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MOTOR NEURAL PROSTHESES FOR RECOVERY OF THE WALKING*

MOTORNA NEURALNA PROTEZA ZA RESTITUCIJU HODANJA*

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Ključne reči
Motorna neuralna proteza, elektri?na stimulacija, upravljanje, hod, cikli?ni pokreti

Abstract

We review the concept of the ”pacemakers” for cyclic movements in humans with central nervous systems injury/disease that are based on electrical stimulation. The system that restores or augments movement is termed Motor Neural Prosthesis (MNP). Many aspects how an MNP interfaces the injured/diseased central nervous system have been resolved and several systems are commercially available; yet, there are remaining problems which require translation of knowledge from the domain of motor control. This knowledge is important since an MNP activates both afferent and efferent pathways of the peripheral nervous system; thereby activate directly motor output but also trigger reflex activities at spinal and cortical levels. This new understanding in parallel with the ability of an MNP to selectively trigger action potentials could allow inhibition that is of major importance. In summary this review advocates the use of artificial control of on MNP that mimics biological control.

INTRODUCTION

Dr. Guillaume-Benjamin-Amand Duchenne de Boulogne (1806-1875) in his research provided evidences of the importance of Galvani’s research [1] for the field of electrophysiology. His work on the facial musculature (Fig. 1) was a definite milestone for the application of electrical stimulation for sensory-motor systems of humans.

The development of technology, better understanding of interfaces that allow safe and controlled man-machine communication, and over all major improvement in the computing power provided to scientists tools to make breakthrough in the domain of assistive technologies termed Neural Prostheses (NP). Examples of efficient, widely accepted NP are heart pacemakers, implantable defibrillators, cochlear pros-

Figure 1: Electrical smile introduced by Duchenne the Boulogne.

theses, phrenic nerve pacers, etc. An incomplete set of neural prostheses that are available includes the systems for reestablishing of the movement that is lost due to the central nervous system injury or disease (Fig. 2).

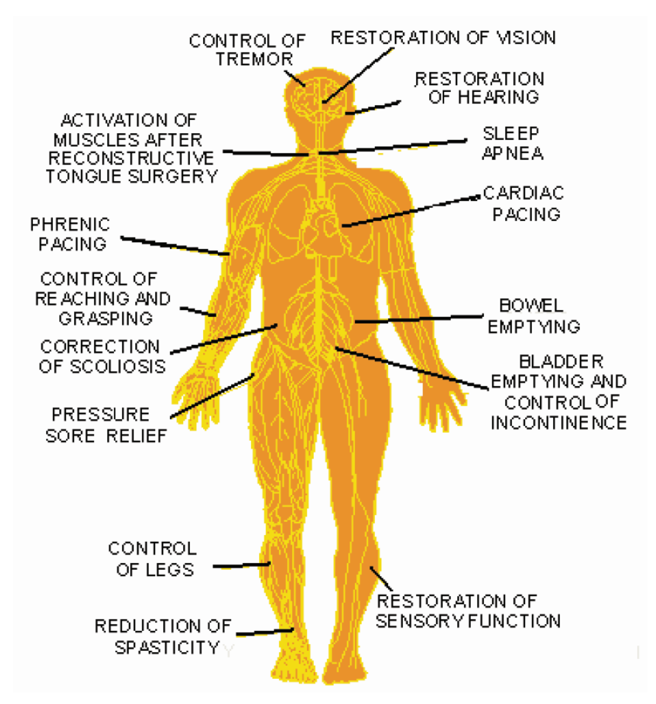

Figure 2: Neural prostheses based on functional electrical stimulation: systems for restoration and augmentation of diminished functions which follow the nervous system injuries/disease

The modern era of electrical stimulation for movement augmentation starts with the works of Liberson [2], where the simple stimulation system assisted stroke patients to overcome the drop foot while walking. The first use of electrical stimulation in upper extremities is attributed to Long and Masciarelli [3] who designed a so called electrical splint in combination with a mechanical apparatus for tetraplegic patients.

