REVIEW

A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems

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Abstract Considerable scientific and technological efforts have been devoted to develop neuroprostheses and hybrid bionic systems that link the human nervous system with electronic or robotic prostheses, with the main aim of restoring motor and sensory functions in disabled patients. A number of neuroprostheses use interfaces with peripheral nerves or muscles for neuromuscular stimulation and signal recording. Herein, we provide a critical overview of the peripheral interfaces available and trace their use from research to clinical application in controlling artificial and robotic prostheses. The first section reviews the different types of non-invasive and invasive electrodes, which include surface and muscular electrodes that can record EMG signals from and stimulate the underlying or implanted muscles. Extraneural electrodes, such as cuff and epineurial electrodes, provide simultaneous interface with many axons in the nerve, whereas intrafascicular, penetrating, and regenerative electrodes may contact small groups of axons within a nerve fascicle. Biological, technological, and material science issues are also reviewed relative to the problems of electrode design and tissue injury. The last section reviews different strategies for the use of information recorded from peripheral interfaces and the current state of control neuroprostheses and hybrid bionic systems.

Key words: muscle electrode, nerve stimulation, neural electrode, neuroprosthesis, peripheral nervous system

Introduction

Humans have long been fascinated by the possibility of interfacing and controlling artificial prostheses with biological signals, and this has led to the development of the field of functional electrical stimulation (FES) and neuroprostheses *(Agnew and McCreery, 1990; Stein et al., 1992; Chapin and Moxon, 2000)*. In recent years, many scientific and technological efforts have been devoted to develop hybrid bionic systems that link, via neural interfaces, the human nervous system with electronic and/or robotic prostheses, with the main aim of restoring motor and sensory functions in patients with spinal cord injuries, brain injuries, or degenerative diseases.

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A number of neuroprostheses, developed to artificially substitute or mimic sensorimotor functions in patients with neurological impairment, include interfacing the peripheral nervous system (PNS) or muscles by means of appropriate electrodes, which may allow neuromuscular stimulation and neural signal recording. Recent developments in the technology of electronic implants and in the understanding of neural functions have also made feasible the construction of interfaces that work by bidirectionally interchanging information between the central nervous system (CNS) and computerized artificial instruments, by means of microwire or microelectrode arrays implanted in the brain *(Lauer et al., 2000; Nicolelis, 2001; Donoghue, 2002)* or in the spinal cord *(Prochazka et al., 2001; Alo and Holsheimer, 2002)*. Recently, several architectures have been developed and tested to control different platforms: (1) FES systems have been developed to artificially replace central motor control and directly stimulate the intact peripheral nerves of patients with CNS injuries, attempting to generate movements or functions that mimic normal actions; (2) artificial prostheses have been aimed at substituting parts of the body (e.g., hands or upper extremities); (3) exoskeletons have been aimed at augmenting or restoring reduced or lost human capabilities; and (4) tele-operated robots have been developed to carry out tasks in environments where the access of human beings is not possible for different reasons.

There are different methods of coupling these devices to the PNS depending on the type of biological signal that is gathered (Table 1). Microelectrode devices that contact peripheral nerves or muscles using an electrical coupling method are the most common and best-known type of interfacing device. Although this coupling method is normally associated with some degree of invasiveness into the biological system, a wide variety of electrode designs have been manufactured and tested *(Heiduschka and Thanos, 1998; Rutten, 2002)*. Contemporary research in neuroprostheses has concentrated on addressing the development and experimental testing of interfaces to the PNS that do not damage the nerve and tissues, allow access to information from sensory afferents, selectively stimulate multiple nerve fibers, and provide graded control of muscle force *(Branner et al., 2001)*. These nerve electrodes are implanted adjacent, around or even within a peripheral nerve trunk or spinal root. Due to the proximity to the nerve, the stimulus intensity required for activation is reduced in comparison with muscular or surface electrodes and, consequently, hazardous electrochemical processes and power consumption of the stimulator system can be decreased *(Loeb and Peck, 1996)*. Selective stimulation of different fascicles of axons composing the nerve may also be achieved. However, nerve electrodes also have the potential to damage the nerves on which they are implanted, whereas muscle electrodes are generally considered as safer (Table 2). These issues and the nature of mechanical, chemical, and electrical compatibilities require additional study before widespread clinical application of the technology.

Table 1. General methods to interface the peripheral nervous system.

Chemical
Sensors, analysis, and modulation
Detection of ionic changes of the environment
Mechanical
Tension or torque transduction
Motion and acceleration
Magnetic
Stimulation and motionless electromagnetic generator
Superconducting quantum interference device sensor (SQUIDS)
Electrical
Potential measurement
Current or voltage stimulation

Nowadays, the most frequent use of PNS interfaces resides in FES, which has clinical applications in various systems designed to control micturition and defecation by stimulating the sacral roots *(Brindley et al., 1986; Creasey, 1993; Van Kerrebroeck et al., 1993; Brindley, 1994; Rijkhoff et al., 1997)*, for reducing pain *(Nashold et al., 1982; Strege et al., 1994; Stanton-Hicks and Salamon, 1997)*, for phrenic nerve pacing for ventilatory assistance *(Glenn et al., 1986; Creasey et al., 1996; Chervin and Guilleminault, 1997)*, for activation of lower extremity motion *(Waters et al., 1985; Popovic, 1992; Haugland and Sinkjaer, 1995; Triolo et al., 1996; Graupe and Kohn, 1997; Popovic et al., 1998; Taylor et al., 1999)*, and for control of hand movements *(Peckham and Keith, 1992; Kilgore, 1997; Wuolle et al., 1999; Bhadra et al., 2001; Popovic, 2003)*. The crucial prerequisites for successful use of an implantable neuroprosthesis are the appropriate indication, careful preoperative testing, differentiated planning of the implant, and functional training adapted to the individual residual functions. Patients are able to use the system for activities of daily living and enhancing their quality of life and independency. New technological developments are taking into account the fact that the most patients with nervous system injury suffer from an incomplete lesion, and thus modular, controllable systems for supporting these functions are being developed *(Rupp and Gerner, 2004)*.

The field seeks to develop forward control of motor activity induced by artificial stimulation provided from selective feedback from afferent nerve fibers conveying information from proprioceptive (muscle spindles and tendon organs) and cutaneous (mechanoreceptors)

Table 2. Advantages and disadvantages of conventional types of peripheral nerve electrodes.

Advantages
Proximity of electrode and nerve reduces the intensity of stimulation required for axonal excitation
Reduction of hazardous electrochemical processes and power consumption of the stimulator system
Minimal mechanical distortion of the electrodes during movement, reducing the chances for lead failure
The electrical characteristics are not affected by changes in muscle length during movement
Selective stimulation of fascicles within the nerve is possible, by multiple-contact electrodes and by manipulating the stimulation pulse parameters
Recording of nerve electrical activity can be achieved with the same electrodes
Disadvantages
Nerves can be damaged by the implanted electrode
Implantation requires delicate surgical procedure, depending on the accessibility of the nerves
Reverse order of recruitment of motor units during electrical stimulation leading to fast-fatigue production
Selective stimulation requires careful testing after implantation given the variability in fascicular architecture of each peripheral nerve

receptors. This requires selective recording of neural activity with multielectrodes, followed by pattern recognition analyses.

The goal of this work is to critically review the main aspects of interfaces with the PNS, particularly the characteristics and suitability of different types of electrodes, and their biomedical applications. This is being carried out in the context of a large collaborative international effort within the EU FET project NEUROBOTICS.

Organization of the PNS

The PNS is constituted by neurons whose cell bodies are located in the spinal cord or within spinal ganglia, their central connections (nerve roots), and their axons, which extend through peripheral nerves to reach target organs. Peripheral nerves contain several types of nerve fibers. Afferent sensory fibers can be unmyelinated or myelinated, the latter ranging from 2 to 20 μm in diameter, and terminate at the periphery either as free endings or in various specialized sensory receptors in the skin, the muscle, and deep tissues. Sensory fibers convey various sensory inputs, mainly mechanical, thermal, and noxious stimuli. Efferent motor fibers originate from motoneurons in the spinal cord anterior horn and end in neuromuscular junctions in skeletal muscles. The majority can be divided into two types: alpha-motor fibers that innervate the skeletal extrafusal muscle fibers and gamma-motor fibers that innervate the spindle muscle fibers. Efferent autonomic nerve fibers in somatic peripheral nerves are mostly constituted by postganglionic sympathetic fibers, generally unmyelinated, that innervate smooth muscle and glandular targets. The number and type of nerve fibers is highly variable, depending on the nerve and the anatomical location. Most of the somatic peripheral nerves are mixed, providing motor, sensory, and autonomic innervation to the corresponding projection territory.

Nerve fibers, both afferent and efferent, are grouped in fascicles surrounded by connective tissue in the peripheral nerve *(Peters et al., 1991)*. The fascicular architecture changes throughout the length of the nerve, with an increasing number of fascicles of smaller size in distal with respect to proximal segments. Nerve fibers are grouped in fascicles that eventually give origin to branches that innervate distinct targets, either muscular or cutaneous (Fig. 1). In addition to bundles of nerve fibers, the peripheral nerves are composed of three supportive sheaths: epineurium, perineurium, and endoneurium. The epineurium is the outermost layer, composed of loose connective tissue and carries blood vessels that supply the nerve. The perineurium surrounds each fascicle in the nerve. It consists of inner layers of flat perineurial cells and an outer layer of collagen fibers organized in longitudinal, circumferential, and oblique bundles. The perineurium is the main contributor to the tensile strength of the nerve, acts as a diffusion barrier, and maintains the endoneurial fluid pressure. The endoneurium is composed of fibroblasts, collagen and reticular fibers, and extracellular matrix, occupying the space between nerve fibers within the fascicle. The endoneurial collagen fibrils are packed around each nerve fiber to form the walls of the endoneurial tubules. Inside these tubules, axons are accompanied by Schwann cells, which either myelinate or just surround the axons.

The natural actions of the body are controlled using the efferent neural signals going from the CNS to the PNS to recruit different muscles. At the same time, the information transduced by the natural sensors (mechanoreceptors, proprioceptors, etc.) are conducted to the CNS by activation of the afferent nerve fibers. Signals are transmitted by the corresponding axons in series of impulses or action potentials, with intensity of the signal mainly coded in impulse frequency along the peripheral axon.

