Bakay, 1998; Kennedy et al., 2000). Recently populations of direction-tuned neurons were found in paralyzed human patients in the BrainGate clinical trials, and these were used in an online, closed-loop prosthesis to control a cursor and the opening and closing of a robotic fist (Hochberg et al., 2006). Truccolo et al. (2008) found that more than 80% of the cells in MI were tuned to observed position and velocity of a target in a pursuit-tracking task. In addition, Truccolo et al. (2008) reported that the intended target was decoded with an accuracy of 80–95% in a 2-D center-out task, consistent with previous research in monkeys (Paninski et al., 2004). These results were striking because even though the patients in the BrainGate trials had severe loss of voluntary control of their limbs and had not used them in years,³ they were still able to modulate their MI neuronal activity in response to intended movements. The modulation of MI neurons not just during action performance but also during action observation is a significant property for motor prostheses and has also been demonstrated

in monkeys (Tkach et al., 2007; Dushanova & Donoghue, 2010). Further information about the properties of single neurons in human motor cortical areas was obtained from patients with Parkinson's disease undergoing surgery for the implantation of DBS electrodes. During DBS surgeries, premotor (area 6) cortical neurons were demonstrated to exhibit directional tuning, and contain movement intent (to move or not to move) information (Ojakangas et al., 2006). Current work regarding the selection of *area* and subregion of implantation for a prosthetic device is summarized later in this chapter.

Grasp Coding

Although direction tuning can be exploited to get an effector to a desired location, manipulating objects often requires grasping them. For motor prostheses, self-feeding is a crucial step toward conferring independence to paralyzed subjects. Ventral premotor (PMv, or area F5; see figure 17.2, plate 16) cortical neurons are involved in finger movements and encode grasp types and grasp aperture in monkeys (Kurata & Tanji, 1986; Rizzolatti et al., 1988; Umiltà et al., 2007; Vargas-Irwin, 2010; Bansal et al., 2012a). Similar grasp types are encoded in similar neuronal firing patterns in PMv (Carpaneto et al., 2011). Although many studies have examined PMv for a specific role in grasp coding, recent work has reported equivalent representation for continuous grasp in MI, and intermixed reach and grasp populations within both MI and PMv (Vargas-Irwin, 2010; Vargas-Irwin et al., 2010; Bansal et al., 2011; Bansal et al., 2012a).

A mouse click may be regarded as a simple grasp manipulation. Initial work in the BrainGate trials simulated a mouse click by asking subjects to imagine squeezing closed or opening their fists (Kim et al., 2011). In more complex applications, monkeys fed themselves by reaching and grasping for food using a robotic arm driven by signals from neuronal populations in MI in real time (Velliste et al., 2008). Paralyzed humans in the BrainGate clinical trial were recently able to reach, grasp, and drink from a coffee cup using a robotic arm driven by MI neurons (Hochberg et al., 2012). A recent clinical trial at the University of Pittsburgh demonstrated brain control of a seven-degrees-of-freedom robotic arm using SUAs from two 96-electrode arrays in MI of a tetraplegic patient (Collinger et al., 2012).

Force Coding

Even as perfect decoding of direction and grasp kinematics would allow a subject to hold an object such as an egg between his or her fingers, applying too much force at the wrong time will crush the egg and create a mess. Therefore, understanding the relationship between SUA and force generation could provide crucial signals for paralyzed patients. Despite this fact, most neurophysiology studies with human patients have so far focused on kinematics, with algorithmic control of force. In monkeys, force is known to modulate firing rates of pyramidal tract neurons (Evarts, 1968; see figure 17.2, plate 16). This property can be used to predict end point or grasping force from MI neurons (Gupta & Ashe, 2009; Ethier et al., 2012). In human patients undergoing DBS surgeries, Patil et al. (2004) demonstrated that neurons in subcortical structures such as the subthalamic nucleus and thalamic motor areas predict gripping force. In applications

such as BrainGate, however, the modulation of neuronal responses with varying levels of imagined force is still unreported. Computing the appropriate force to apply is complex and depends on proprioceptive feedback that may be diminished in paralyzed patients.⁴ The issue of *feedback* and how it may be conveyed to movement or force-generating neurons will be discussed later in this chapter. In addition, imagining moving a heavy load versus a lighter load may provide a gain control mechanism by which otherwise quiescent neurons bolster their firing rates and are then read out by a neural implant.

