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# The Functional Reanimation of Paralyzed Limbs

## Biomimetic Strategies

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The functional reanimation of paralyzed limbs has been a longstanding goal of neural prosthetic research, but clinically successful applications have been elusive. Natural voluntary limb movement requires four major elements: actuators (i.e., motor units), sensors (i.e., somatosensory afferents), commands (i.e., cerebral cortical activity), and control (i.e., integration of the previous three elements at various levels of the neuraxis). Prosthetic equivalents of each of these elements are, as yet, primitive and often cumbersome to deploy, but new technologies promise substantial improvements for all. This article focuses on one such technology, bionic neuon (BION) modular microimplants, and its relationship to alternative and complementary technologies. The challenge remains to select and integrate them into systems that can be tailored efficiently to the widely disparate needs of patients with various patterns of weakness and paralysis.

### Current Status of Functional Electrical Stimulation

The electrical stimulation of neuromuscular systems has been employed clinically since the discovery of electric fish. The seemingly magical powers of electricity inspired many quack treatments and cures for sensorimotor disorders ranging from arthritis to stroke [1]. In the first half of the 20th century, well-controlled electronic technology for stimulation and recording led to the elucidation of electrical signaling in the nervous system. Because of their relative accessibility, peripheral motor control and sensory transduction led the way. Thus, it was natural in the second half of the 20th century to begin to apply the methodology and physiology to a more reasoned approach to electrical treatment of motor dysfunction. Most of these treatments fall into the categories of therapeutic or neuromodulatory stimulation, neither of which requires interactive control. For example, electrical stimulation to strengthen a muscle that has undergone disuse atrophy usually consists of a simple, repetitive exercise program [2]. Electrical stimulation to inhibit bladder spasticity performs a modulatory function similar to spinal cord stimulation to block pain [3].

Functional electrical stimulation (FES) connotes the production of voluntarily controlled movement that is immediately useful to the patient. Even the simplest applications (e.g., prevention of foot drop during walking in stroke patients) require a sensor to trigger the stimulation according to the ongoing behavior of the patient [4]. More ambitious applications, such as assisted grasp in quadriplegic patients, require proportional controls, such as voluntary movement of the contralateral shoulder [5]. A few centers have provided such prostheses to a few hundred patients in these two categories [6], [7], but commercial success and widespread availability remain elusive.

The holy grail in FES has long been making paraplegics walk. The past 40 years of research into this clinical problem have succeeded mostly in revealing how difficult a task bipedal locomotion is and how little we understand about how it is accomplished by intact individuals. Laboratory demonstrations have employed FES equipment that is cumbersome to don and operate and that is safe to operate only under highly controlled conditions [8]. Ironically, efforts to provide mobility and access through community infrastructure and architectural design (as mandated by the Americans with Disabilities Act of 1990) have been much more successful in facilitating activities of daily living. Many researchers in this field have retreated to the goal of providing simple standing to allow wheelchair-bound patients to access high objects [9]. While useful and desirable, it remains uncertain whether conservative healthcare providers will reimburse hospitals and patients for the costs of systems with such limited capabilities. This is particularly true for the surgically implanted systems that may be necessary to reduce the donning, doffing, and calibration problems inherent in externally worn neuromuscular stimulators.

This article focuses on the requirements for FES-assisted reach and grasp in quadriplegic patients, a heterogeneous group with a wide range of needs. This set of applications seems to offer at least some trade-offs of cost, benefit, and risk that might be attractive to patients and to the healthcare system. It also provides a set of challenges to science and technology that lie at the edge of what can be accomplished in the coming decade. The manipulation of objects by robots provides precedents that have been used to inform strategies for the design and control of FES systems [10]. We argue, however, that the components, tasks, and performance of robotic systems are unsuited to the daily activities and musculoskeletal structures of humans. Our strategy is to understand as much as possible about the natural biological system in order to design, select, and train biomimetic FES systems that will interface gracefully with disabled patients.