Principles of the operation of an MNP

Current methods to treat central nervous disorders are based on: (1) replacement of lost neural activity; (2) retraining of the central nervous system by repetitive practice; (3) neuromodulation, i.e., artificial restoration of the balance of activities in affected regions of the central nervous system. The development of improved assistive MNP in Belgrade starts from the concept of the integration of the three above said methods: augmentation of diminished or generation of absent function by use of electrical, magnetic, and mechanical stimulation of the neuromuscular system in parallel with the task oriented intensive voluntary exercise. This follows results from studies related to plastic changes in the human brain and spinal cord that were promoted by motor re-learning and sensory experience. A long-term reorganization of human motor cortex driven by short-term sensory nerve stimulation has been shown [4]. Such study of long-term reorganization of the motor cortex mediated by afferent stimulation has never been done on lower limb muscles and can become an exciting new method in neurorehabilitation. Recent experiments at our and other laboratories have shown that pattern nerve stimulation of specific anatomical sites results in specific sensory-motor pathways activation, which may be used to elicit functional motor responses in motor impaired patients [4].

The augmented intensive exercise by electrical stimulation that was termed Functional Electrical Therapy (FET) of the paretic arm in post-stroke patients showed significantly better recovery compared with the conventional treatment [5,6]. FET is a protocol that combined the voluntary intensive exercise, and electrical stimulation that was timed to activate several muscle groups in a pattern that mimicked the activation being characteristic of able-bodied subjects. The role of this stimulation was to provide augmentation of the muscle activation of paretic muscles, yet also the augmentation of the sensory flow towards the upper motor neuron. The basis for this assumption was the finding that chronic tetraplegic patients improved their functioning after prolonged use of a neural prosthesis [7,8]. The hypothesis was that the patterned nerve stimulation, when applied at the right site and at the right time during a movement, functionally excited the central motor patterns; thereby, contributed to re-learning and long-term reorganization of the sensory-motor systems.

When considering walking, contrary to goal oriented movement, three major requirements are: 1) production of a basic cyclic rhythm which can control extremities and the trunk against gravity, and propel it in the intended direction; 2) postural control of the moving body; and 3) adaptation of movements to meet environmental demands, tasks and preferred modalities of propulsion.

Some of the findings in animal studies are important for understanding human locomotion better. The role of proprioception and cutaneous inputs, modulation of reflexes, suprasegmental control of movements are applicable directly for studies of human mobility; thereby, we start by reviewing some animal models and findings from these experiments. Because locomotion is achieved through the repetition of a well-defined movement, the emphasis in research to date has been on identifying principles and mechanisms that govern the generation of this basic rhythm. The idea of a central pattern generator for animal locomotion is generally attributed to Brown [9] being influenced by Sherrington [10] who had developed the concept of reflexes and favored the idea of locomotion being generated by a closed chain of such reflexes. The idea of autonomous central generators for a behavior such as locomotion was not fashionable and it took about 70 years for the concept to be generally accepted. It took the work of Shik and Orlovsky [11] who rediscovered the high decerebrate preparation that Brown himself had pioneered. Electrical stimulation of a region in the midbrain, which has become known as the mesencephalic locomotor region or MLR, produces rhythmic alternation of the limbs of a cat placed over a moving treadmill belt. Because the higher centers have been removed, the cat was not able to balance itself and was suspended, but the limb movements convincingly showed most patterns of normal locomotion. Higher levels of stimulation produced trotting and even galloping patterns.

Although the midbrain controls locomotion, it is not part of the central pattern generator. This was demonstrated in spinal cats by the application of drugs such as L-Dopa and clonidine, that are thought to mimic the action of the transmitters released by descending systems [12, 13]. Thus, the pattern generators for locomotion in four-legged animals such as the cat and the rat can be localized to the spinal cord. Indeed, sectioning the spinal cord between the fore and hind limbs these drugs will produce alternation of the hindlimbs alone. Since the pattern between the two hindlimbs can vary from being out of phase, as in walking or trotting, to being in phase, as in galloping, the simplest hypothesis is that there is a central pattern generator controlling each limb and the four generators in a quadruped such as a cat are coordinated through intraspinal connections.