Each spinal motoneuron makes synaptic contact with many muscle fibers, constituting a motor unit. Considering that the neuromuscular synapse is a one-to-one synapse, the excitation of a motoneuron produces the same frequency of action potentials and the following contraction of all muscle fibers in the motor

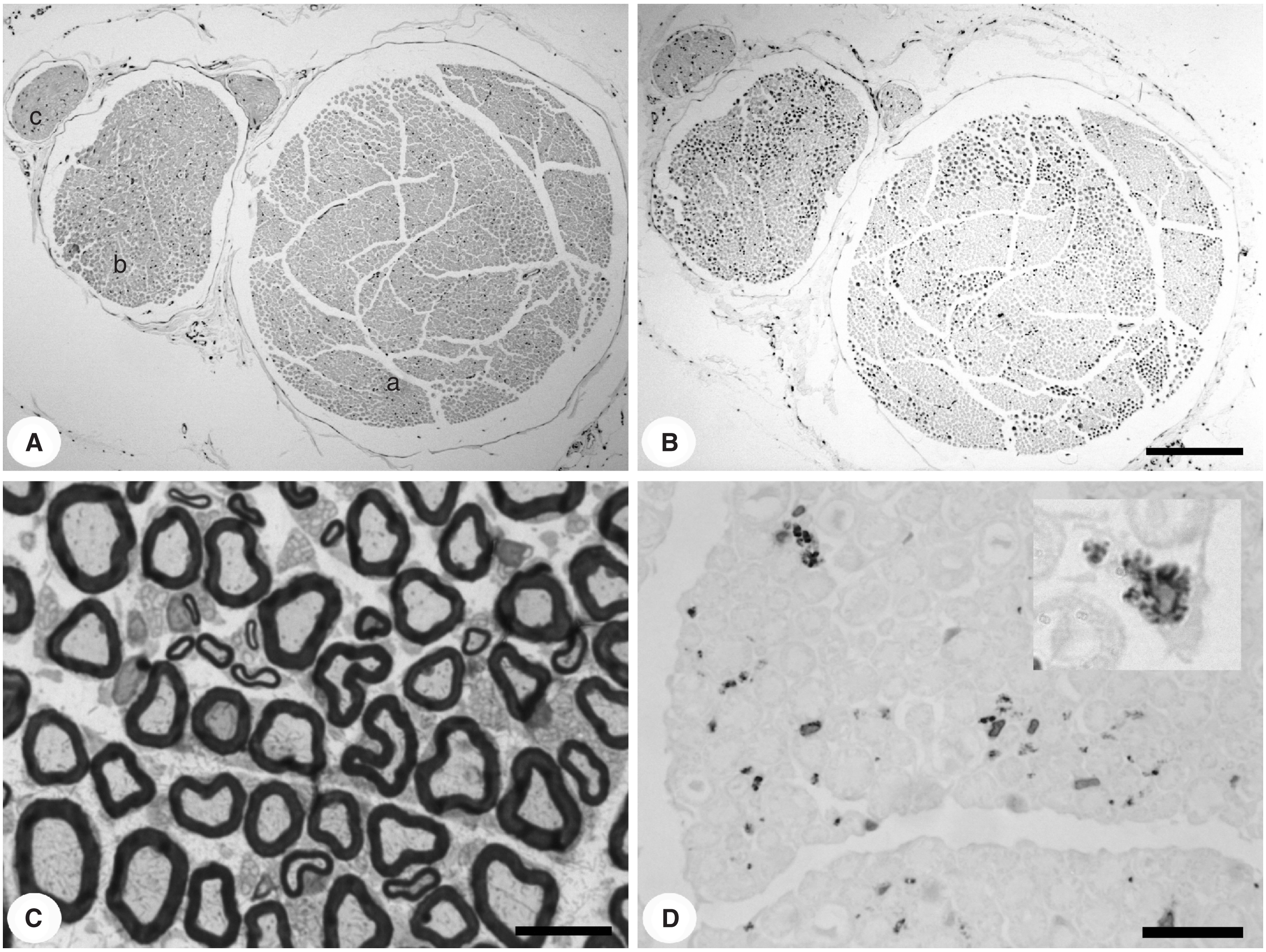

Figure 1. Structure of the peripheral nerve. (A) Transverse section of the rat sciatic nerve showing the distinct fascicles (a: tibial; b: peroneal; c: sural branches). The endoneurial compartments are encircled by the perineurium and the outer loose epineurium. (B) Grouping of motor fibers in the rat sciatic nerve. The nerve was immunolabeled against ChAT and counterstained with hematoxilin. (C) Semithin cross-section stained with toluidine blue showing at high magnification small- and medium-size myelinated fibers and intermingled unmyelinated fibers. (D) Transverse section of the rat sciatic nerve immunolabeled against GFAP that identifies unmyelinated fibers. Bars = 200 μm in (A) and (B); 10 μm in (C); 20 μm in (D).

unit. The nervous system produces graded contraction of each muscle by increasing the number of motor units activated and by increasing the frequency of action potentials to each motor unit. Recruitment of motor units follows an order of size, with slow fatigue-resistant motor units activated first and large fast-fatigue motor units activated only at high levels of tension.

Interface Electrodes

As used in bioengineering, the term interface includes all the elements of a system between the machine processor and the human tissues (i.e., from the biological target), the electrode or sensor and internal wires, through the connection that links the inner body with the outer processor, the data-acquisition circuitry, and the command unit for controlling the artifact or effector. One key component for an interface design is the electrode that captures bioelectrical activity or applies current into the living tissue, and the interface material transforming biological activity into electrical signals.

From an engineering point of view, the neural interface is a bidirectional transducer that establishes a neuro-technical contact between a technical device and a neural structure within the body. The objective of this transducer is to record bioelectrical signals from natural sensors of the body and the artificial excitation of nerves and/or muscles. From a biological point of view, such an interface is a foreign body. Both views have to be brought together to consider the requirements and complex aspects of biocompatibility *(Heiduschka and Thanos, 1998; Stieglitz, 2004)*. Nearly all evaluation aspects have been summarized in the standard ISO 10993 'Biological evaluation of medical devices.' In general, the compatibility between a technical and a biological system *(Bronzino, 1995)* can be divided into the *structural biocompatibility* and the *surface biocompatibility*. The structural biocompatibility comprises the adaptation of the artificial material structure to the mechanical properties of the surrounding tissue. Device design and material properties should mimic the biological structure of the target tissue. The surface biocompatibility deals with the interaction of the chemical, physical, biological, and morphological surface properties of the foreign material and the target tissue with the desired interaction. In the integrative result, a material can be stated as biocompatible if substances are only released in non-toxic concentrations and the biological environment reacts only with a mild foreign body reaction and encapsulation with connective tissue. A material is surely incompatible if substances are released in toxic concentrations or antigens are produced that cause immunoreactions (e.g., allergies, inflammation, necrosis, or even implant rejection). Attempts to develop material surfaces that may be recognized as biological and form truly biocompatible interfaces with the tissue are under investigation, although they have yet to be integrated in functional neural interfaces.

Chronic and electrically active implants in neural prostheses have to fulfill high demands with respect of biostability and biofunctionality. The designs and size, as well as the material choice and their interface surface, have to ensure temporally stable transducer properties of the electrode–electrolyte interface throughout the lifetime of the implant. For non-invasive position control, the material should be radiographically visible. Good candidates for ohmic electrode–tissue contacts are gold, platinum (Pt), platinum-iridium, tungsten, and tantalum *(Geddes and Roeder, 2001; 2003)*. Capacitive electrodes such as titanium nitride might reduce the risk of corrosion under stimulation conditions, but their performance highly varies with the fabrication technology *(Janders et al., 1996; Weiland et al., 2002)*. The choice of an adequate electrode size and material, in combination with a 'structural compatible' design, is always a compromise between electrode impedance, signal-to-noise ratio, and selectivity.

The theoretical basis of electrode surface and usable characteristics and testable models of electrode design have been optimized *(McNeal, 1976; Rattay, 1990; Rutten, 2002; Sinkjaer et al., 2003)*. Neuromuscular stimulating electrodes should provide stimulation below the charge-carrying capacity and density that induce reversible electrochemical processes and axonal damage *(Brummer et al., 1983; Naples et al., 1990; Roblee and Rose, 1990; Loeb and Peck, 1996)*. Time variations in the current required to generate a particular level of neuromuscular activation are attributable to changes in the induced fields resulting from tissue encapsulation or inflammation, changes in the electrode position relative to the nerve, and changes in the physiological properties of the neuromuscular system, including degeneration and regeneration of stimulated nerve fibers *(Grill and Mortimer, 1998)*.

The number of electrodes to be used depends on the working application: low number of electrodes for robust use and limited functionality or high numbers for good spatial resolution and selectivity (Table 3). Selective electrical interfacing aims at contacting nerve fibers as selectively as possible, requiring devices and fabrication technology in the size of micrometers. However, the use of many small electrodes does not always grant the expected selectivity within the praxis. For example, nerve fibers are recruited by electrical stimulation according to their thickness, therefore large motor fibers innervating the fast-fatigue and strong motor units are activated earlier than the physiologically first-recruited thinner fibers controlling slow fatigue-resistant motor units. This is called inverse recruitment within the electrical stimulation.

Considering the application of different types of electrodes, the desired selectivity of stimulation or recording from individual nerve fibers or motor units increases in parallel with the invasivity of the electrode implantation (Fig. 2). For example (see following sections), surface and muscular electrodes can record EMG activity from and stimulate only the underlying or implanted muscles. Extraneural electrodes, such as cuff and epineurial electrodes, provide simultaneous interface with many axons in the nerve, whereas intrafascicular and sieve electrodes inserted in the nerve may interface small groups of axons within a nerve fascicle. On another hand, the state of the nerve varies; cuff and intrafascicular electrodes can be applied to intact nerves in acute or chronic studies, whereas, by definition, regenerative sieve electrodes are implanted in transected nerves that need to regenerate across the electrode sieve over several months.

Non-Invasive Electrodes

Surface electrodes

The only non-invasive electrodes are surface electrodes applied to the skin of the subject for the recording of ECG, EMG, or EEG *(Birbaumer et al., 2004)*. Felt-pad metal electrodes and carbon-rubber electrodes are adequate for transcutaneous motor stimulation considering their electrical impedance and their ease of application, durability, and lack of skin reactivity *(Nelson et al., 1980)*. Although surface electrodes are normally used for recording biological

Table 3. Electrodes used for interfacing the peripheral and central nervous systems and their biomedical applications.