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## Distributed Wireless Interfaces

The biological limb obviously consists of many sensors and actuators distributed throughout the mechanically complex musculoskeletal apparatus. Much has been made of the apparent redundancy of this system [11], which seems to require the central nervous system (CNS) to perform complex computations to optimize the extraction of state information from these sensors and to compute the optimal distribution of drive to the actuators. In fact, redundancy can only be determined in the context of a particular motor task. Given a sufficiently simple task, almost any system can be shown to have redundant elements; conversely, given a sufficiently complex task, it can be shown that virtually any reduction in the number or diversity of elements could reduce performance [12].

The set of tasks that patients may desire to perform is essentially open ended. Thus, the clinician will need an armamentarium of interfaces that can be deployed widely in the patient and augmented in the future. This has led us to focus on injectable, wireless modules that obtain power from and exchange data with an external controller; see Figure 1(a) and [13] These BIONs mimic the modular and distributed nature of the peripheral neuromuscular system. They can be configured in the patient to deal with the diverse patterns of complete and partial paralysis, denervation atrophy, spasticity, and sensory loss that tend to occur within misleadingly simple diagnostic categories such as stroke and spinal cord injury.

### *Where to Access the Actuators?*

Activation of muscle is the sine qua non of FES, so it is not surprising that most of the technology development to date has focused on the interface with the actuators. Muscle fibers themselves are electrically excitable but require massive currents and long pulses [14]. Muscles are subdivided typically into ~50–500 motor units, each of which consists of one motoneuron plus a few hundred muscle fibers that it innervates (see [15] for a review of muscle physiology relevant to this topic). The cell bodies of the motoneurons are located in the ventral horn of the spinal cord (or brain stem), and their axons course through various peripheral plexi and nerves until they enter the target muscle, usually as a single muscle nerve, and then branch to innervate their target muscle fibers (Figure 1). The motor unit organization is largely preserved in patients with spinal cord injuries and strokes (but not in primary degenerative disorders of motoneurons, such as amyotrophic lateral sclerosis, or in peripheral nerve and plexus lesions).