Proof that the circuitry wholly within the spinal cord was sufficient, as well as necessary, was obtained in experiments in which dorsal roots were cut to prevent sensory feedback (reviewed by Grillner [12]). Although the patterns are less precise, the cat can still generate walking rhythms. These experiments are not totally convincing, since it is technically difficult to remove absolutely all sensory feedback. However, in other experiments an animal was paralyzed using the neuromuscular blocking agent, curare. Then, there is no movement and hence no rhythmic feedback from sensors. Nonetheless, rhythmic bursts of activity in motoneurons can be observed when the cord is stimulated electrically from the MLR or from application of drugs. These studies provide solid evidence for the existence of a central pattern generator in experimental animals, but the form of the neural oscillator is still uncertain.

Brown proposed the idea of mutually inhibitory half-centers which has dominated thinking ever since (Fig. 3). In this concept descending inputs can excite either half center, but are probably stronger to one center. Thus, it becomes more excited that the other, and the active center inhibits the less active one more through mutually inhibitory connections, which in turn removes inhibition from the more active center. Thus, there is positive feedback around the loop of Fig. 3, since a „minus times a minus" gives a plus. Central to Brown's concept was the notion of fatigue; as the more active center fatigues, at some point it can no longer inhibit the less active center and the two switch roles and the rhythmicity continues for some period of time.

It has been technically, exceedingly difficult to prove or disprove this hypothesis in vertebrate locomotion. Grillner et al. [14] have worked out the circuitry for locomotion in a simple vertebrate, the lamprey, and this is illustrated in Fig. 4.

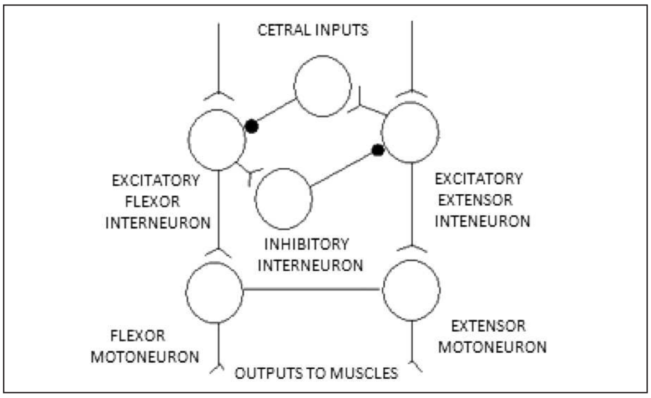

Figure 3: Half-center hypothesis that which has dominated thinking on neural oscillators for locomotion. Excitatory connections (") and inhibitory connections (Y) are shown.

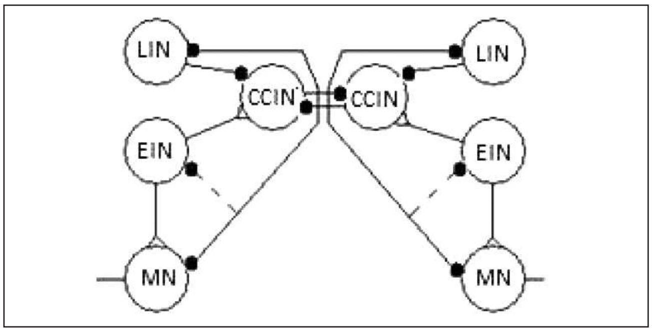

Figure 4: Neuronal circuitry for locomotion (swimming) in the lamprey. The acronyms are: EIN - excitatory) interneurons, LIN - inhibitory interneurons, MN - motoneurons, CCIN - neurons which have axons that cross over the midline. Adapted from Grillner et al., [14].

Lampreys swim rather than walk so this is the form of locomotion illustrated in the Fig. In the middle of the diagram are two mutually inhibitory neurons, as expected from the half-center hypothesis. These so-called CCIN neurons have axons that cross over the midline and appear to be involved in alternation of the two sides of the body that is required for rhythmic swimming. There are other excitatory (EIN) and inhibitory (LIN) interneurons that elaborate and reinforce the basic half-center. Grillner and colleagues have simulated the patterns using values for synaptic connections and ionic properties that they studied experimentally. The patterns in all the cell types in the simulations agree quite well with the experimental data.