Electrodes					
Type	Mode	Number	Contact site	Application	Status
Surface	Recording	<25	Skull	Brain–computer interface	Clinical practice
Surface	Recording	2	Residual muscles	Artificial limb control	Clinical practice
Surface	Stimulation	4	Surface muscles	Muscle stimulation	Clinical practice
Epimysial	Stimulation	8	Hand/arm muscles	Grasping	Clinical practice
Epimysial	Stimulation	16	Leg muscles	Standing/walking	Research
Intramuscular	Stimulation	1–256	Skeletal muscle	Stimulation	Research
Epineurial	Stimulation	4	Phrenic nerve	Breathing	Clinical practice
Epineurial	Stimulation	2	Peroneal nerve	Drop foot	Clinical practice
Book	Stimulation	3	Sacral spinal roots	Bladder management	Clinical practice
Helical	Stimulation	1	Vagal nerve	Seizure suppression	Clinical practice
Helical	Stimulation	1	Vagal nerve	Sleep apnea	Clinical practice
Cuff	Recording	1	Sural nerve	Functional electrical stimulation control	Research/ clinical practice
Intrafascicular	Recording/ stimulation	1–4	Peripheral nerve	Artificial limb control	Research
Cuff	Stimulation	4	Optic nerve		
Epineurial	Stimulation	16–25	Retina/ganglion cells	Blindness	Research
Intracortical	Stimulation	<1,024	Visual cortex		
Intracochlea	Stimulation	<23	Auditory nerve fibers	Deafness (cochlea)	Clinical practice
Epispinal	Stimulation	4	Spinal column	Pain suppression	Clinical practice
Epispinal	Stimulation	4	Spinal column	Incontinence	Clinical practice
Grid array	Stimulation	<22	Nucleus cochlearis	Deafness (brainstem)	Research/ clinical practice
Grid array	Recording	<129	Cortex, epidural	Epilepsy monitoring	Clinical practice
Intracortical	Stimulation	2	Subthalamic nuclei	Parkinson's disease	Clinical practice
Intracortical	Recording	100	Cortex	n.a.	Research

signals, they can also be employed to supply a perceivable sensation to the skin or to excite nerve tracts or muscles underneath the skin *(Patterson and Lockwood, 1993; Taylor et al., 1999)*. Their main advantage of being non-invasive and easily adaptable is counteracted by several disadvantages, such as the need for daily placement and frequent calibration, and by the low reproducibility and quality of acquired signals. The impedance at the electrode–skin interface is largely variable between individuals at low frequencies, whereas at high frequencies the decline of impedance values with time depends on the electrode type *(Hewson et al., 2003)*. Nevertheless, surface electrodes for stimulation are extensively used in rehabilitation as components of simple stimulating devices to activate skeletal muscles or to reduce chronic pain (TENS units) by activating large afferent fibers in peripheral nerves supplying the affected cutaneous region *(Stanton-Hicks and Salamon, 1997)*. They are also used in more sophisticated FES systems for correction of foot drop in hemiplegic patients *(Haugland and Sinkjaer, 1995; Taylor et al., 1999)*, for standing and short-distance walking assistance *(Graupe and Kohn, 1997)*, for control of postural hypotension *(Taylor et al., 2002)*, and also for recording EMG signals devoted to artificial limb control *(Zardoshti-Kermani et al., 1995; Zecca et al., 2002)* or for non-invasive slow brain–computer interfaces *(Pfurtscheller et al., 2000; Birbaumer et al., 2004)*. Currently, recorded EMG signals are used to determine the activation time of a muscle, to estimate the force produced during muscle contraction and to estimate the rate of muscle fatigue. For recording purposes, electrodes made of silver/silver chloride in the form of bars (10 × 1 mm) have been found to give adequate signal-to-noise ratio. The active

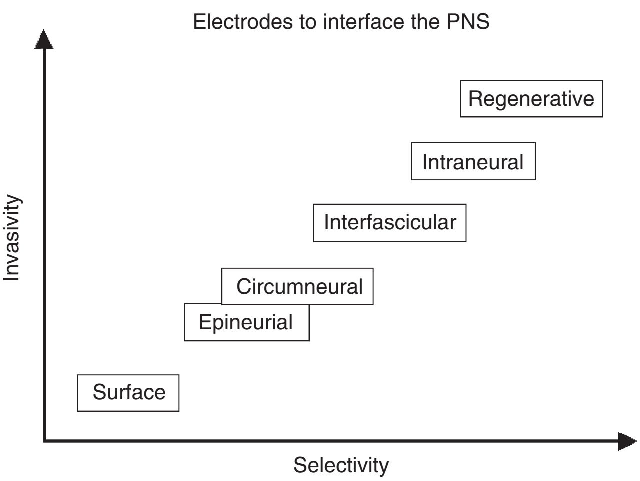

Figure 2. The different types of electrodes applied to interface peripheral nerves classified regarding invasivity and selectivity. This represents a general classification, despite that selectivity actually depends on the type of nerve and anatomical and physiological considerations for each particular application. PNS, peripheral nervous system.

recording electrode should be located near but not on the motor point because at this point the stability of signals suffers from minor physical displacement of the electrode *(De Luca, 2002)*. Multichannel (linear and high-density arrays) surface EMG electrodes have been developed that enable measurements of motor unit potentials size and number and provide topographical information that is beyond the capability of intramuscular needle electrodes *(Zwarts and Stegeman, 2003)*.

Non-electrical interfaces

Magnetoneurography is a non-invasive method that allows tracing and visualizing in three dimensions the propagation of compound action currents along peripheral nerves. Extremely weak magnetic fields generated by the ion flows of evoked compound nerve action potentials can be detected using superconducting quantum interference device (SQUID) sensors with high spatial and temporal resolution *(Hoshiyama et al., 1999)*. The main clinical perspective of magnetoneurography lies in the diagnosis of proximal mononeuropathies (plexus and root lesions), where conventional electrophysiological tests sometimes fail *(Mackert, 2004)*. To minimize external contamination, measurements are usually performed inside a magnetically shielded room, thus limiting its application for control of neuroprostheses. Further technical developments to increase sensitivity of measurements are needed before magnetic interfaces can be used for single-unit activity recordings.

Contracting skeletal muscle produces vibrations and emits sounds that are easily recorded with a standard microphone or an accelerometer. Muscle sounds have been used to measure twitch force, monitor fatigue and in the diagnosis of muscle diseases. Acoustic signals increase in parallel with surface EMG signals during voluntary and evoked contraction, but acoustic amplitude decays with fatigue whereas EMG amplitude does not *(Barry et al., 1985; 1992)* . Analysis of acoustic and vibration signals can be carried out similarly to electrical signals. As a control signal for externally powered prostheses, acoustic myography may present some advantages over surface EMG because it is unaffected by changes in skin impedance, less sensitive to placement on the muscle, and requires less amplification and electrical shielding. Disadvantagesinclude the susceptibility to interference by environmental noise and vibrations and limited experience with its use. Myoacoustical signals obtained via a single microphone have been proved feasible for the control of a prosthetic hand. The patients learned to open and close the hand reliably after a few minutes of practice *(Barry et al., 1986)*.

Muscle Electrodes

Epimysial and intramuscular electrodes

Epimysial electrodes are surgically placed directly on the surface of the muscle and are fixed by sutures or small anchors to the epimysium. They are composed of a platinum-iridium disk as conductor and a silastic backing sheath for insulation and attachment. In general, they offer a good signal-to-noise ratio because of their position and large surface and provide exact selectivity, namely the implanted muscle. Although they can be used for EMG recording, the main application area is for muscle stimulation (Fig. 3). Epimysial electrodes have proven their suitability in current complex motor prostheses that require coordinated stimulation of several muscles, for example, grasping system for tetraplegics (Freehand System) *(Bhadra et al., 2001)* and standing and walking systems for paraplegics *(Triolo et al., 1996; Kobetic et al., 1999)*. After a short training period, they can be used for muscle activation. Management may be difficult when many epimysial electrodes on different muscles are used because of the interconnection between them, providing additional risks and possible source of failure. In addition, high energy consumption is required to activate the muscle.

Intramuscular implanted electrodes can be as simple as the bared tip of insulated wires, but often in FES applications they consist of a single-strand, multifilament stainless steel wire insulated with Teflon and wound in a helical conformation. The electrode can be inserted without surgery with a percutaneous guide to place the uninsulated tip into the muscle, leaving the wire routed outside of the skin. These

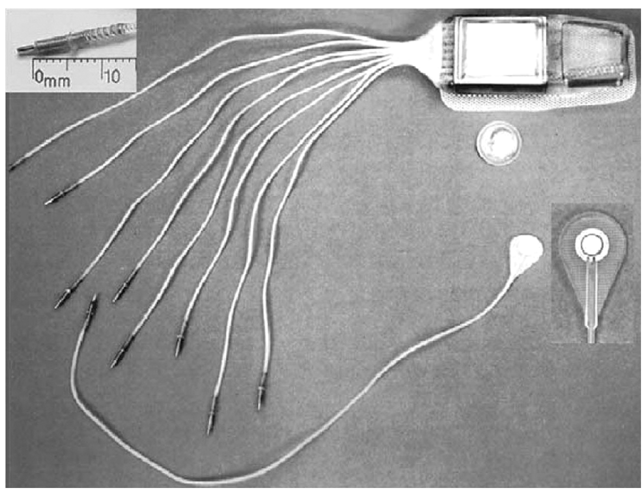

Figure 3. Eight-channel implantable stimulator with one epimysial electrode. Inserts show close-up view of the lead end on the top left and of the epimysial electrode on the right *(from Bhadra et al., 2001, with permission)*.

electrodes may damage many muscle fibers, but in most instances this loss will not represent a noticeable reduction in muscle force *(Mortimer et al., 1980)*. Electrode and lead failures or infections have been found to be rare and the electrode response was stable over time in patients with intramuscular or epimysial electrodes during more than 3 years *(Kilgore et al., 2003)*. Intramuscular electrodes can be used for both stimulation and recording. There is wide experience in the FES field with these electrodes *(Handa et al., 1989; Peckham and Keith, 1992)*. Compared with nerve cuff electrodes, intramuscular electrodes have been shown to produce more reliable, more graded, and less fatigable recruitment of motor units *(Singh et al., 2000)*.

Adequate EMG signals can be obtained with epimysial and intramuscular electrodes, but the fatigue of the muscle and the derived change of the recorded signal have to be taken into account for long-term use. For large muscles, the EMG activity mainly reflects the action potentials of motor units located more superficial or closer to the electrode. Although epimysial and intramuscular electrodes do not directly contact peripheral nerves, they achieve muscle activation by exciting the nerve fibers arborized within the muscle in which they are implanted. For muscular electrical stimulation, the control of relatively complex movements may be achieved using a large set of electrodes, each one activating a different muscle. This requires the implantation and maintenance of many electrodes subjected to considerable mechanical stress caused by strong muscle contractions *(Devasahayam, 1992)*. In addition, the currents required to produce contractions are high and may induce discomfort and tissue damage *(Chae and Hart, 1998)*. Another problem derives from the lack of selective, size-programmed activation of motor units within each muscle, thus limiting the period of use by muscle fatigue *(Crago et al., 1980; Grandjean and Mortimer, 1986)*. A final issue with percutaneous electrodes is that muscle contractions may result in eventual breakage, although these problems have become less frequent with the improvement of electrodes and lead wires *(Onishi et al., 2000)*. Electrical stimulation delivered through intramuscular or epimysial electrodes has been applied for maintenance of denervated muscles after plexus or peripheral nerve injuries, in order to avoid disuse atrophy *(Nicolaidis and Williams, 2001)*. In this situation, voltage pulses should be higher and of longer duration than for activation of innervated muscles so as to directly excite the muscle fiber membrane. To avoid problems derived from excess charge delivery, stimulation is given in cycles, and the system is explanted once regenerating axons reinnervate the muscles of interest. Direct muscle stimulation may be also used to recover chronically denervated muscles, although activation requires long duration pulses and extremely high current that are usually not generated by common FES devices *(Kern et al., 2002)*.