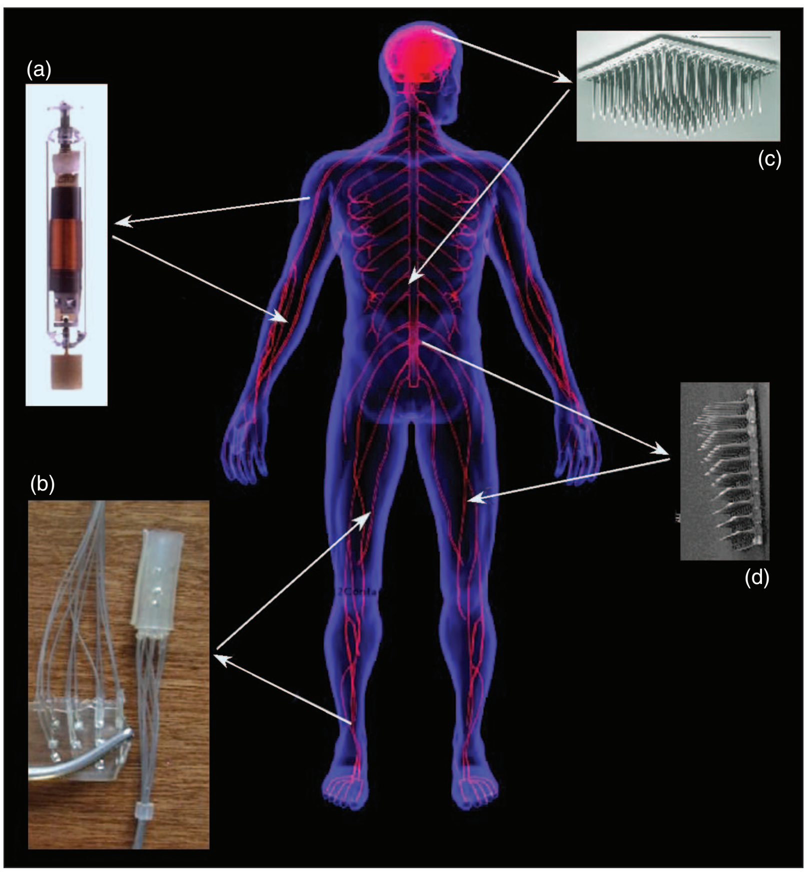



**Fig. 1.** Bidirectional neural interfaces for FES systems: (a) BION wireless modules can be injected into muscles to stimulate motor units and record EMG for myoelectric control; (b) multicontact nerve cuff electrodes can stimulate individual fascicles of nerve trunks and record multiunit afferent activity from peripheral nerves (photo courtesy of Warren Grill, Duke University); (c) Utah microelectrode arrays can record command information from motor cortex and stimulate spinal circuits; and (d) Utah slant arrays can record single unit activity from somatosensory afferents in nerve trunks and dorsal root ganglia and stimulate motor axons in nerve trunks.

The goal of the actuator interface is to provide discrete, repeatable, and finely graded excitation of multiple subsets of motor units that can then be combined variously to achieve the safe, effective, and efficient production of motor tasks. Efficiency can be thought of in two ways: the energetic cost of using a particular combination of motor units to perform a task and the systems cost to build, deploy, and maintain the interface itself. Various sites can be compared from this perspective:

- *Spinal cord*: The cell bodies of the motoneurons supplying an individual muscle tend to lie in a narrow motor nucleus. The motor nuclei for quite different muscles tend to lie adjacent to each other, however, making it difficult to recruit them selectively, even with microstimulation via penetrating microelectrodes [Figure 1(c)]. Instead, such microstimulation has been used to excite the interneuronal circuits that tend to recruit combinations of motor units that have been called *movement primitives* [16]. Unfortunately, the activation of partially overlapping sets of various types of interneurons and sensory axons results in primitives whose combinations are nonlinear and even unstable [17], [42]. These disadvantages may outweigh the obvious attraction of being able to control all of the muscles to arms or legs bilaterally from a single surgical site.
- *Mixed peripheral nerves*: The motor axons to a single muscle tend to be grouped into fascicles even within large peripheral nerves that provide sensory and motor innervation to several muscles and skin regions. This makes them attractive targets for surgically implanted interfaces if they

can achieve selective and stable recruitment of each of the muscles. Nerve cuff electrodes with multiple, circumferential contacts have demonstrated selectivity in experimental animals [Figure 1(b)], but care must be taken to avoid nerve damage from compression or torsion from their attached leads [18]. Motor axons are relatively homogeneous in size and electrical threshold, therefore, small changes in pulse parameters or the position of the cuff on the nerve can cause large changes in recruitment [19]. Alternatively, arrays of penetrating microelectrodes can be used to target small populations of motor axons that can then be combined as needed; see Figure 1(d) and [20]. It remains to be determined whether such invasive arrays and their large numbers of leads can be deployed safely and reliably in the moving limbs of patients.

➤ *Muscles:* Macroelectrodes deployed in the muscle tend to recruit motor units based on the proximity of their nearest axonal branch to the stimulating electrode rather than their size [19]. When located near the nerve entry zone, they generally produce stable and gradual recruitment of any desired fraction of a single muscle [21], but this depends on details of neuromuscular architecture that vary from site to site. Intramuscular electrodes with leads that must be routed surgically to a central controller are tedious to implant in large numbers of widespread muscles and are difficult to repair or augment with new channels. Wireless modules such as BIONs [Figure 1(a)] can be injected as an outpatient procedure, but they are more complex to engineer and pose challenges to implant correctly via injection without surgical exposure.

### *Which Sensing Modalities Are Required?*

It is instructive to note that the natural neuromuscular control system devotes most of its peripheral information carrying capacity to proprioceptive signals from the muscles rather than motor commands to them. The roles and circuitry related to these sensors are fairly well-known from animal experiments and clinical pathology, but relatively little development has gone into their prosthetic replacement. The importance of both proprioceptive and cutaneous feedback for manipulating objects (e.g., pressure, slip detection, finger position) is also well known from both human psychophysics and robotics [22]. Unfortunately, mechanical transducers are even more difficult than stimulating electrodes to build and deploy in large numbers on or in moving body parts. Nevertheless, several modalities would appear to be both useful and feasible (Figure 2).