Trajectories in Space and Time

So far we have described a static view of the neuronal encoding of reach and grasp parameters such as end-point position, grasp aperture, and force. Reach and grasp movements, however, occur not just in 3-D space, but also in time. Thus, improved understanding of how neurons code for trajectories of movements may enable prostheses with better performance. Recent work has found that the activity of monkey motor cortical neurons is better explained by preferred “pathlets” or trajectories for reach and grasp rather than by preferred directions that are independent in space and time (Hatsopoulos et al., 2007; Saleh et al., 2010; Saleh et al., 2012). This is a remarkable validation of a concept proposed by Leyton & Sherrington (1917): “The motor cortex may be regarded as a synthetic organ for compounding and recompounding in varied ways movements of varied kinds of scope from comparatively small, though in themselves well coordinated, fractional movements.” Furthermore, these trajectories might be generated by the coordinated activation of related muscles or *muscle synergies* (d’Avella et al., 2003; Overduin et al., 2012) by pathlet coding neurons.

For motor prostheses, there has been progress with the application of direction and velocity tuning based models in controlling a robotic arm driven by neuronal signals (Hochberg et al., 2012). Hochberg et al. (2012) used a Kalman filter based decoder (Wu et al., 2006), which is a linear state–space dynamical system model. The decoder is trained with the neuronal activity when the patient imagines moving a robotic arm to certain targets placed along the cardinal axes. Such a decoder learns an implicit knowledge of kinematic trajectories in the form of the state–space transition matrix but does not explicitly model the activity of each neuron as contributing toward a pathlet. Future work may explore whether pathlets are a better approach to building an encoding/decoding model for motor prostheses. Recent work, however, suggests that the predictive power of pathlet models is weaker than that of models using spiking history of other simultaneously recorded neurons (Truccolo et al., 2010). Thus, including spiking history in the model may be another way of improving decoding performance (Truccolo et al., 2005).

Areal Organization of Motor Coding Regions, and Sensorimotor Computation

Understanding the areal organization of motor coding for prostheses is motivated by targeting the recording electrodes toward the region(s) that will maximize the information content of the relevant motor parameter. MI is the main contributor to corticospinal motor neurons pathways

and therefore a natural area for the placement of electrodes for motor prostheses. The BrainGate clinical trials report considerable success with placing the electrode array in the “knob”-shaped motor hand area (Yousry et al., 1997) of MI. Outside of MI many areas are known to code for motor parameters that may not just be useful in cases of damage to MI but also potentially offer additional information beyond that in MI. Anterior to MI, dorsal premotor cortex PMd and PMv neurons are interconnected with MI (Pandya & Yeterian, 1996; Dum & Strick, 2005; see figure 17.2, plate 16) and encode reach and grasp parameters often earlier than MI in delay paradigms (Kurata & Tanji, 1986; Rizzolatti et al., 1988; Fu et al., 1993; Messier & Kalaska, 2000; Umiltà et al., 2007; Stark & Abeles, 2007; Stark et al., 2007). Premotor areas could serve as sources of additional information for prostheses (Bansal et al., 2012a). Medial frontal cortical regions such as the supplementary motor area (SMA; figure 17.2, plate 16) are key to planning sequential movements in monkeys (Tanji and Shima, 1994) and related to movement intention in humans (Fried et al., 1991; Fried et al., 2011). SMA and PMd neurons have been used to decode two target sequences in real time (Shanechi et al., 2012). Prefrontal and frontopolar cortices are reported to encode increasingly abstract parameters related to movements such as higher order goals (Tsujimoto et al., 2011).