Of interest is the BION (BIOnic Neuron) implantable microstimulator developed by Loeb *et al. (2001)* (Fig. 4). This device consists of a small cylindrical capsule (16 × 2 mm) whose internal components are connected to electrodes sealed hermetically into its ends. A second-generation device uses a hermetically sealed ceramic case with platinum electrodes *(Arcos et al.,*

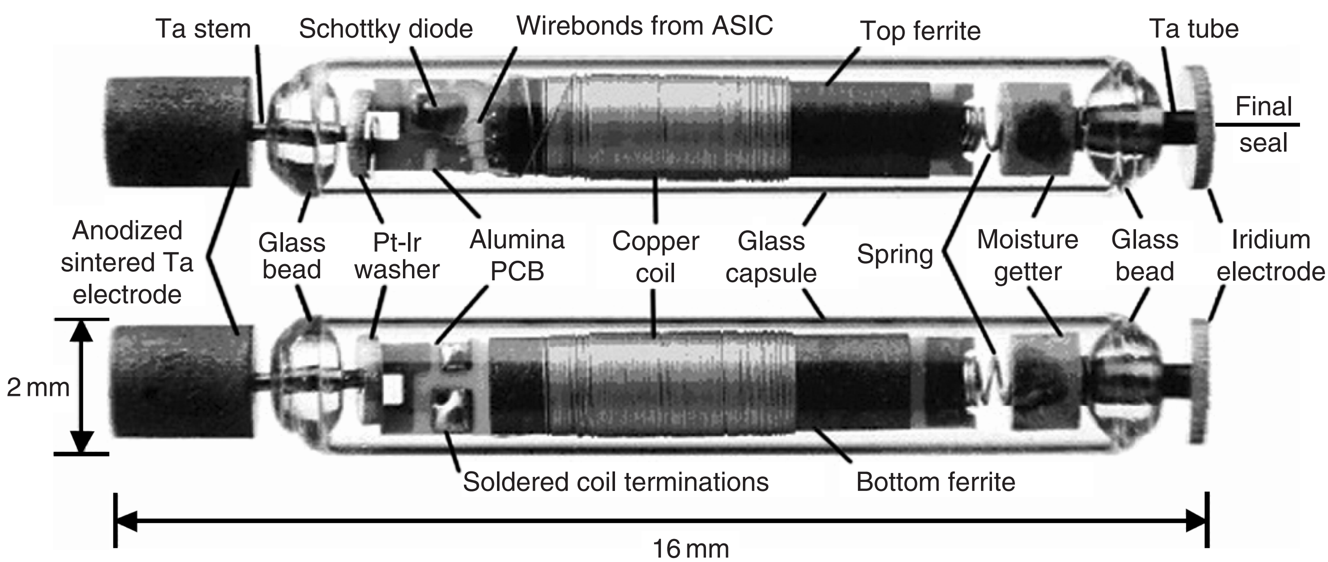

Figure 4. Main components and hermetic packaging scheme of a BION-1 implantable electrode *(from Singh et al., 2001, with permission)*. ASIC, application-specific integrated circuit; Ir, iridium; PCB, printed circuit board; Pt, platinum; Ta, tantalum.

2002). BIONs can be implanted within muscles by percutaneous injection with the aid of an insertion tool. The microstimulator is the main component of a 255-channel wireless stimulating system controlled by a radio frequency link. Tests performed indicated that the BION is a stable, biocompatible, and effective electrode when implanted passively or used to stimulate muscles in experimental animals for long-term implantation *(Cameron et al., 1998)*. These microstimulators have been used in human patients for muscle electrical stimulation to prevent disuse atrophy and secondary complications *(Dupont-Salter et al., 2004)*. Recently, the BIONs were reported to be useful in a FES system to correct foot drop. Compared with surface stimulation of the common peroneal nerve, stimulation with BIONs provided more selective activation of specific muscles such as tibialis anterior and extensor digitorum longus *(Weber et al., 2004)*.

Extraneural Electrodes

Epineurial and helicoidal electrodes

These types of electrodes are fabricated as longitudinal strips of biocompatible insulation material holding two or more contact sites (Fig. 5). In most instances, they are based on platinum or platinum-iridium wires. Epineurial electrodes are placed on the nerve and secured by suturing to the epineurium.

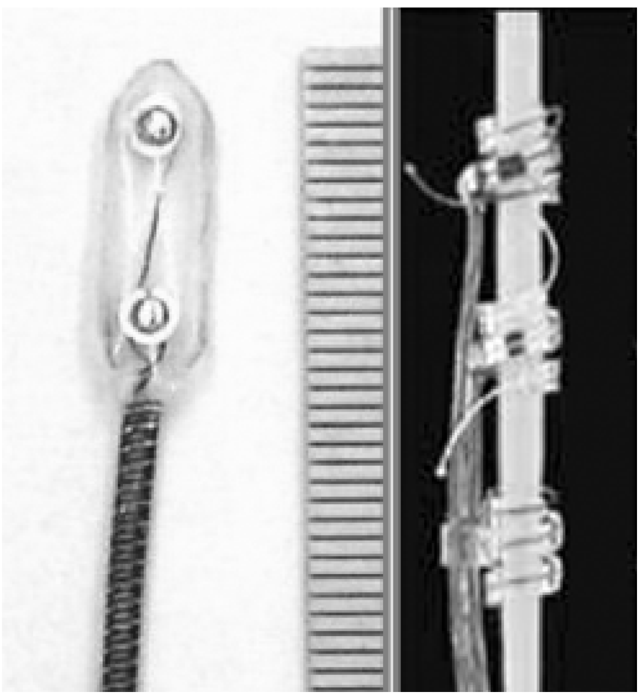

Figure 5. Examples of epineurial electrode (from Finetech Implantable Drop Foot) at the left and of helicoidal electrode (Cyberonics, Huntington Medical Research Institute) at the right.

Thus, they require delicate surgery and can be torn from the nerve if there is tension in the leads or excessive motion. However, they are unlikely to damage the nerve trunk and have good stability that allows for selective activation of particular nerve fascicles. Microsurgical techniques are used to attach numerous electrodes directly to the nerve, allowing for bipolar and selective stimulation. Epineurial electrodes are used in biomedical FES applications for breathing control by phrenic nerve stimulation *(Creasey et al., 1996)*, foot-drop improvement *(Liberson et al., 1961)*, and relief of neuropathic pain *(Strege et al., 1994)*. The latter application is of limited benefit because it should be applied only when pain involves one nerve territory in the head or the limbs and has frequent morbidity associated with electrode approximation, electrode displacement, and lead failure *(Hassenbusch et al., 1996)*. Interestingly, in FES systems for phrenic nerve and for pain control, the cuff electrodes used in the past have been substituted for button-type epineurial electrodes to reduce the risk for traumatic injury to the nerve *(Chervin and Guilleminault, 1997; Stanton-Hicks and Salamon, 1997)*.

Helicoidal electrodes, placed circumjacent to the nerve, are made of flexible platinum ribbon with an open helical design (Fig. 5), allowing the electrode to conform to the shape of the nerve and minimizing mechanical trauma *(Naples et al., 1990)*. They are easy to implant and explant as needed. However, its open structural shape explains the low selectivity of the electrode *(Agnew et al., 1989)*. Helical electrodes are widely used for FES of the vagus nerve, which has found therapeutical applications for the control of intractable epilepsy, sleep apnea, and treatment of depressive syndromes *(McLachlan, 1997; Fisher and Handforth, 1999)*. Extensive studies on animal peripheral nerves following electrical stimulation with similar devices suggest that the parameters of stimulation used in humans should provide an adequate margin of safety against nerve injury. Postoperative infections after helicoidal electrode implants in vagus nerve patients occur in less than 3% of cases, requiring removal of the device in 1%. Occasional fracture of the electrode wire has been reported *(McLachlan, 1997)*.

Book electrodes

Book electrodes are of widespread clinical use for urinary bladder management in spinal cord-injured persons. The prototype was introduced in 1972 by Brindley *(1972)* to contact the anterior sacral spinal roots. The device consists of a silicone rubber block with slots. In each slot, three platinum foils are embedded as electrodes. The middle electrode serves as cathode while the outer electrodes are used as anodes. The spinal roots are placed in the slots comparable to a bookmark laid in-between the pages of a book, thereby giving the device its name. The slots are then covered with a flap made of silicone and fixed with silicone glue. The first micturition because of electrical nerve root stimulation was reported in 1973 *(Brindley, 1973)*. Cooper wires establish the connection between the electrodes and an implantable control unit. Their helical cable design gives good mechanical strength and high flexibility *(Donaldson, 1983)*. After more than 10 years of development, Brindley's group reported the first 50 cases of a radio frequency-controlled implant from series production with medical approval called sacral anterior root stimulator (SARS) in humans *(Brindley et al., 1986)*. The implant was commercialized as Finetech-Brindley stimulator, and less than a decade later 500 patients benefited from the system *(Brindley, 1994)*. This experience has been successfully transferred into clinical practice *(Jezernik et al., 2002)*, even though improvements are desirable to improve selectivity of stimulation and to overcome the sphincter-detrusor dysynergia that causes post-stimulus voiding. Because ventral root stimulation produces simultaneous contraction of both sphincter and detrusor muscles, voiding is achieved in brief spurts at the end of the stimulation, when the striated sphincter muscle relaxes faster than the smooth detrusor muscle. Nowadays, there are 2,000 patients worldwide that carry a urinary bladder stimulator *(Rijkhoff, 2004)*. Besides the intradural surgical implantation, an epidural implantation procedure was developed *(Sauerwein et al., 1990)* to enhance the group of patients who may benefit from this kind of neural prosthesis. The implantation is mostly combined with deafferentation of the dorsal sacral roots to interrupt reflex circuits and to restore a residual volume of the bladder and continence. The disadvantages of this surgical procedure include the loss of reflex defecation and of reflex erection and ejaculation in male patients. The SARS can be also used to restore male sexual and reproductive function *(Stief et al., 1992; Brindley, 1995)*. Even after a long clinical experience with excellent results, the electrodes are still very bulky and there is a high demand for miniaturization with regard to minimally invasive surgery and the risk of open vertebral column procedures.

Cuff electrodes

Cuff electrodes are composed of an insulating tubular sheath that completely encircles the nerve and contains two or more electrode contacts exposed at their inner surface that are connected to insulated lead wires (Fig. 6). Cuff electrodes are the type of PNS interface electrode most investigated in basic and applied research. They have been fabricated in several configurations, the most common being 'split-cylinder' and 'spiral' cuffs *(Naples et al., 1990)*.

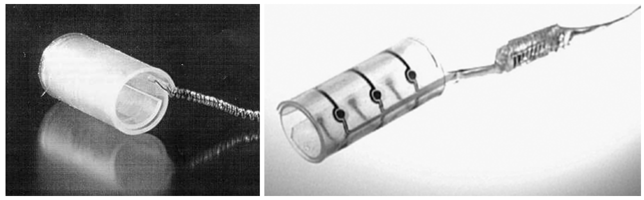

Figure 6. Examples of cuff electrode made on silicone and hybrid silicone-polyimide cuff electrode (from IBMT).