➤ *Magnetic goniometer:* A Hall-effect sensor can detect the relative motion of a nearby permanent magnet anchored to bone on the opposite side of a joint [23].

➤ *Artificial muscle spindle:* Joint movement is normally sensed by its effect on the stretch of spindle receptors in muscles crossing the joint. If the muscles already contain electronic microstimulators that can transmit and receive signals, then these can be used as sensors of relative motion between such modules. A brief pulse of current from stimulating electrodes in one module produces widespread potential gradients because of anisotropic volume conduction through the body tissues; these can be detected by electromyographical (EMG) detection circuitry connected to the electrodes of another module, depending on distance and orientation (Figure 2). It may also be possible for implants to emit and detect brief radio frequency magnetic pulses, which will propagate more uniformly through body tissues and air [24].

➤ *DC accelerometers:* Natural limbs do not have sensors for acceleration or gravity, but motor control must take these effects into account. Normally, this is done by reflecting the information from the gravity and acceleration sensors of the vestibular organs in the head out to the limb segments based on an internal representation of body posture derived largely from muscle spindles. Prosthetic FES systems generally will not have access to vestibular information or head and trunk posture. Microelectromechanical systems (MEMS) technology makes it possible to incorporate accelerometers into injectable, hermetically sealed packages such as BIONs [25], [38].

➤ *Magnetic reference frame:* Quadriplegic patients will generally be using their FES systems for reach and grasp while they are seated in a battery-powered wheelchair. The wheelchair then provides a convenient frame on which to affix orthogonal transmitting coils to create a local reference frame for magnetic position sensors. Each BION module contains an axially oriented inductive coil that normally receives power and data from an external coil-driver (e.g., worn in the sleeve of a jacket to power implants in the arm and hand muscles). By briefly activating each reference frame coil while the power coil-driver is turned off, it is possible to obtain data from each BION implant that is related to its position and orientation in the reference frame. The relationship is complex, but it should benefit from optimal signal processing methods to combine signals from

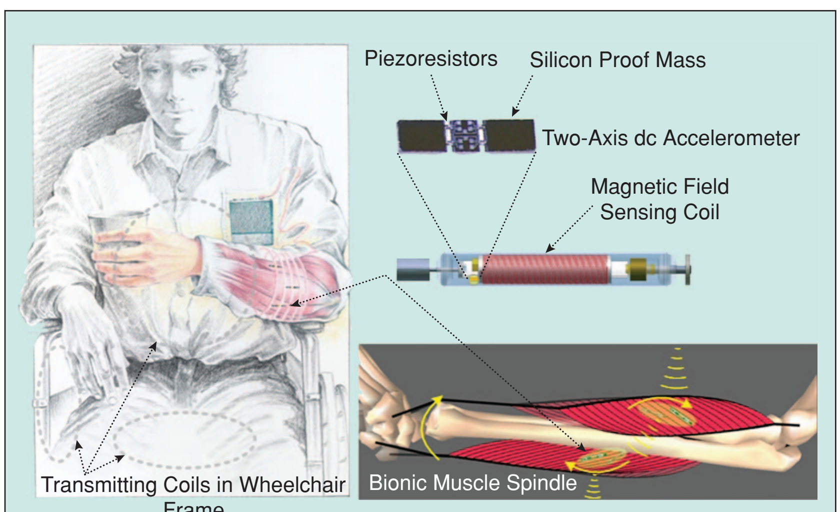



**Fig. 2.** BION2 prosthetic sensors for posture and movement (from top): a two-axis MEMS accelerometer small enough to incorporate into the injectable capsule and able to sense gravitational pull (±2g, .01g resolution, DC-50 Hz); a magnetic field sensor driven sequentially by orthogonal RF coils mounted in the wheelchair frame; and a BIONic muscle spindle based on measuring the amplitude of the stimulus artifact as propagated through the anisotropic, volume conductive tissues of the limb (37), (38).