Although movements are not evoked by stimulating sites posterior to postcentral gyrus (Leyton & Sherrington, 1917), the posterior parietal cortex (PPC) serves a crucial role in sensorimotor computations and has been demonstrated as a useful source of reach end-point, trajectory, and grasp information (Musallam et al., 2004; Mulliken et al., 2008; Townsend et al., 2011). The PPC is composed of many regions in monkeys such as the lateral intraparietal area, ventral intraparietal area, central intraparietal area, AIP (figure 17.2, plate 16), area 7 (figure 17.2, plate 16), and the medial superior temporal area (Andersen et al., 1997), with corresponding human counterparts (Grefkes & Fink, 2005). These areas compute movement plans in diverse (but not exclusive) frames of reference such as in eye, head, hand, body, world, or object-centered coordinates using multimodal information (including posture) as inputs. The diversity of reference frames enables the computation of coordinated movements of body parts such as the neck, arms, and eyes to achieve a final goal. Furthermore, the responses of neurons in these areas are considered to be intermediate between purely sensory or motor representations and modulated by cognitive signals such as attention, intention, reward, and decision making (Andersen et al., 1997; Glimcher, 2004). On the one hand, these representations could provide additional information to drive a motor prosthesis compared to those in MI. On the other hand, the influence of these cognitive variables may make it harder to disentangle the precise motor intentions of a paralyzed subject. Complicating this simple assessment are the observations that MI neurons also exhibit postural modulation (Ajemian et al., 2008) and cognitive features such as serial order (Carpenter et al., 1999), and they may not just direct muscles but also participate in coordinate transformations (Takei et al., 1999). Despite these complications, both the BrainGate and Pittsburgh clinical trials have targeted MI, and the use of other areas remains to be explored in human prostheses.

Feedback

Visual and proprioceptive feedback play a significant role in generating smooth movements (Scott, 2004) by providing, for example, limb or effector position information to motor control areas such as area 5 (see figure 17.2, plate 16) in parietal cortex (Kalaska et al., 1983) and MI (Goldring & Ratcheson, 1972). While visual feedback might be typically unaffected, proprioceptive feedback processing may be impaired to various degrees in patients with paralysis. While proprioceptive feedback is not strictly necessary to generate motor control signals, as demonstrated in the clinical trials mentioned earlier, providing proprioceptive feedback could enhance BMI performance (Suminski et al., 2010). In paralyzed patients with impaired feedback afferents, electrical or optical stimulation may provide an approach toward “writing in” proprioceptive information (Diester et al., 2011; Gilja et al., 2011). In healthy motor control, the process of converting motor commands to movements of the limb, as well as the estimation of limb position, is subject to errors. The proprioceptive feedback in a prosthesis could thus provide information about limb or effector position although, even in its absence, visual feedback might compensate for it to some extent. The nature and extent of this compensatory ability remain to be quantified (Scheidt et al., 2005).

State-Space Models

Alternative motor coding proposals have suggested that MI neurons are not directly coding for parameters such as arm/hand position or velocity but are coding for some state variables intrinsic to the system generating movements such as muscle length and velocity (e.g., Oby et al., 2012). There have been proposals that the motor system learns optimal feedback control laws to act on these state variables (Scott, 2004). Recent work has modeled the high-dimensional neuronal population activity (that can be quite noisy for each neuron from trial to trial: e.g., Nawrot et al., 2008) at any instant as a point on a *low-dimensional manifold*. In this view, the neuronal activity over time related to generating a movement trajectory describes a “neural trajectory” in this low-dimensional space that stays more similar compared to the noisy individual neurons and that may be indicative of a dynamical control system for generating actions (Santhanam et al., 2009; Yu et al., 2009; Shenoy et al., 2011; Churchland et al., 2012). Santhanam et al. (2009) reported significant improvements (~75%) using a factor analysis based decoding approach, which exploited the correlated trial-to-trial variability. These approaches remain to be tested in prostheses applications.