They have shown that the switching between the two sides occurs by multiple mechanisms. The firing rate of the CCIN decreases because of intrinsic mechanisms that involve summation of after-potential and ionic mechanisms. These are the modern basis for what Brown called fatigue. In addition, the LIN has a high threshold and so its action is delayed. When it eventually fires it will inhibit the CCIN and help to terminate the burst. Thus, there are network properties, as well as intrinsic mechanisms involved in the switching. Finally, connections from sensory cells known as edge cells, which monitor the bending of the trunk, feed back to the segmental oscillator and also reinforce the pattern. Further points to note are: 1) even in this primitive vertebrate there are descending inputs from the brainstem that turn the locomotion on. 2) Although only the circuit for a single segment is shown, the circuit is reproduced many times and intersegmental connections are present to produce the smooth travelling wave that is necessary for swimming [15].

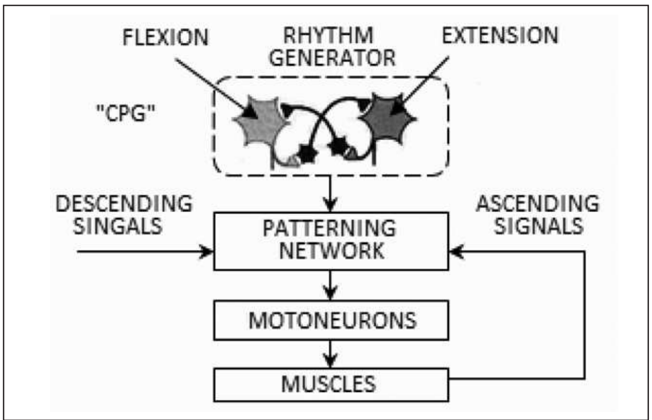

Figure 5: The model of the cyclic motor generator based on the central pattern generator (CPG).

Many of the synaptic transmitters used in the lamprey are common to higher vertebrates so there may well be common principles. However, preliminary work on the circuit for walking in an amphibian suggests that there may be important differences as well [16]. Sensory regulation may be much more important in terrestrial locomotion, since the requirements for balance are so much greater. For example, not allowing the hip to extend can prevent the swing phase of locomotion from occurring [17] as can loading at the ankle [18]. Recent work suggests that the receptors involved in the latter are the Golgi tendon organs, which, with their positive feedback during the stance phase will maintain the stance phase [19]. This trend toward the importance of sensory inputs to maintain balance during forward progression should be even more evident in bipedal animals such as humans (Fig. 5).

An important and relevant question is: Can the models and principles for control of locomotion developed from animal models be applied to humans? Although it was not proven that there is a spinal pattern generator in humans, some evidence of a half center organization in paraplegic subjects was published. [20,21].

Model of the MNP for restoration of the walking

The typical model of the effects of MNP considers that the stimulation has an effect of the muscle of interest either by direct stimulation of the motoneuron (Fig. 6A), or the reflex (Fig .6B). However, the actual effect of the MNP is the modification of the complete flow of information that is being modulated by the central nervous system (Fig. 6C). This is of special interest when the MNP is used in stroke, cerebral palsy, multiple sclerosis, incomplete spinal cord injured patients subjects and other etiologies where the spinal cord is partly conductive.

When the MNP is used to assist function (e.g., electrical stimulation of the ankle dorsiflexors being timed with the swing phase of the gait to eliminate drop foot) two effects are achieved: 1) the gait is improved, and 2) in some patients a short- or longer-lasting ”carry-over” effect can be registered [22,23]. This result can be explained by considering the following three components: 1) the MNP improves the mobility and strength of the remaining motor units to which the patient has voluntary access, 2) the voluntary efforts become more effective due to the training, and 3) the MNP might be reducing the spasticity; thereby, allow improved function. However, the most likely reason for the carry over effects comes from the changes in the suprasegmental (including cortical) mechanisms that are being reorganized.