**Functional reanimation of paralyzed limbs has been a longstanding goal of neural prosthetic research.**

multiple implants to estimate posture and movement of limb segments [26]. It will be important to include redundant information from other prosthetic sensor technologies in order to detect and compensate for distortions to the magnetic fields caused by large metal objects that may come between magnetic emitters and sensors.

➤ *Neurograms:* The biological receptors are still functional in most patients, so it is attractive to record their activity instead of having to build artificial sensors. Nerve cuff electrodes have been used to record the multiunit activity of small peripheral nerves [Figure 1(b)]. The signals are small (typically 5–20 $\mu$V at 1–10 kHz), but they can be useful if the nerve contains a fairly homogeneous population of large caliber afferents that tend to be activated together, such as light touch receptors from adjacent fingers or spindle afferents from synergistic muscles [4]. Alternatively, arrays of penetrating microelectrodes can record discriminable single units from peripheral nerves or dorsal root ganglia [typically, 20–200 $\mu$V; Figure 1(d)], but large numbers will generally be needed to assure a reasonable sampling of the desired information [27], [20].

Prosthetic sensors are likely to suffer from many sources of noise and drift not unlike biological sensors. It will be important to implement diverse and partially redundant sets of sensors and to develop biomimetic strategies such as neural networks and Kalman filtering [26] in order to obtain robust estimates of state variables under a variety of conditions of use.

## Sources of Command Signals

The FES system must respond to the moment-to-moment needs of patients without unduly distracting their attention. In general, the patients who have the most severe loss of voluntary motor function (e.g., high-level quadriplegics) will need to control FES systems with the most degrees of freedom. A similar paradox occurs in prosthetic electromechanical limbs. Several sources of command information are listed here in ascending order of sophistication.

➤ *Intentional voluntary command signals*: The simplest approach is for the patient to use residual voluntary actions such as voice or movement of body parts to operate one or more switches, potentiometers, or joysticks, as might be done in any consumer electronic appliance. These voluntary commands require the patient's attention and might trigger a preprogrammed FES control or provide a continuous signal for moment-to-moment control of electrical stimulation levels. The Freehand system for assisted grasp used a two-axis joystick taped to the chest and operated by residual shoulder motion in the contralateral arm [5]. Paraplegic patients have used hand-controlled switches to trigger the FES of their paralyzed legs at appropriate moments during a rowing exercise [40].

➤ *Intention detection from residual muscle control:* If the patient can already perform part of the task voluntarily, then it may be possible to detect that movement to control the FES component. In the FES rowing exercise, measurements of upper-body movements were used to automatically detect the patient's intention and drive the FES of the paralyzed legs [41]. FES to prevent foot drop during walking uses either a pressure switch in the heel of the shoe or the tilt angle of the shin to determine the timing of stimulation of the ankle dorsiflexion muscles [7]. It may be better to detect the movements themselves rather than the myoelectric signal from the voluntarily activated muscles. Patients with powered prosthetic limbs have difficulty producing more than two to three distinguishable EMG amplitudes from one or two vestigial muscles in the stump. Control of muscle motion should be much better because most patients have intact proprioception for muscles still under voluntary control, which greatly improves their ability to produce finely graded command movements [28]. By employing muscles involved in the task itself, the patient should be able to take advantage of reflected perceptions of contact and load from the insensate portions of the limb, much as tool users learn to infer what is happening at the end of an inert tool from sensations reflected back to the hand. External sensors worn on a paralyzed limb are physically cumbersome and mechanically vulnerable. As implantable sensors (see previous and Figure 2) become available, they should provide a more desirable alternative for command as well as feedback information.