Plasticity⁵

For a motor prosthesis to work over an extended period of time, it will need to adapt to changing neuronal properties. MI is known to change its properties following traumatic injury or during skill-learning and everyday actions (Sanes & Donoghue, 2000). Many BMI studies with monkeys have shown an improvement in decoding performance over days suggesting that the monkeys’ neurons learn to control the effectors better over time (Carmena et al., 2003; Taylor et al., 2002;

Musallam et al., 2004; Ganguly & Carmena, 2009; Jarosiewicz et al., 2008). A similar improvement was seen in human clinical trials (Collinger et al., 2012). Thus, neuronal plasticity has critical implications for motor prostheses. Typically, decoding algorithms initially strive to tap into the natural tuning properties of the neurons as determined by imagined or observed movements. To achieve skilled control, the subject can engage plasticity mechanisms as they modulate their neuronal responses in trying to *transmit* their intentions to a relatively stable decoding algorithm. Plasticity (or noise), however, may alter the responses of neurons involuntarily (Rokni et al., 2007), requiring a change in the algorithm to infer the subjects' true intentions. The specific balance between tuning the decoding algorithm and allowing the brain to adapt to a fixed algorithm remains to be established.

Technical Considerations

Signal Selection: Single Unit Activity versus Other Signals for Motor Prostheses

An extracellular microelectrode placed intracortically records a field potential (voltage) signal, which can be filtered into many frequency bands from 0.1 to about 5000 Hz. At the higher range of frequencies (300–5000 Hz), action potentials are detected and then sorted. Action potentials are the only signals corresponding directly to the activity of single neurons. Unsorted activity of many single units, and the band-pass filtered field potential signal at frequencies greater than 100 Hz (thought to reflect the spiking of many single units) are both confusingly referred to as multiunit activity (MUA). In our previous work (Bansal et al., 2012a) and here we refer to the high-frequency band-pass filtered signal as MUA, and “unsorted spikes” are referred to explicitly. Lower frequency bands (<100 Hz) of the field potential (FP) are called local field potentials (LFPs) when recorded using microwires, as their activity is thought to reflect the averaged synaptic inputs (and outputs) in a local brain region. Low-frequency LFPs (<2 Hz; *lf*-LFPs) including the movement-event-related potential, MUAs, and SUAs have all been demonstrated to contain information about movement kinematics. The middle-frequency bands such as the alpha (8–12 Hz) and beta (12–30 Hz) bands have relatively weaker kinematic representation (Zhuang et al., 2010) but contain go/no-go state information (Hwang and Andersen, 2009). EEG and electrocorticography (ECoG) also measure FP signals (using electrodes placed, respectively, on the surface of the scalp or brain), but on a relatively coarser spatial scale than those measured using intracortical microelectrodes (Waldert et al., 2009). EEG and ECoG also contain information related to reaching and grasping movements (Wolpaw and McFarland, 2004; Schalk et al., 2007; Kubánek et al., 2009; Bradberry et al., 2010; Pistohl et al., 2011; Milekovic et al., 2012).

If SUA in motor cortex corresponds to the output that ultimately drives muscles and generates movement, then it would seem to be the most informative signal for acquiring movement intentions for a prosthetic device. Despite this intuition, initial results suggested that *lf*-LFPs or MUAs are more informative than SUAs (Mehringer et al., 2003; Stark and Abeles, 2007) in regimes with a handful of simultaneously recorded neurons and average-selection-based decoding algo-

rhythms. More recent work, however, with 96-channel multielectrode arrays and computationally intensive greedy-selection algorithms, has suggested that SUAs contain more information than MUAs and *lf*-LFPs (Bansal et al., 2012a) for 3-D reach and grasp in both MI and PMv. Following similar reasoning, human clinical trials have mostly used SUA for motor prostheses (Hochberg et al., 2006; Hochberg et al., 2012; Collinger et al., 2012) although a recent study has used ECoG (Wang et al., 2013). The FP signals may provide other advantages such as stability, invasiveness trade-offs, and simpler signal processing. We briefly review some of the trade-offs next.