Namely, there are imaging [24,25] and neurophysiological [26,27] evidences that cortical excitability changes after electrical stimulation. In parallel, there are similar evidences repetitive active movement of a paretic limb results with similar changes. The MNP thereby should be considered as a tool that facilitates the modified activity in the cortical areas, and possibly contributes to the cortical plasticity that leads to new motor schema and improved motor function [28-30]. This model was addressed by Rushton[31]. He suggested that most likely the burst of externally generated charge pulses activates bursts of firing of the anterior horn cell and provide the necessary signal for cortical alterations. This hypothesis follows the explanation by Hebb [32]. Hebb proposed that some modifiable synapses would be strengthened if presynaptic firing coincided with or was shortly followed by postsynaptic discharge (success breeds success). Hebb-type

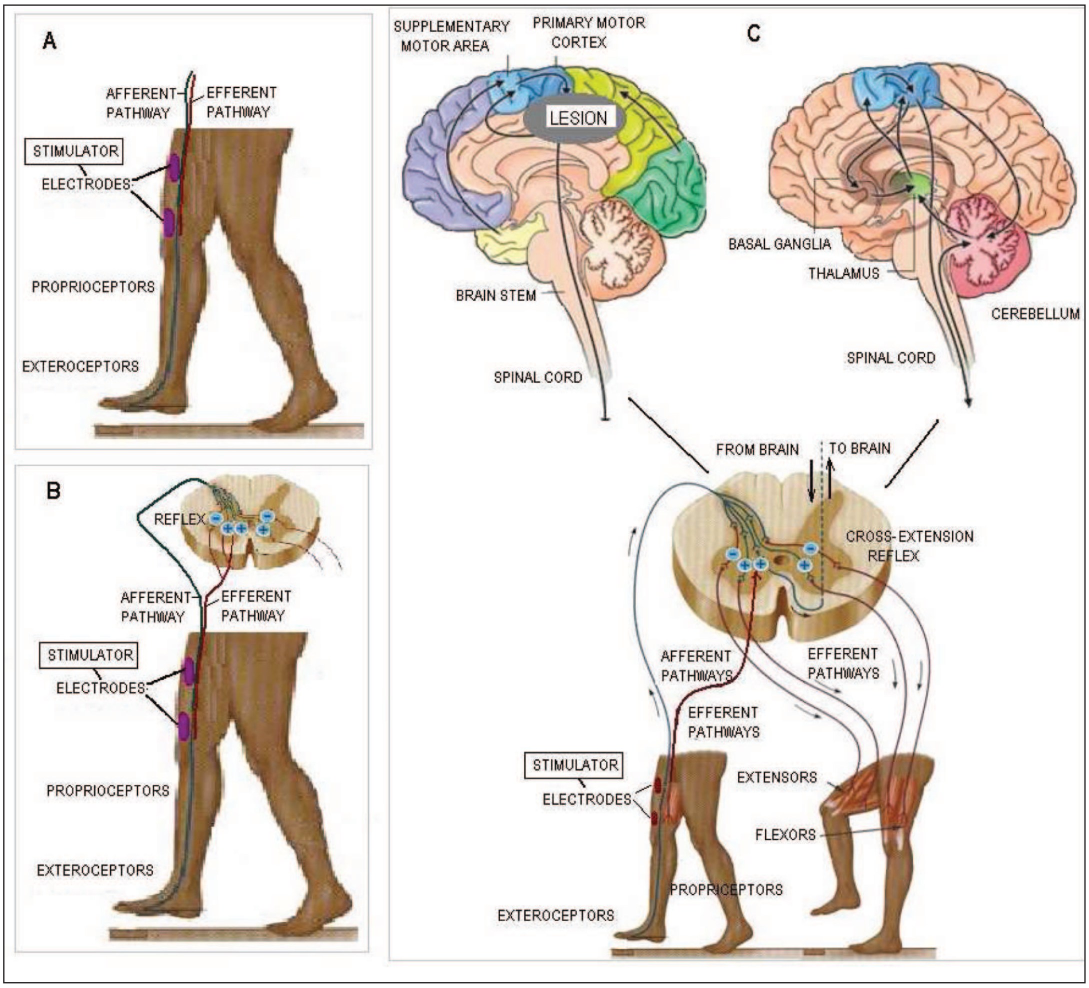

Figure 6: A) The model of the MNP activating directly the paralyzed muscle by generating action potentials at the motoneuron; B) The model of the MNP activating spinal reflex that activates the synergistic movement; C) The model of the MNP activating the neural network that includes both lower and upper motor neuron.

synapses have since been used with the particular interest in the brain, in the context of learning and memory. The underlying mechanism is thought to be what is known as Long-Term Potentiation [33,34].