Cuff electrodes placed around the nerves have several advantages compared with surface, intramuscular, and epimysial electrodes: they allow for correct positioning of electrode leads to minimize mechanical distortion and lead failure, and the stimulating current is confined to the inner space of the electrode, thus avoiding the stimulation of other neighboring nerves and tissues *(Loeb and Peck, 1996)*. An order-of-magnitude reduction in required stimulus current is needed with cuff electrodes. In comparison with other, more invasive types of nerve interfaces, such as penetrating and regenerative electrodes, cuff electrodes are less prone to damage the nerve and easier to implant.

In spite of the fact that cuff electrodes have been implanted in patients for decades, nerves can be damaged by the presence of the cuff due to the delicacy of the nerve tissue and the physical properties of the electrodes *(Nielson et al., 1976; Waters et al., 1985; Krarup et al., 1989; Naples et al., 1990; Larsen et al., 1998)*, especially in peripheral nerves of the limbs, subjected to a wide range of motion. With regard to mechanical properties, cuff electrodes should be flexible and self-sizing in order to avoid stretching and compression of the nerve. The helix-shaped and the spiral-cuff electrodes have a slightly larger diameter than the nerve to be implanted, the shortest length and thinnest wall possible without compromising their mechanical stability, and avoid sharp edges and blunt corners to prevent nerve damage *(Naples et al., 1990; Hoffer and Kallesøe, 2001)*. Although snug-fitting nerve cuffs have been advocated to reduce the stimulus charge injection or to obtain a high signal-to-noise ratio for neural recordings *(Naples et al., 1990)*, different studies have shown that chronic implantation of snug cuffs modifies the nerve shape and produces a loss of large nerve fibers, which are the most sensitive to compression *(Krarup et al., 1989; Grill and Mortimer, 1998; Larsen et al., 1998)*.

From a functional point of view, cuff electrodes can be used to stimulate the enclosed nerve leading to the activation of efferent motor or autonomic nerve fibers. Simple configurations are bipolar and tripolar (using the central pole as cathode and two outer poles as anodes), which reduce current leaks out of the cuff. Multichannel cuff electrodes enable selective stimulation of separate axonal fascicles within the nerve, each one supplying innervation to a different muscle *(Rozman et al., 1993; Veraart et al., 1993; Grill and Mortimer, 1996a; Walter et al., 1997; Navarro et al., 2001)*. The reduced size and thickness of recent polymer cuffs *(Stieglitz et al., 2000)* also opens the possibility of implantation of several small cuffs around different fascicles or branches of nerves and, consequently, the achievement of selective functional stimulation of a higher number of muscles *(Rodríguez et al., 2000; Stieglitz et al., 2003)*. The use of short pulsewidths and the introduction of a subthreshold transverse current from a steering anode allows restriction of the region of excitation of the nerve trunk, significantly improving the selectivity of stimulation *(Gorman and Mortimer, 1986; Sweeney et al., 1990; Grill and Mortimer, 1996b; Navarro et al., 2001)*. Strategies to achieve a physiological recruitment order include the application of selective anodal blocking of large fibers that have been stimulated along with the smaller fibers but whose action potentials cannot traverse the block region. For example, quasi-trapezoidal stimulation pulses have been shown to induce more gradual contraction than rectangular pulses, an effect that was attributed to activation of fatigue-resistant motor units before activation of large fast-fatigue units with cuff electrodes *(Fang and Mortimer, 1991; Rozman et al., 1993)*.

Research in animals with chronically implanted tripolar cuff electrodes showed that they can be used for long-term recording of both afferent and efferent nerve activity *(Stein et al., 1977; Popovic et al., 1993; Hoffer and Kallesøe, 2001)*. The ENG activity recorded from a nerve with electrodes placed around its periphery is dominated by the excitation of large myelinated fibers and those located at superficial locations. The nerve activity recorded with cuff electrodes during functional stimulation is multiunitary, as the current of action potentials from individual axons will summate and does not allow for the identification of single spikes (Fig. 7). Therefore, the selectivity of ENG recording is limited by the number of axons simultaneously firing and by the surface area and location of the active contact electrodes of the cuff. However, pattern recognition analyses may allow for classification of the functional type of signals, and off-line signal processing provides useful information, such as the amount of nerve activity elicited. The amplitude of the recorded signals depends on the distance between the recording electrode sites and on the cuff electrode impedance. In general, long (interelectrode distance close to the wavelength of the action potential) and snug-fitting cuffs provide larger signals *(Loeb et al., 1977; Hoffer and Kallesøe, 2001)*. Good sealed cuffs avoid nerve current leak and contamination from nearby excited muscles. Tripolar (central active electrode vs. two reference electrodes near the ends of the cuff) electrode configuration is preferred to reduce noise pickup *(Stein et al., 1977)*; it provides a biophysically ideal way to use a differential amplifier to reject almost completely the large bioelectric signals arising from outside the cuff (e.g., EMG). Microfabrication of cuffs containing metal electrode contacts allows for improved reproducibility of dimensions, avoiding mismatch of contact impedances. Multipolar cuffs containing several contacts arranged in tripoles increase the possibilities of selective recording from different fascicles in the nerve, although the amplitude of the multiunitary signals decreases in comparison with those obtained with a simple tripolar configuration using three circular metal contacts.

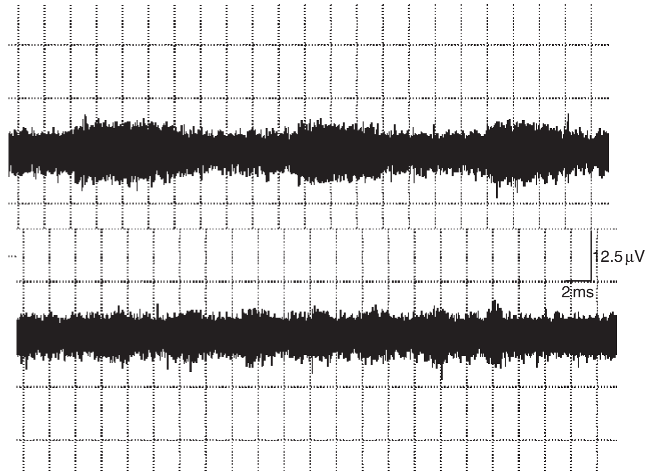

Figure 7. Nerve activity recorded with a cuff electrode implanted around the rat sciatic nerve in response to repeated contacts with a von Frey filament (top panel) and to repeated brushes (bottom panel) of the hindpaw.

Flat-interface nerve electrodes

A design variation of the cuff electrode is the flat-interface nerve electrode (FINE) developed by Durand and coworkers *(Tyler and Durand, 2002)*. The FINE is an extraneural electrode designed to reshape peripheral nerves into a favorable geometry for selective stimulation (Fig. 8). By flattening the nerve into a more elliptical shape, fascicles become more accessible and central fibers are moved closer to the stimulating electrode in comparison with cylindrical cuffs. The surface area of the nerve is also enlarged, therefore increasing the interface surface and allowing more contacts to be placed around the nerve. Modeling studies have suggested that the more the nerve is reshaped, the better the selectivity for stimulation and recording

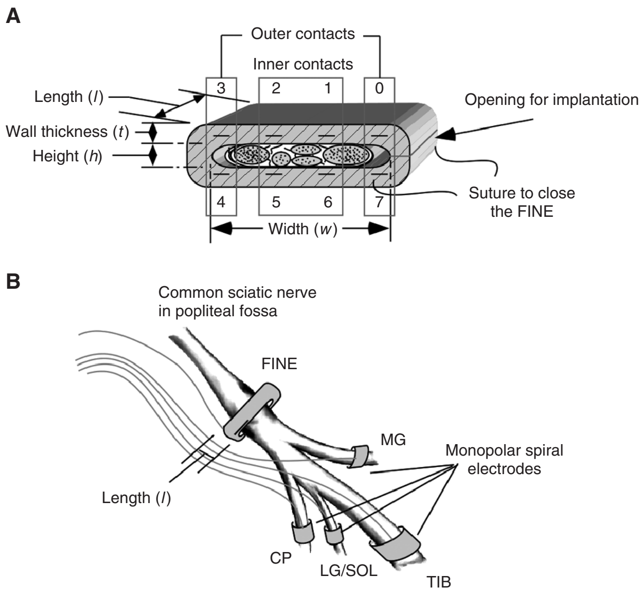

Figure 8. Flat-interface nerve electrode (FINE) electrode design and implant location. (A) Schematic cross-section of a FINE on a plurifascicular nerve. (B) Location of the experimental electrodes on the sciatic nerve *(from Tyler and Durand, 2002, with permission)*. CP, common peroneal; LG/SOL, lateral gastrocnemius/soleus; MG, medial gastrocnemius; TIB, tibial.

(Perez-Orive and Durand, 2000; Choi et al., 2001). Results on acute experiments showed that it is possible to selectively activate individual fascicles of the cat sciatic nerve with the FINE, as well as groups of fibers within the fascicles, and revealed the strong dependency of selectivity on the relative locations of the fascicle and the electrode contacts *(Tyler and Durand, 2002; Leventhal and Durand, 2003)*. Chronic studies in laboratory animals with FINE implanted over 1–3 months showed that electrodes applying high reshaping force induced nerve damage, whereas those with moderate and small forces did not cause any detectable change in nerve physiology and histology. Electrodes that moderately flattened the nerve demonstrated the best selectivity for limb motion measurements, which were maintained throughout the implant time *(Tyler and Durand, 2003; Leventhal and Durand, 2004)*. The FINE seems a promising alternative for neuroprosthetic devices, although there are no reports of clinical use.

Interfascicular electrodes

The interfascicular design combines the simplicity of the extraneural electrodes with the closer axon contact and stimulation selectivity of intrafascicular electrodes. The interfascicular electrode places electrical contacts within the nerve, but outside the fascicles, by blunt penetrating the epineurium without compromising the integrity of the perineurium. The electrode is referred to as the slowly penetrating interfascicular nerve electrode (SPINE) *(Tyler and Durand, 1994)*. The SPINE (Fig. 9) consists of a silicone tube with blunt elements extending radially into the lumen of the tube that penetrate within the epineurium during implantation. The elements place stimulation contacts within the nerve for greater access to the central axonal population. Experimental results showed that interfascicular stimulation provided additional recruitment to enhance surface stimulation. Interfascicular stimulation is functionally selective based on the depth of penetration and on the side of the penetrating element. Histological cross-sections showed that the SPINE rearranges the epineurium and penetrates deep within a multifascicular nerve but did not disrupt the perineurium *(Tyler and Durand, 1997)*. There was no gross evidence of axonal damage after 1 day, but chronic implants have not been reported.