Speed and Accuracy Santhanam et al. (2006) used an information theoretic measure to quantify the rate of end-point information extracted from SUA in monkey PMd. They reported obtaining up to 6.5 bits per second of information, allowing for 3.5 brain-controlled trials per second. Although not a direct comparison, this rate appears to be superior to information extracted from EEG, ECoG, and magnetoencephalography (<1 bit), and LFP (<2 bits) based methods (Waldert et al., 2009). The superior performance of SUA is probably related to the lower spatial correlation in that signal compared to the FP based signals (Bansal et al., 2012a). In the average case, however, *lf*-LFPs can outperform SUA (Mehring et al., 2003; Bansal et al., 2011). Furthermore, ECoG and EEG may contain more information than previously thought as recent studies have successfully reconstructed 3-D reach parameters offline (see table 17.1) from ECoG (Chao et al., 2010) and EEG (Bradberry et al., 2010). However, recent work directly comparing ECoG with intracortical spikes and LFPs has reported much worse performance with epidural ECoG compared to spikes or LFPs (Flint et al., 2012). Further work is needed to test the precision of online, closed-loop 3-D control that can be achieved using these techniques.

Ease of Control A distinct advantage of SUA based prostheses is the relative ease of control. Subjects imagine moving their arm, and the corresponding signals are directly interpreted to control a robotic arm (Hochberg et al., 2006; Hochberg et al., 2012; Collinger et al., 2012). On the other end of the recording spectrum, EEG based methods typically rely on the subject's performing a mental exercise that is not directly related to the desired action. For example, an EEG based 2-D cursor control prosthesis was designed based on biofeedback (Wolpaw & McFarland, 2004). Subjects controlled the two dimensions by modulating the power of mu

Table 17.1

Comparison of continuous reach (and grasp) offline decoding performance across three recording techniques in monkeys

Technique	Mean decoding performance (r)
Intracortical microelectrode arrays (Bansal et al., 2012a: spikes + LFPs)	0.76 (3-D endpoint position, velocity, and grasp aperture)
Electrocorticography (Chao et al., 2010)	0.72 (3-D endpoint position)
Scalp EEG (Bradberry et al., 2010)	0.35 (endpoint y and z velocity)

Decoding performance reports the mean Pearson's correlation coefficient (r) between original and reconstructed kinematic parameters obtained from several studies. EEG, electroencephalography; LFP, local field potential.

(alpha) and beta rhythms. The subjects took several days to learn basic cursor control because of the indirect controlling methods. In contrast, within-session control of cursors and robotic arms was achieved using SUAs (Hochberg et al., 2006; Hochberg et al., 2012). Unassisted 2-D and 3-D control within a few days has recently been achieved with ECoG in a paraplegic subject (Wang et al., 2013). LFPs have been used to control a switch by a paralyzed subject, but higher-dimensional control remains unexplored (Kennedy et al., 2004).

Invasiveness Despite the above-mentioned limitations, scalp EEG has the unique advantage that it requires neither invasive surgery nor the subsequent placement of electrodes that penetrate cortex. ECoG requires a craniotomy, and electrodes are placed epidurally or subdurally. SUA (and LFP) recordings are most informative and provide ease of control but require both a craniotomy and the placement of penetrating electrodes, although anecdotal evidence suggests that depth electrodes in epilepsy patients are tolerated more readily than subdural electrodes. The size of the craniotomy, however, may be reduced to a small burr hole (slightly larger than the 4×4 mm 96-microelectrode array, which is roughly the size of one ECoG electrode) that is targeted over the electrode placement location. The relative trade-offs of these approaches in terms of pain and long-term infection rates remain to be quantified.