The model presented in Fig. 6 directly suggests how the control of the MNP should be organized. The artificial control needs to have hybrid hierarchical structure in order to allow its integration into the preserved mechanisms of humans with disability, but also to maximize the effects of the training of the CNS in the most natural order.

Artificial control for MNP systems: cloning biological control principles

Hybrid means, in general, heterogeneous in nature or composition. The term ”hybrid systems” is describes systems with behavior defined by entities or processes of distinct characteristics. The hybrid systems of interest here are bodily systems where the behavior is determined by interacting continuous and discrete dynamics. The hybrid control systems typically arise from the interaction of discrete planning algorithms and continuous processes, and, as such, they provide the basic framework and methodology for the analysis and synthesis of autonomous and intelligent systems, i.e., planning to move the hand and grasp an object. The hybrid control systems contain two distinct types of components,

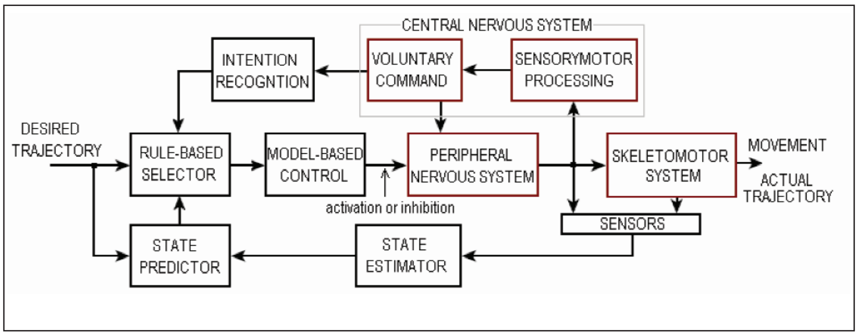

Figure 7: The model of the hybrid hierarchical controller for the MNP system. Rule-based selector that implements the temporal and spatial synergies operates as a discrete controller, while the activation and inhibition follows optimal control that is developed by using model characteristics (continuous control). State estimator transforms the continuous signals into discrete control variables which after being used in the discrete state predictor are used for the selection of the rules within the rule-base selector.

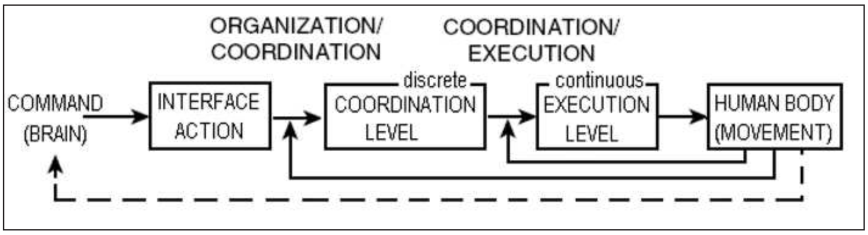

Figure 8: The model of life-like hybrid hierarchical controller for MNP

subsystems with continuous dynamics and subsystems with discrete-event dynamics that interact with each other.

Another important way in which hybrid systems arise is from the hierarchical organization of complex control systems (Fig. 7). In these systems, a hierarchical organization helps manage the complexity, and higher levels in the hierarchy require less detailed models (discrete abstractions) of the functioning of the lower levels, necessitating the interaction of discrete and continuous components.

There are analogies between certain current approaches to hybrid control and digital control system methodologies. In digital control, one could carry the control design in the continuous-time domain, then approximate or emulate the controller by way of a discrete controller and implement it using an interface consisting of a sample and a hold device (analog to digital - A/D and digital to analog -D/A, respectively). Alternatively, one could first obtain a discrete model of the plant taken together with the interface and then carry the controller design in the discrete domain. In hybrid systems, in a manner analogous to the latter case, one may obtain a discrete-event model of the plant together with the interface using automata or Petri nets.

The schema of an HHC based (Fig. 7) controller for movement incorporates three levels (Fig. 8). We selected to describe the model of walking; yet, similar models can be easily envisioned for other movements.