Intraneural Electrodes

Intrafascicular electrodes

Electrodes placed inside a peripheral nerve have been developed in order to allow enhanced selectivity with respect to extraneural electrodes and also to increase the signal-to-noise ratio of recordings. Intrafascicular electrodes are placed within the nerve and are in direct contact with the tissue they are intended to activate or record. Stimulation through them specifically activates the nerve fascicle in which they are implanted with little cross-talk to adjacent fascicles. Several intrafascicular electrodes may be implanted for multiple stimulation. Comparatively smaller stimulus intensities can be used to achieve equivalent levels to those of extraneural electrodes *(Yoshida et al., 2000)*. Flexible intrafascicular electrodes could involve silicon- or polyimide-based substrates or the use of intrinsically conductive fibers.

Longitudinally implanted intrafascicular electrodes (LIFEs) offer a means of interfacing to restricted subsets of axons within fasciculated peripheral nerves. LIFEs are constructed from thin insulated conducting wires, such as Pt-Ir or metallized Kevlar fibers *(Malagodi et al., 1989; McNaughton and Horch, 1996; Yoshida et al., 2000; Lawrence et al., 2003)*; the active site zone is a short length (250–1,500 μm) of the wire bared of the insulation (Fig. 10). Single-channel intrafascicular electrodes started the LIFE line and were useful in initial experiments that led to multichannel electrode applications. Flexible polymer filaments are preferred to metal wires because the stiffness of the latter presumably leads to motion of the electrode that elicits fibrous encapsulation and subsequent gradual

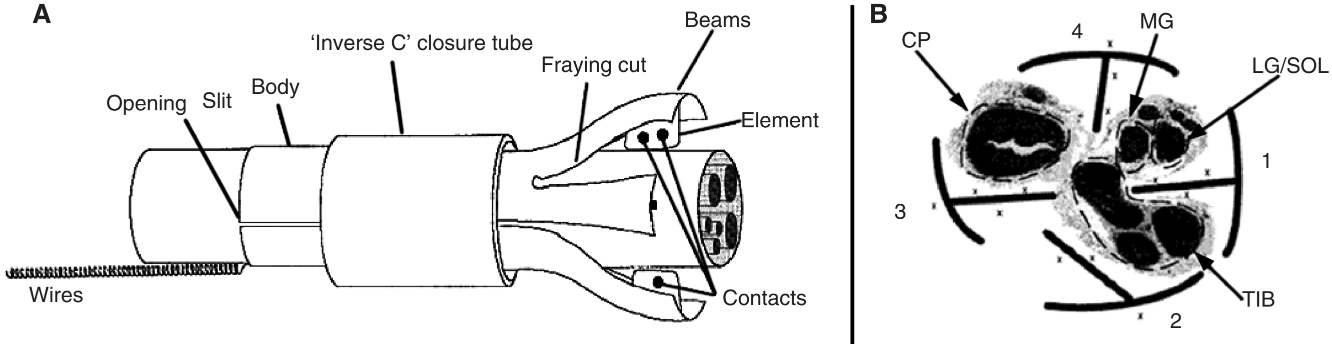

Figure 9. (A) Schematic representation of a slowly penetrating interfascicular nerve electrode. Each element is slowly urged into the epineurium by a small force applied by the beams. The center of the electrode is closed with a second tube around the center. Two interfascicular contacts are located on one side of each penetrating element. (B) Cross-section of an implanted nerve. The four elements penetrated within the nerve separating the nerve into three compartments. Tibial (TIB), lateral gastrocnemius/soleus (LG/SOL), medial gastrocnemius (MG), and common peroneal (CP) fascicles are indicated *(from Tyler and Durand, 1997, with permission)*.

decrease in the recorded amplitude of axon potentials *(Lefurge et al., 1991)*. The use of multistrand Kevlar LIFEs (m-polyLIFE) increases the tensile strength and signal-to-noise ratio *(Lawrence et al., 2004)*. Intrafascicular electrodes are implanted longitudinally within individual nerve fascicles by pushing a tungsten-guiding needle within the endoneurium parallel to the course of the nerve fibers a few millimeters and then pulling the electrode through the fascicle until the active zone of the electrode is centered in the fascicle. The histology of animal nerves that had metal or polymer LIFEs implanted for a period of 6 months revealed that the implants are biocompatible and that no damage was caused by the presence of the electrode, although a slight increase in connective tissue surrounding the implant site was evident in the long-term *(Lefurge et al., 1991; Lawrence et al., 2002)*.

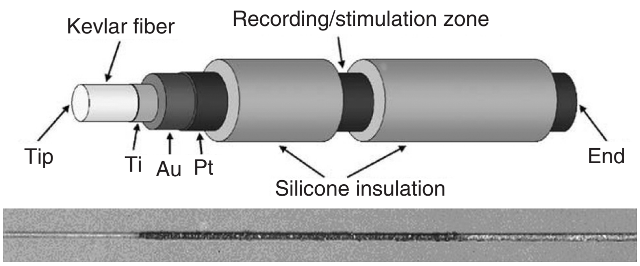

Figure 10. Schematic representation of a polymer-based intrafascicular electrode (polyLIFE). The polyLIFE consists of a Kevlar® fiber, metallized with titanium (Ti), gold (Au), and platinum (Pt) and insulated with silicone. The recording/stimulation zone consists of approximately 1 mm non-insulated portion of the metallized fiber. At the bottom panel, micrograph of the recording/stimulating zone of a LIFE made from metallized Kevlar fiber. In the center is the recording/stimulating region where platinum black has been deposited *(from Lawrence et al., 2003; McNaughton and Horch, 1996, with permission)*.

The LIFEs offer good selectivity for stimulation *(Nannini and Horch, 1991; Yoshida and Horch, 1993)* and for multiunit extracellular recording *(Goodall et al., 1991; McNaughton and Horch, 1994; Yoshida and Stein, 1999)*, and their geometry, make them suitable for long-term implantations *(Lefurge et al., 1991)*. These properties make LIFEs useful for application in FES systems and also in basic studies of neural coding and control. Activity arising from cutaneous receptors in response to stimuli has been recorded in several studies, although activity was found to be small and difficult to distinguish from the background noise in the recording *(Malmstrom et al., 1998; Yoshida et al., 2000)*. Intrafascicular electrodes were initially developed for use with FES and are currently being tested for long-term safety in animals and efficacy in humans. LIFEs have been implanted in severed nerves proximally to the stump of eight subjects with limb amputation *(Dhillon et al., 2004)*. Electrophysiological tests conducted for 2 consecutive days after the surgery indicated that it was possible to record volitional motor nerve activity associated with missing limb movements. Electrical stimulation through the implanted electrodes elicited graded sensations of touch, joint movement, and position, referring to the missing limb. This suggested that peripheral nerve interfaces could be used to provide amputees with prosthetic limbs that have more natural feel and control than is possible with current myoelectric and body-powered prostheses. While the selectivity of the LIFE is excellent, it is challenging to implant a few of these electrodes in different fascicles and therefore selectively stimulate fiber bundles to the appropriate muscle groups.

Penetrating microelectrodes

Microneurography has widely been used in humans as one of the low invasive methods for the measurement of multiunit peripheral nerve activity and has become an invaluable tool for investigating somatosensory, motor and autonomic physiology and pathophysiology *(Vallbo et al., 1979; Hagbarth, 1993; 2002)*. Usually, a tungsten microelectrode is inserted percutaneously into fascicles of limb and facial peripheral nerves of conscious human subjects to monitor activities of afferent or efferent nerve fibers. Unitary recordings of practically all types of nerve fibers have been studied and reported. Despite the production of microlesions caused by the electrode insertion into the nerve, the morbidity with the procedure is acceptably low *(Gandevia and Hales, 1997)*. Microstimulation through the electrode can be used to activate single axons, although in most cases stimulation affects small groups of axons in the fascicle *(Ochoa and Torebjörk, 1983; Torebjörk et al., 1987)*. An interesting study used a microelectrode to stimulate the sensory nerve of an operator to indicate contact with an object by a remote robotic hand *(Shimojo et al., 2003)*. However, the use of multiple wire needles for interfacing a high number of nerve fibers has practical problems for long-term use.

In acute experiments, multiple-wire-microelectrode arrays were inserted into rat nerves to investigate selective stimulation of motor units *(Smit et al., 1999)*. Although involving a more invasive insertion procedure, electrode arrays provided neural contacts with low-force recruitment properties similar to those of single wires. Array results revealed partial blocking of neural conduction, similar to that reported with microneurographic insertion with single needles. The arrays were capable of evoking threshold forces selectively with high efficiency. Motor recruitment was found more stable with stimulation by intrafascicular multielectrodes than by extraneural electrodes. Especially for intrafascicular electrodes, no strict inverse recruitment was observed *(Veltink et al., 1989)*.

Multielectrodes that carry a variable number of electrode sites mounted on a needle or incorporated in glass, silicon, or polyimide carriers have been developed in 1D, 2D, or 3D arrays (Fig. 11). Different design approaches and fabrication techniques including precision mechanics and micromachining techniques have been introduced for multiunit electrodes *(Drake et al., 1988; Ehrfeld and Munchmeyer, 1991; Norman et al., 1998; Yoon et al., 2000; Stieglitz and Gross, 2002; Takeuchi et al., 2004)*, and some can be supplied with onboard microelectronics. Although primarily designed and used as CNS interfaces, some have also been tested as PNS interfaces. Because implanting such devices is associated with potential damage to the nervous tissue, especially if the substrate is stiff, efforts have been directed at miniaturizing the penetrating portion, developing insertion devices, and using flexible substrates.

Silicon-based shaft microprobes have been produced for years at the Center for Integrated Sensors and Circuits of the University of Michigan, leading to a large number of single-shaft, multishaft, or 3D stacked multishafts *(Drake et al., 1988; Hetke et al., 1994; Hoogerwerf and Wise, 1994; Kim and Wise, 1996; Kipke et al., 2003)*. These probes are fabricated using advanced microfabrication techniques also employed in the semiconductor industry. The substrate is either needle- or wedge-shaped to allow penetration in the nervous tissue. Thus, recording or stimulation affects axons not only at surface locations but also at defined depths where active sites are placed in the electrode. Shaft electrodes allow great flexibility in their application in acute experiments but are not easy to use in long-term experiments and are difficult to insert in peripheral nerves. A silicon-based ribbon electrode with high flexibility demonstrated successful function after chronic implantation of up to 1 year *(Hetke et al., 1994)*, but this interconnect cable was not designed for implants in the highly mobile somatic peripheral nerve and was too stiff and brittle for intrafascicular application *(Najafi and Hetke, 1990)*. Multichannel silicon microelectrodes were implanted in several acute and chronic preparations within the cochlear nerve of animals for auditory stimulation. They induced stimulation with thresholds substantially lower than with scala tympani electrodes and with a high degree of specificity *(Arts et al., 2003)*. Nevertheless, the loss of neurons in spiral ganglion and cochlear nucleus was found, thought to be due to difficulty with electrode insertion and chronic motion of the implants. Silicon probes with multiple electrode sites have been recently tested for microstimulation of the sacral spinal cord for bladder contraction *(McCreery et al., 2004)*. Highly flexible polyimide-based devices have been developed for interfacing peripheral nerves *(González and Rodríguez, 1997; Stieglitz and Meyer, 1997)*, but they have not been fully tested for intrafascicular nerve recording and stimulation.