Signal Stability (Unit Yield) and Tuning Stability A significant issue with SUA based prostheses is the number of neurons from which the electrode array can measure signals. As mentioned earlier, the power of using SUAs lies in the several independent degrees of freedom that many neurons recorded across multiple electrodes encode, compared to a relatively correlated signal measured by the FP channels. Nevertheless, if the recording quality deteriorates over time (such as because of drastic impedance changes), and the number of neurons falls, then the prosthesis designer may consider alternative approaches such as using LFP bands as supplemental signals and/or inserting multiple arrays in one or more cortical areas for redundancy (Bansal et al., 2012a). The BrainGate and Pittsburgh clinical trials have used the Utah array (manufactured by Bionics, Cyberkinetics, and Blackrock Microsystems over the past decade), which is a $\sim 4 \times 4$ mm microelectrode array with 96 recording channels that floats over the brain and can record from approximately 100 neurons in motor areas. The numbers of recorded units trends upward in the first 100 days (Collinger et al., 2012), and the electrodes can record SUA for over 3–5 years (Simeral et al., 2011; Hochberg et al., 2012) despite possible initial vascular damage, bleeding, and inflammatory response. Spike shape stays stable during a session (~ 1 hour), but the underlying population changes slightly over time (Suner et al., 2005). In addition, spike-tuning properties can stay stable over at least a two-day period (Chestek et al., 2007). The amplitudes of recorded units may trend downward over time, but this trend is uncorrelated with decoding performance (Chestek et al., 2011). The number of recorded units may eventually decrease over time as the signal degrades over the lifetime of the electrodes (Schwartz et al., 2006). In addition, the Utah array incorporates a fixed-length electrode design that does not

allow for moving the electrodes toward neurons with potentially more information (Andersen et al., 2004). Current work has also tried to ascertain the best layer to target to extract the most information and found greater information in superficial layers within 0.5 mm of the cortical surface compared to deeper layers >1.0 mm (Markowitz et al., 2011).

Reach and grasp information may also be obtained from unsorted spiking activity. Unsorted spikes based decoders may confer greater stability and the advantage of simpler (and less energy demanding) computation compared to a prosthesis system that requires online spike sorting (Ventura, 2008; Chestek et al., 2011). Finally, ECoG based approaches have reported both significant signal and tuning stability over days (visual system in human epilepsy patients: Bansal et al., 2012b) and months (motor system in monkeys: Chao et al., 2010). On account of their potentially greater tuning stability, ECoG based prostheses may require less calibration on a daily basis compared to SUA based prostheses.

Owing to the invasiveness of both SUA and ECoG based prostheses, they would need to last several years while recording useful signals, with minimal risk of infection, and minimal technician support (for recalibration of filters etc.) to make them appealing for a greater number of paralyzed patients. The exact cost-benefit calculation may have to be performed on a case-by-case basis depending on each patient's residual motor abilities.

Decoding Algorithm Design

Successful applications of BMIs have adopted a three-step decoding process (Velliste et al., 2008; Hochberg et al., 2012; Collinger et al., 2012). In step 1, an initial model is trained using movements that are imagined or observed by the subject. In step 2, this initial model is used to guide an effector, but the actual movements are corrected toward a most direct path toward the target. The data during this step are used to refine the initial model. In step 3, the effector is allowed to completely run in brain-control mode with no assistance from the technician or knowledge of target in the algorithm.

A recent study has improved the decoding performance and doubled the speed with which monkeys acquire targets using real-time brain control (Gilja et al., 2012). The novelty of this approach was the use of brain-control data to fit the Kalman filter model, combined with including position and velocity in the same model (the latter has demonstrated improvement in Brain-Gate trials; see Kim et al., 2008). The use of brain-control data in filter training supports an optimal feedback controller view of motor and premotor cortex. Instead of building a static filter using data from previous trials with imagined movements, in this approach the patient's brain is assumed to generate neuronal firing that directs the cursor toward the target at each step along the trajectory, thus incorporating a continuous visual signal about the current cursor position and effectively minimizing an error between cursor and target location (see figure 17.3, plate 17). This process may be qualitatively similar to how a nonparalyzed brain might incorporate visual information and continuously adjust the motor commands that direct muscles toward targets. Once the cursor reaches the target, the neuronal activity is set to correspond to zero velocity,