The entry artificial control structure is the interface between the user and the machine. This interface is the principal command channel, and it allows the user to trigger or control in a continuous manner the operation volitionally. The interface initiates the activity of a discrete, rule-base controller. This rule-base controller operates as a discrete, sample data feedback system, and its main role is to distribute the commands to the lowest actuator levels. The rule-base controller is implementing the finite-state model of movement, and the rules have to include sets that are appropriate for various types of disabilities; yet, to the limitations imposed by the complexity of the MNP system available. The actuator level deals with specific muscle groups responsible for the flexion or the extension of a single joint, or in other cases, the action of several joints when a multiarticular muscle is externally stimulated. The actuator level implements the continuous feedback control and structural modeling. This approach has been tested in several MNP applications for upper and lower extremities [35-42].

The lower, actuator control level is responsible for executing decisions from the coordination level. Executing commands in the sense of artificial reflexes means that the electrical stimulation has to be delivered to a group of muscles that are controlling a joint. Single joint control is achieved through a coordinated action of several muscles acting at the neighboring segments.

Hardware of an MNP

An MNP based on electrical stimulation generates or augments movement (reviewed in Popovi? and Sinkjær, [43]). The MNP delivers trains of electrical charge pulses, mimicking to an extent the natural flow of excitation signals generated by the CNS in healthy humans. The components of an MNP are: 1) stimulator, 2) electrodes, 2) sensors, and 4) command interface. 1) Stimulator is a device which generates bursts of electrical charge pulses that are send to nerves. The frequency of pulses must be high enough to lead to fused contraction, but low enough to minimize fatigues. The pulse duration needs to be short enough to guaranty generation of action potential, but minimize tissue and electrodes changes. The activation (positive) pulse needs to be followed by the short lasting negative pulse in order to balance the charge delivered to tissues and minimize the tissue damage and electrode corrosion. The amplitudes of pulses need to be high enough to allow excitation of the desired neural tissue, but do not spread to other systems. Typical values of these parameters are: f = 20-50 pulses per second, T = 0.15-0.4 ms, I = 10-100 mA. 2) There are many types of electrodes that are used today: surface electrodes and various types of implantable electrodes. The criteria for surface electrodes are the following: low impedance and even distribution of current, flexibility to maintain good skin contact, ease of application and removal, and suitable mounting for days without irritation of the skin. A surface electrode has three elements: the conductor, the interfacial layer, and the adhesive. Usage of conductive polymer and conductive adhesives proved to be effective for clinical and home usage. Implantable electrodes can be divided into those in which the electrode is secured to the muscle exciting the motoneurons, and those, which are contacting the nerve that contains the motoneurons. The advantages of subcutaneous electrodes vs. surface electrodes are better selectivity, repeatable excitation, and permanent positioning. The sensation to the users is much more comfortable since the electrodes are placed away from the pain receptors, and the current amplitude is much lower. 3) Sensors are needed in MNP for the command interface (e.g., activating the neural prosthesis, changing the mode of operation). The optimal sensors system will use the natural information from the biological sensors. The sensors systems of various kinds are of interest: the contact force or pressure over the area of contact (grasping, standing, and walking), the position of the joints (prehension, reaching, standing, and walking), and level of activity of the muscle. The constraints imposed on the sensors for MNP are significant; they must be cosmetically acceptable and easy to mount, they should be self-contained, have low power consumption, and must provide adequate information. In most available MNP sensors are placed externally. The sensor positioned at the surface of the body is not a suitable solution for many situations (e.g., an external-force sensor on the digits of the hand requires donning and needs a cable to communicate with the control box, and it should work in variable temperature conditions and hazardous environment). The alternative is to use implanted sensors. They have to meet the same performance specifications while functioning in a more hostile environment. These sensors should communicate with the remote control box, and the device must be powered via radio-frequency (RF) link. The ultimate solution is to use available sensor in the organism; to record from nerves and muscles and process the information in a real-time useful signal. This solution requires the ability to interface without the nerves and interpret the signals they are supplying to the central nervous system. 4) The ideal command interface would be the cortical activity that is normally employed by a healthy individual. Current research is dedicating much attention to the design of brain computer interface (electroencefalography - EEG) brain machine interface (electrocorticogram - ECoG). The practical use of this command channel is in its infancy. The command interface can use some dedicated activity (muscle activity - EMG, movement, etc.). Voice control, gaze control, nonrelated movement or muscle actions are the alternatives that provide multichannel input.