Separate research groups from the University of Utah and the University of Twente fabricated multielectrode arrays (MEAs) with 100 or more needle-shaped electrodes in silicon or silicon-glass technology for neural applications. Most of the long experience with MEAs involves their use as cortical interface *(Nordhausen et al., 1996)*. Silicon-glass technology has been used to produce 3D arrays of 128 electrodes with varying height from 250 to 600 μm *(Rutten et al., 1995; 1999)*. In a series of experimental and modeling studies, Rutten and colleagues concluded that an electrode separation of 120 μm was optimal for selective interfacing peripheral nerves, such as the rat peroneal

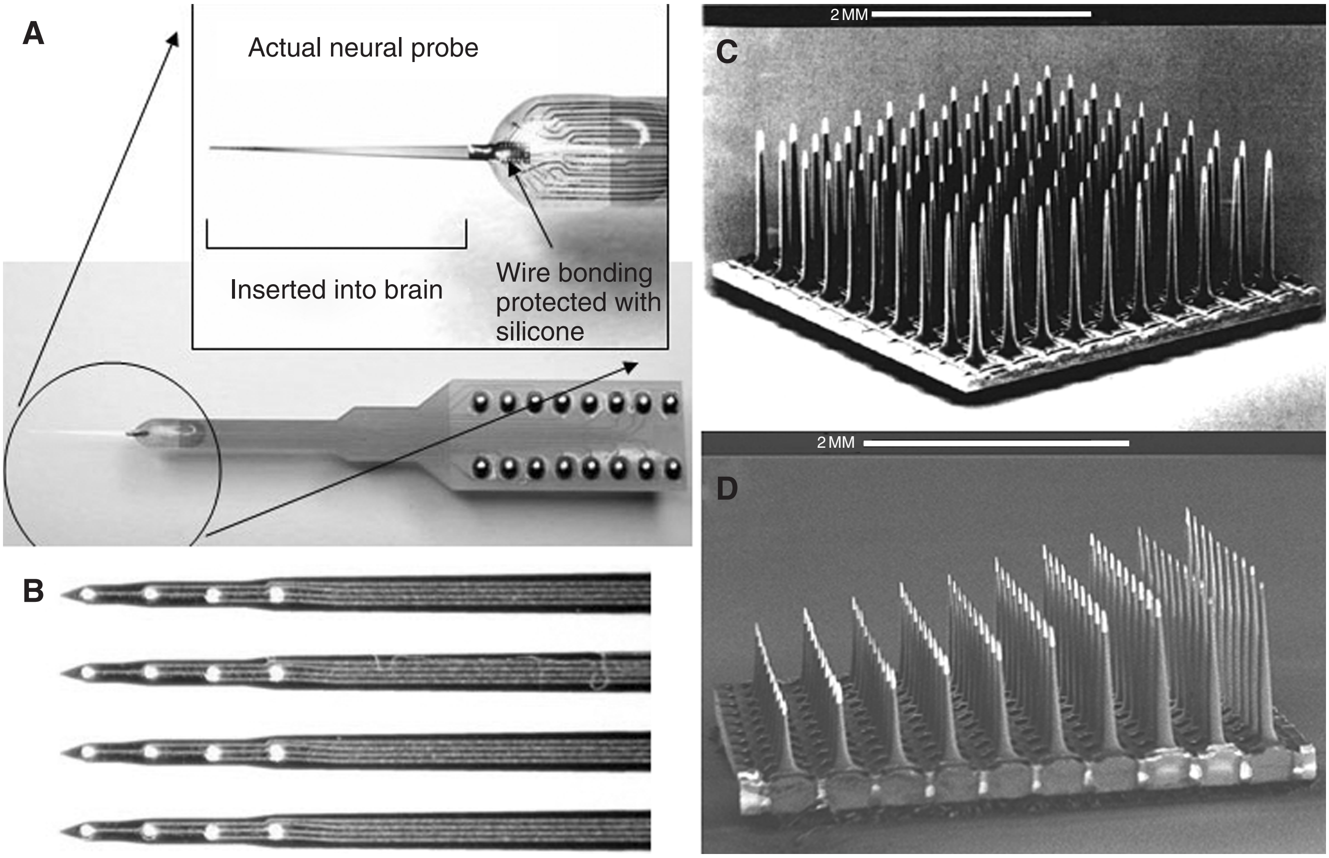

Figure 11. Penetrating electrodes developed at the University of Michigan (left) (from Neuronexus Inc.) and at the University of Utah (right) *(from Aoyagi et al., 2003; Branner et al., 2001, with permission)*.

containing around 350 alphamotor fibers *(Rutten, 2002)*. Thus, a trade-off must be made between selectivity of stimulation and the total number of nerve fibers that can be activated; optimal selectivity requires the use of redundant electrodes in the 3D configuration *(Rutten et al., 1999)*.

Intraneural Utah MEAs made of silicon with 25 and 100 individual needle electrodes have been inserted into a peripheral nerve in experimental animals using a pneumatic insertion device without significantly disturbing nerve function. To decrease the number of redundant electrodes and provide access to more fascicles within the nerve, a slanted array with electrodes of varying length, ranging from 0.5 to 1.5 mm with 0.1 mm difference in length between rows of neighboring electrodes, has been developed *(Branner et al., 2001)*. Electrodes in the array were capable of selectively recording single-unit responses from mechanoreceptors, although only in 10–20% of the electrodes, and evoked graded recruitment of force in muscle groups in a highly selective fashion with current injections in the 1–20 μA range *(Branner and Norman, 2000; Branner et al., 2001)*. Recruitment curves for the electrode array were broader with twitch thresholds starting at much lower currents than usual for cuff electrodes. Both the recording and stimulation were stable over the 36-h-long period of the experiments. However, the rigid structure of such electrodes and the tethering forces produced by the lead wires may induce problems when applied to limb nerves. Electrodes without and with lead wires were implanted for up to 7 months in cat sciatic nerves *(Branner et al., 2004)*. The surgical technique highly affected the long-term results. The stimulation properties stabilized in 80% of the electrodes over the course of the experiment, but the recorded sensory signals were not stable over time. A histological analysis indicated that the morphology and fiber density of the nerve around the electrodes were normal. The Utah MEA is also capable of recording more effectively from more dorsal root ganglion neurons than has been achieved by conventional recording techniques, providing a more stable option for chronic implantation *(Aoyagi et al., 2003)*. A case report on a healthy volunteer who had a MEA implanted in the median nerve for 3 months gives support to the potential of such devices for bidirectional interfacing the PNS *(Warwick et al., 2003)*. The subject received feedback information from force and slip sensors in a prosthetic hand and subsequently used the array to control the hand for grasping an unseen object. One negative aspect was the gradual degradation of the electrode wire bundle.

Regenerative electrodes

Regenerative electrodes are designed to interface a high number of nerve fibers by using an array of holes, with electrodes built around them, implanted between the severed stumps of a peripheral nerve *(Llinás et al., 1973; Edell, 1986; Kovacs et al., 1992; Dario et al., 1998)*. Regenerating axons eventually grow through the holes (Fig. 12), making it possible to record action potentials from and to stimulate individual axons or small fascicles. Applicability of regenerative electrodes is dependent on the success of axonal regeneration through the perforations or holes, the possibility of nerve damage from the mechanical load imposed by the electrode or from constrictive forces within the holes, and the biocompatibility of the components *(Rosen et al., 1990; Navarro et al., 1996)*.

Different techniques and materials have been used during the last 30 years in the construction of regenerative electrodes. Early electrodes were made from non-semiconductor materials by mechanically drilling holes into epoxy modules *(Mannard et al., 1974)*. With the advent of microelectronic technologies, it became possible to construct silicon electrodes with smaller dimensions and higher number of holes (Fig. 13) *(Akin et al., 1994; Kovacs et al., 1994; Navarro et al., 1996; Wallman et al., 2001)*. Using multiple-hole silicon arrays, the researchers demonstrated axonal regeneration and even neural activity recording was demonstrated in peripheral nerves of rat, frog, and fish *(Kovacs et al., 1994; Navarro et al., 1996; Bradley et al., 1997; Della Santina et al., 1997; Mensinger et al., 2000)*. However, such silicon interfaces cause frequent signs of axonopathy and constitute a physical barrier that limits the elongation of regenerating axons depending on the size of the holes *(Edell, 1986; Rosen et al., 1990; Navarro et al., 1996; Zhao et al., 1997)*. Ideally a one-to-one design would allow access to each individual regenerated axon grown through one hole (2–10 μm in diameter). However, this has been proved impossible; nerve regeneration fails with holes of such small size. An equilibrium should be considered between the number of holes in the dice and their diameter in the range of 40–65 μm. More adaptive polyimide-based electrodes were introduced more recently *(Stieglitz et al., 1997; Navarro et al., 1998)*. Polyimide can be micromachined in various designs suitable for implantation (Fig. 14). Polyimide-based electrodes have been shown to be biocompatible and stable over months of *in vivo* implantation and allow for much better regeneration than silicon dice *(Navarro et al., 1998; Ceballos et al., 2002; Lago et al., 2005)*. The presence of a polyimide-based regenerative electrode showed no chronic foreign body response, and the immunohistochemically measured pattern of characteristic proteins was comparable with a healing reaction without any implant *(Klinge et al., 2001a)*. Modifications of the structure have been suggested including an increase in the diameter of holes and enlarging the total open area within the sieve electrode in order to facilitate regeneration of a larger number of axons and to reduce potential chronic damage to regenerated axons. In parallel with technological advances, neurobiological strategies need to be investigated and applied to enhance regeneration of motor axons and to rescue regenerated axons from compressive forces *(Negredo et al., 2004; Lago et al., 2005)*. No human implants of regenerative electrodes have been reported.

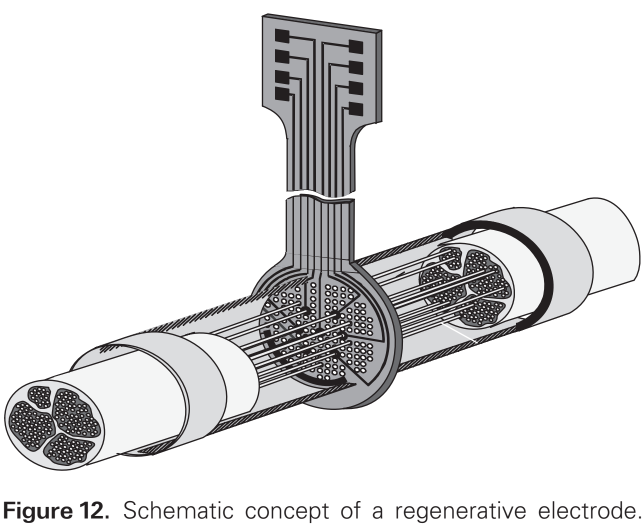

Figure 12. Schematic concept of a regenerative electrode. Nerve fibers of a sectioned nerve grow through the holes of the electrode encased in a guidance tube.