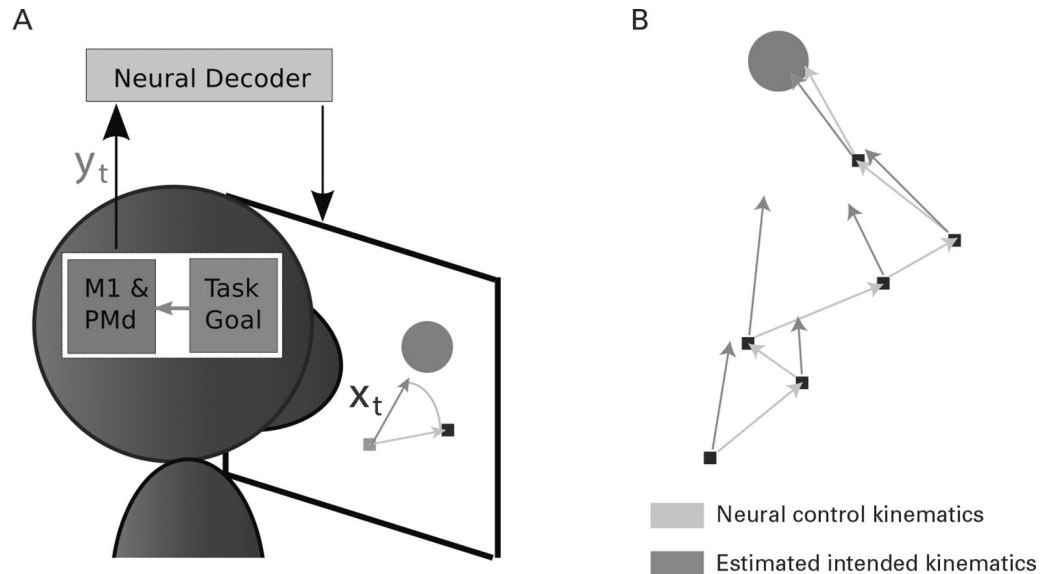


Figure 17.3 (plate 17)

Generating an “intention-based” kinematic training set. (A) The user is engaged in online control with a neural cursor. During each moment in the session, the neural decoder drives the cursor with a velocity shown as a red vector. Gilja et al. assumed that the monkey intended the cursor to generate a velocity towards the target in that moment, so following data collection the researchers rotate this vector to generate an estimate of intended velocity, shown as a blue vector. Note that this blue vector was not rendered on the screen as part of the experiment but is drawn there just to aid in explanation. This new set of kinematics is the training set used to train the control algorithm. M1, primary motor cortex; PMd, dorsal premotor cortex. (B) An example of this transformation applied to successive cursor updates. Figure reproduced and legend modified from Gilja et al. (2012) with permission from *Nature Neuroscience*.

mimicking target hold periods, and providing for a training signal that during brain-control trials achieves controlled movements that are similarly able to acquire and hold targets without overshooting them. The improvement due to the combined use of position and velocity information speaks to the postural or position effects on motor cortex neuronal tuning (Ajemian et al., 2008).

Future Direction

The vision of motor prostheses is one toward an electrode array that encapsulates recording, amplification, analog-to-digital conversion, power supply, and wireless transmission in a compact, implantable unit that runs at body temperature (Donoghue, 2008; Gilja et al., 2010). A separate, cell-phone-sized computer worn by the subject may then process the wirelessly transmitted signals to guide an effector such as a robotic arm or the subject’s muscles via a functional electrical stimulation system. Together, these systems will aim to provide an *unterminated, free-running* prosthesis that will confer to a quadriplegic user paraplegic levels of function and, thus, independence from technicians or nurses. Wireless interfaces will minimize the