Details on the various methods that are implemented for the control of movement by means of neural prostheses of upper and lower extremities can be found in Chapter 5 of the book Control of Movement for the Physically Disabled [43].

CONCLUSIONS

The technology has spawned many different types of control system; each suited to a particular application. The biological organisms have evolved control systems to suit many of species and physiological functions. We propose the integration of these two control strategies. In rehabilitation of movements the aim is to activate joints in a controlled way so as to restore as much motor function as possible in humans with motor disabilities. The control strategies implemented in most of rehabilitation devices have so far been fairly simple, and have been developed largely in relation to the design of machines rather than to the design of nervous systems. Neuroscience data show that some of these strategies have converged, so as to be quite similar to those in living systems. The methods that we selected is the one which integrates three methods, all incorporating as the condition sine qua non the quantitative assessment before and during the rehabilitation process (Fig. 9).

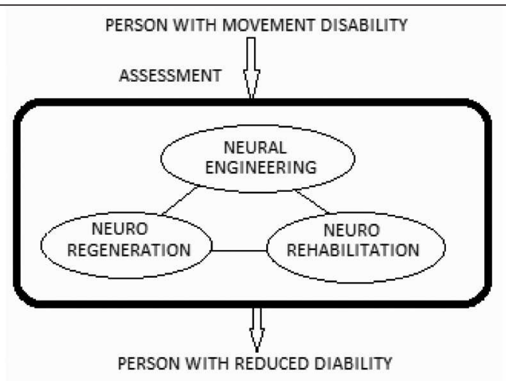

Figure 9: The model for the optimal restoration of function

Neuroregeneration of the central nervous system is a method that will eventually provide a cure. Although it is still only a perspective, it must be kept in mind as an emerging option; thus, it is very important to preserve as much as possible all resources so that they can be integrated when the time comes. Neurorehabilitation is a method that allows the preserved structures to find their best use if appropriately trained. The intensive, task dependent exercise is showing dramatic effects in handicapped humans (e.g., non-ambulating subjects can unassisted walk for some distances). The possible role of central motor programs that exist at the level of spinal cord, although controversial, is an option that deserves more attention. Neural engineering is where the ultimate successes at this stage must come. The development of new implantable devices that interface directly the central and peripheral nervous system allowing wireless communication with the outside world opens new horizons. The technology makes major impact and provide that has been difficult to imagine, yet the control that resembles to natural control is still a bottleneck for success. Assessment is instrumental to understand the functional impairment and identify the neurophysiologic changes caused by the injury/ disease. The ultimate goal is to improve the quality of life of persons with disability. We suggest that only a comprehensive work that will maximize the usage of the knowledge of motor control and integrate the technology into the natural control systems is likely to be accepted by the users.

Apstrakt

U radu je prikazan koncept „pacemakera” za ciklične pokrete osoba sa povredama/obol–jenjima centralnog nervnog sistema koji koriste električnu stimulaciju. Sistem koji uspostavlja ili poboljšava pokret se naziva Motorna Neuralna Proteza (MNP). Mnogi as–pekti komunikacije MNP sa nervnim sistemom su danas rešeni i postoji niz komercijalnih sistema, ali postoje problemi koji treba da se reše translacijom znanja iz domena motorne kontrole u MNP. Prenos ovih znanja je važan jer MNP aktivira aferentne i eferentne puteve u periferijskom nervnom sistemu, i na taj način direktne aktivacije mišića aktivira i reflek–sne mehanizme na nivou kičmene moždine i mozga. Integracija rezultata iz domena neu–ronauka i razvoj komponenti MNP koje selektivno generišu akcione potencijale bi moglo da omogući i generisanje inhibicije i time značajno unapređenje funkcionalnosti MNP. Ovaj pregledni rad ima za cilj da promoviše metode upravljanja MNP koje su u pojednos–tavljenom obliku „klon” upravljačkih mehanizama karakterističnih za živi svet.

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