➤ *Brain interfaces:* There has been much interest recently in extracting commands directly from electrical signals in the brain, particularly the sensorimotor and parietal regions of cerebral cortex. Sophisticated processing of simple scalp-recorded EEG signals provides low data rates that might be useful for simple triggering [29]. Highly invasive intracortical arrays of microelectrodes should provide higher data rates [Figure 1(c)], but their long-term safety and reliability remain to be demonstrated [30]. Experiments to date have focused on extracting kinematic information (e.g., end-point position and velocity) rather than solving kinetic problems such as those inherent in the control of a multiarticulated limb subject to inertia and gravity. Given the uncertainties and limitations of brain-computer interface technology, it is worth remembering that even severely paralyzed patients usually have some residual voluntary movements with intact proprioceptive feedback (e.g., head, eyes, and tongue) that may afford better control more simply.

## Hierarchical Adaptive Control

At one extreme of complexity, sensorimotor control of posture and movement emerges from the collective contributions of myriad subsystems along the neuraxis, with multiple centers in each of the spinal cord, brainstem, cerebellum, thalamus, basal ganglia, and cerebral cortex. At the other extreme, it is often treated as the simple summation of feedforward commands for movement plus reflexive sensory feedback. Before pursuing biomimetic design strategies, it would be nice to know how much of the natural structure is important to meet the limited objectives of the FES system and how much reflects irrelevant consequences of phylogenetic development. For better, and worse, the experience of designing and testing FES systems for real patients may be one of the most effective ways to answer these profound questions.

One intermediate starting point is illustrated schematically in Figure 3 [31]. It reflects the often overlooked fact that much of the descending control from the motor cortex does not project directly onto motoneurons but onto spinal interneurons [32]. Those interneurons also receive inputs from diverse sensors that are responsible for most of what is loosely described as spinal reflexes. They project broadly to many different motor nuclei and to other interneurons. This has two important consequences for the relationship between motor planning in the brain and motor execution by the musculoskeletal system.

➤ The response of a muscle to a descending command is not invariant but rather depends on the concurrent sensory feedback that biases the spinal interneurons.
➤ Descending activity that leads to the activation of muscles also specifies implicitly the gain of spinal reflexes because those reflexes depend on the biasing of the various spinal interneurons by descending excitation and inhibition.

It is important to remember also that the mechanical output of the muscles themselves does not depend only on their motoneuronal activation. Unlike the torque motors of robots, the torque produced at a joint by a muscle at a given level of activation depends strongly on posture and motion. The active tension produced by muscle fibers depends on their sarcomere length and the torque depends on the moment arm, both of which tend to change with joint angles. Active tension also depends strongly on sarcomere velocity, with substantial reductions when shortening at modest rates and abrupt increases when stretched from isometric length. These effects depend on muscle fiber type and level of activation, making them difficult to anticipate in control strategies based on inverse dynamics (computing the desired muscle activation from the intended trajectory of limb movement). They may be critical, however, allowing the musculoskeletal system to respond rapidly and gracefully to perturbations that are too rapid to be handled by sluggish reflexes [33].

Even if the FES controller is not designed to be isorepresentational with the natural sensorimotor control system, it must interface with the natural system at two points: command input and musculoskeletal output. The more the FES controller behaves like the parts of the nervous system that have been bypassed, the better the human brain may be able to make use of a large library of expectations and strategies that it developed before the neurological deficit occurred. This provides another argument for understanding and attempting to emulate at least some of the structure and function of the natural system.

## Model-Based Training Systems

Before embarking on an expensive and invasive therapeutic intervention in a given patient, it will be most useful to know the likelihood of a successful outcome. Computer simulations of musculoskeletal mechanics have been used to identify which muscles are necessary and sufficient to accomplish specific tasks in a paralyzed arm [34]. In principle, such simulations can be extended to identify the utility or necessity of particular types of sensory information or feedback circuitry in order to achieve stable performance in the face of anticipated perturbations or uncertainties of load.