risk of infection that may be carried into the brain via cables that are usually connected in wired systems to the intracortical electrode array. Algorithms such as those described above are working toward requiring minimal calibration (Gilja et al., 2012). To facilitate a free-running prosthesis, a critical addition to current algorithm designs that focus on the kinematics of movements will be the ability to decode the LFP or spiking signals related to when the subject wants to move (Hwang & Andersen, 2009; Fried et al., 2011). Although single units may provide the most information related to continuous, complex movements (Bansal et al., 2012a), FP based approaches such as EEG may provide less *invasive* prostheses for subjects with less severe impairments. The exact relationship between level of impairment or injury and the invasiveness of prosthesis or signal selection remains to be established. In addition, prostheses that use SUA, LFPs, and FPs from ECoG or EEG, and from multiple cortical regions, may provide more robust, fault-tolerant performance (Bansal et al., 2012a). Another useful addition to current designs could be the extraction of a reward or error signal related to how well the subject's intention is being interpreted by the decoding algorithm. When this error signal exceeds some threshold, the prosthesis would then try to recalibrate itself. This signal may provide a solution to the problem of when to *recalibrate* the decoding algorithm versus allowing the patient to adapt to a stable but imperfect algorithm.

Perhaps, the immediate next set of improvements in prostheses may arrive in the form of the decoding of *force* information from neuronal ensembles, and some form of proprioceptive *feedback* conveyed back to the patient. In parallel, prosthesis designers may explore more *abstract approaches* where the patient's neurons provide higher order goal information such as "Turn on the light" instead of just the intermediate kinematic information of controlling an arm. *Decoding algorithms* that incorporate dimensionality reduction approaches and spiking history of ensemble neurons may improve the encoding and decoding models. More generally, improvements can be expected in the *number of simultaneous neurons* an electrode array records from. Although early studies suggested that thousands of neurons might be necessary to decode movements accurately, recent clinical studies have obtained impressive performance with tens of neurons to a few hundred neurons (Hochberg et al., 2012; Collinger et al., 2012). In laboratory studies with monkeys, decoding performance of complex 3-D reach and grasp movements saturates with the best 30 neurons (Vargas-Irwin et al., 2010; Bansal et al., 2012a). Still, just as reliably recording from ~100 neurons compared to ~10 neurons changed the conclusions about the best signal for decoding reach and grasp from LFP and MUA to SUA (Bansal et al., 2012a), recording from thousands of neurons may bring an improved understanding of collective neuronal dynamics (Truccolo et al., 2010) and new, unexpected insights (Stevenson & Kording, 2011).

Further out in the future, one might expect advances in *synthetic biology* to produce something akin to the science-fiction vision of swallowable pills that grow into electrodes, reach the right location in the brain, and are powered by the brain's glucose. These would alleviate the need for invasive surgical procedures to implant the electrode arrays and the engineering challenges of delivering power to an implanted, wireless, and power-hungry device. Without these challenges, one can also foresee BMIs becoming more commonplace for healthy individuals in an

augmenting role, which could stretch beyond motor function to enhanced sensory, mnemonic, and cognitive functions (Donoghue, 2002; Serruya & Kahana, 2008).

Notes

1. It might be argued that for an effective motor prosthesis, achieving the patient's desired end goal might be good enough, and the details of kinematics and dynamics of the movement do not matter. Nevertheless, knowing the full kinematics and dynamics could avoid the complexity of inferring joint kinematics from end goal and also help provide control signals for a functional electrical stimulation system that might one day restore movement by activating a paralyzed patient's muscles (Peckham & Knutson, 2005; Moritz et al., 2008; Chadwick et al., 2011; Ethier et al., 2012).
2. Neurotrophic electrodes are filled with neurites or growth factors that facilitate the growth of neuronal processes into them.
3. One of these patients had suffered a spinal cord injury, and another patient had suffered a pontine stroke.
4. See <http://www.cbsnews.com/video/watch/?id=50137987n> for a video clip demonstrating the results related to Collinger et al. (2012) and an illustration of this issue (at around 11 min, 30 s).
5. The separate technical issue of signal stability will be discussed in a later section.

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