The human brain is the most powerful adaptive controller known for musculoskeletal systems, but it takes an infant several years of essentially trial-and-error learning to develop even modest dexterity for reach and grasp tasks. It is a general property of neural networks that they require large numbers of iterations to converge on useful sets of weighting coefficients. FES systems are likely to have at least two neural-networklike adaptive components that require training: the prosthetic controller and the brain of the patient learning to operate the system. Both of these learn to

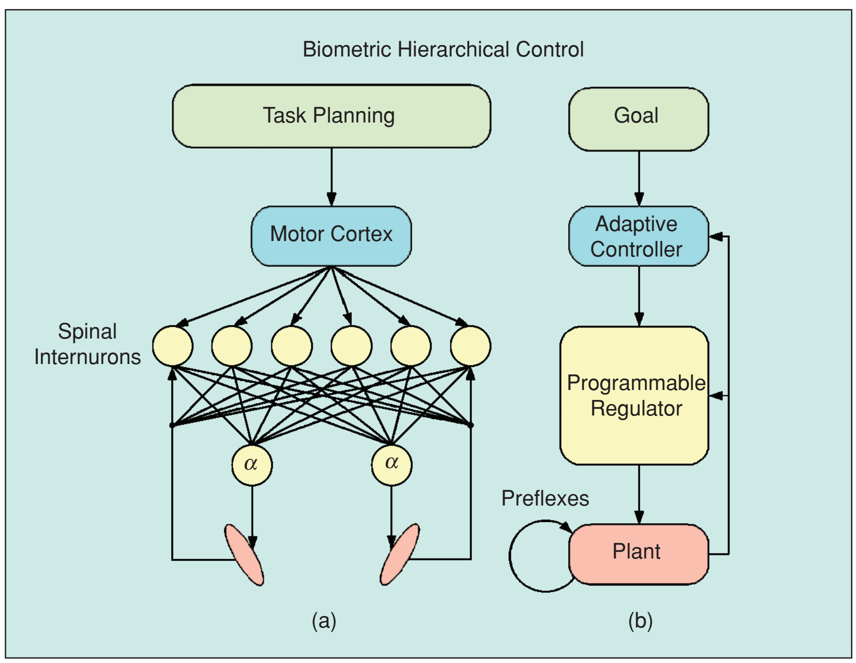



**Fig. 3.** Elements of hierarchical sensorimotor control in (a) biological and (b) neural prosthetic systems. The intended goal of the movement is formulated in cortical areas such as the parietal lobe or inferred from residual voluntary movements made by the patient. The motor cortex learns to generate output signals that cause the spinal cord and muscles to perform the movement in a robust manner. The limb copes gracefully with noise and perturbations by means of the intrinsic mechanical properties of muscle (preflexes) and the distributed interneuronal networks of the spinal cord (reflexes) (39), (31).

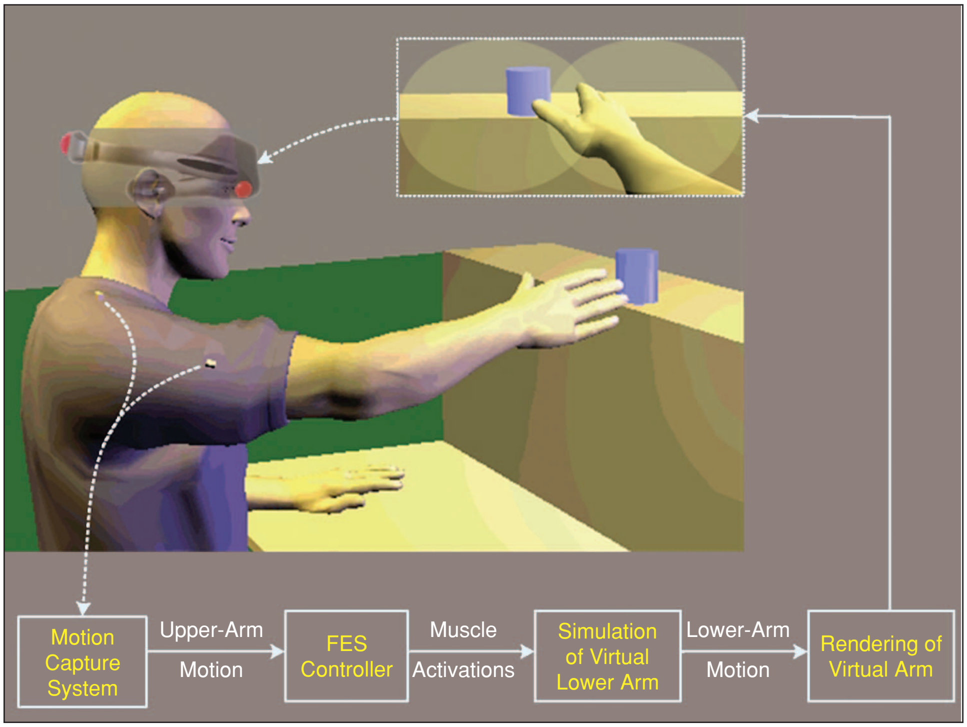



**Fig. 4.** Virtual-reality system for the design and fitting of FES based on a computer model of the musculoskeletal system and prosthetic interfaces. Command signals are extracted from the movements of the shoulder (which are largely preserved in most quadriplegic patients) and used to drive the computer model. The projected limb movement is displayed to the subject via stereovision goggles; the subject must learn to adjust his command movements to perform the virtual task correctly.

improve their performance only by comparing state information from the moving limb with the intended trajectory of state information. It will be undesirable and perhaps unsafe, however, for adult patients to repeat the extended learning period of infants. Model-based simulations of the FES-equipped arm can be run through virtually unlimited numbers of simulations in order to get their control systems to converge to acceptable performance before the FES interface is ever installed in the patient [35].

One open question is whether the adaptive properties of the FES controller should be turned off before the patient starts learning to use the system. The CNS seems to train at least some of its hierarchical systems sequentially by means of critical periods in which large-scale plasticity is first enabled and then extinguished [36], perhaps to provide a stable foundation for learning in the higher-level subsystems.

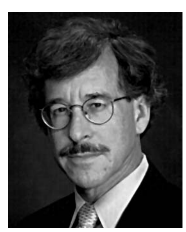
Dynamic simulations can be used to drive a virtual reality display of simulated arm movement that would allow an intact subject to experience and compare the behavior of an FES-driven limb to his/her own limb while performing a task (Figure 4). This could provide useful insights for the engineers and clinicians who must design and fit such systems for patients. It could be particularly useful for designing algorithms to extract command information from the residual voluntary movements of paralyzed patients. Note that when the simulated system is performing well (i.e., its movements match those of the intact subject), the mechanical motion and loading of the proximal muscles and joints should be similar to what would be sensed by the residual proprioception in most spinal cord-injured patients.

## Conclusions

Advanced interfaces under development for sensing and control of biological limb movement provide hope that paralyzed limbs can be functionally reanimated through neural prosthetics. Nevertheless, the control of multiarticulated limbs in unpredictable environments remains a daunting problem in robotics even with well-behaved and complete sets of sensors and actuators. Biological control systems provide an existence proof for what is possible with flesh-and-blood limbs and opportunities to identify and to imitate proven strategies. Neural prosthetics provides an opportunity to demonstrate how well we understand those strategies by restoring functional use of biological limbs in patients with profound disabilities.

## Acknowledgments

The technologies and ideas described here are the product of research supported currently by the Alfred Mann Institute, National Institutes of Health Bioengineering Research Partnership R01EB002094 and the National Science Foundation Engineering Research Center on Biomimetic MicroElectronic Systems (EEC-0310723). They reflect the work of many colleagues, collaborators, and students over many years, as cited in the references.



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Most of his current research is directed toward neural prosthetics to reanimate paralyzed muscles and limbs using a new technology that he and his collaborators developed called BIONs. This work is supported by an NIH Bioengineering Research

Partnership and is one of the testbeds in the National Science Foundation Engineering Research Center on Biomimetic MicroElectronic Systems, for which he is deputy director.

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