One of the most logical and challenging applications of regenerative electrodes consists of their implantation in severed nerves of an amputee's limb for bidirectional interface in a feedback-controlled neuroprosthesis. On the one hand, recording of neural efferent signals can be used for the motion control of a mechanical prosthesis *(Edell, 1986)*, and on the other hand, sensory feedback from tactile and force sensors might be provided to the user through stimulation of afferent nerve fibers within the residual limb *(Riso, 1999)*. Unfortunately, multichannel regenerative electrodes can be applied only to transected nerves and some time is needed for interfacing the regenerated axons, thus precluding acute experiments. From chronically implanted regenerative electrodes, it has

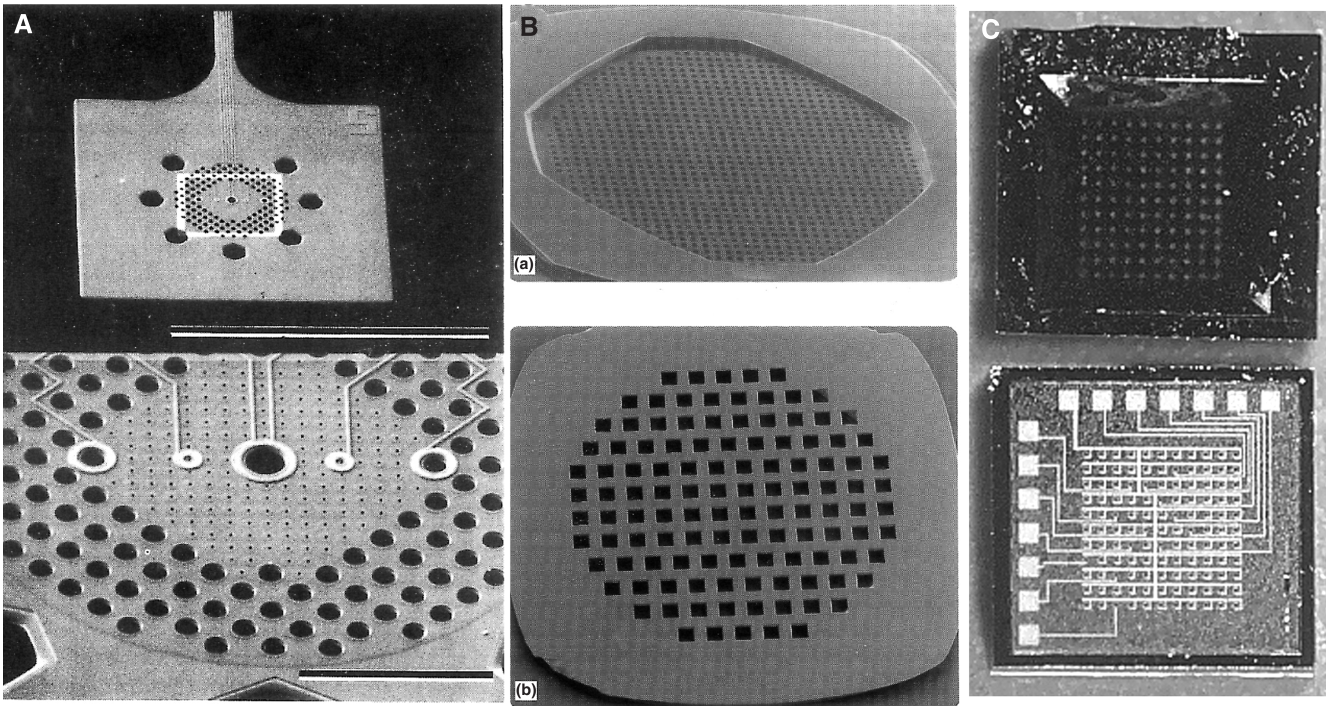

Figure 13. Examples of regenerative sieve electrodes made on silicon developed at the University of Michigan (A) *(from Akin et al., 1994, with permission)*, the University of Lund (B) *(from Wallman et al., 2001, with permission)*, and the Microelectronics National Center (C) (CNM, Barcelona).

been possible to stimulate different nerve bundles and to record nerve action potentials in response to functional stimulation *(Navarro et al., 1998; Ceballos et al., 2002)*, although technical difficulties have to be taken into account. The limits on the amplitude and discriminability of single-unit action potentials recordable from nerve fibers inside tubular electrodes *(Loeb et al., 1977)* may also apply to regenerative electrodes, thus decreasing the actual amplitude of recorded signals. The fact that the electrodes are placed around instead of parallel to the nerve fibers, the size and length of each electrode hole, and the smaller than

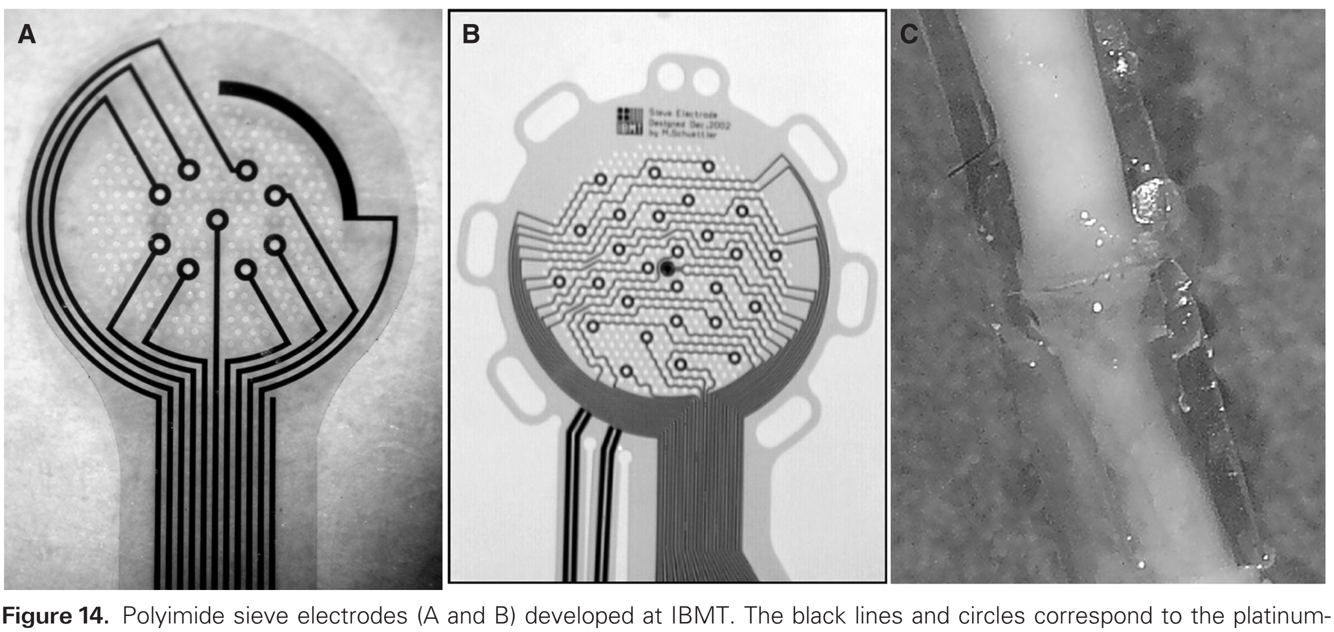

Figure 14. Polyimide sieve electrodes (A and B) developed at IBMT. The black lines and circles correspond to the platinum-deposited contact electrodes. Micrograph of a regenerated nerve through a polyimide sieve electrode (C).

normal diameter and internodal length of regenerated fibers should be considered in further studies.

A more simple alternative procedure for the extraction of information from lesioned nerves for use in the control of prosthetic devices has been described. Amplified motor signals can be obtained from lesioned nerves by allowing them to innervate isolated slips of host muscle, from which EMG signals can be recorded by wire electrodes *(Wells et al., 2001)*. Further work is required to determine the long-term stability of the interface with respect to innervation by the foreign nerve, signal characteristics, and the fidelity of the signals to reflect the motor activity of muscles originally denervated. This method has been applied in a patient with upper arm amputation in whom residual brachial plexus nerves were anastomosed to pectoralis muscles. The few reformed motor units allowed for the simultaneous control of two degrees of freedom with a myoelectric prosthesis *(Kuiken et al., 2004)*.

Technological Issues

Materials for the electrodes

The stability of the materials in the electrode is crucial because, once implanted, it should remain within the body of the patient for many years. Thus, the electrode has to be resistant to corrosion during stimulation and to the attack of biological fluids, enzymes, and macrophages produced during the initial foreign body reaction. It has to be composed of inert materials, both passively and when subjected to electrical stimulation because deterioration of the device may result in implant failure and the release of toxic products. Materials typically used are platinum, iridium, tungsten, and stainless steel as conductors and silicone elastomer, polytetrafluoroethylene, and polyimide as insulating carriers *(Naples et al., 1990; Heiduschka and Thanos, 1998)*. Important requirements for the electrode materials include minimal energy consumption during stimulation, stable electrochemical characteristics, good phase boundary behavior for polarization and afterpotentials, adjustable and stable impedance and frequency response, and stability against artifacts and noises *(Stieglitz and Meyer, 1997)*.

Materials for substrates, insulation, and encapsulation

Silicon and flexible polymers such as polyimide are the most widespread substrate materials in micromachining and are the materials of choice in precision mechanics. Because the silicon- and polyimide-based interfaces are founded on micromachining techniques, they have an advantage over hand-made electrodes in that one has the ability to modify designs with high precision (fast prototyping) and can assert precise control over active zone size and repeatability. For silicon to obtain any degree of flexibility, the dimensions must be reduced to such a degree that the final product is mechanically fragile. Process technology to do this in combination with integration of electrodes and conductive paths requires several process steps *(Najafi et al., 1985)*. The fabrication of silicon-based interconnection cables was shown to be technologically feasible *(Hetke et al., 1990; 1994)*, but cost, technology, and limited cable length limit widespread use in neural prostheses applications. One advantage of silicon-based microdevices is the ability of monolithic integration of electronic circuits for recording and signal processing *(Najafi and Wise, 1986; Ji et al., 1990)*. The passivation and packaging of silicon-based devices should be carefully considered to ensure long-term stable behavior of electrodes with integrated electronic devices. If parts of standard electronic processes were directly transferred for implant passivation, degradation during implantation deteriorated not only the insulation layer but also functional integrated structures within 1 year *(Haemmerle et al., 2002)*. Other process steps that used chemical vapor deposition also showed that materials such as silicon nitride and silicon oxide are not stable as monolayers in a physiologic environment *(Connolly et al., 1992; Edell et al., 1993)*. Better stability was achieved with multilayers *(Cogan et al., 1993; Vogt and Hauptmann, 1995)*.

Polyimide-based neural implants *(Stieglitz et al., 2000)* showed good biocompatibility *(Haggerty and Lusted, 1989; Richardson et al., 1993)* with respect to toxicity as well as biostability *(Navarro et al., 1998; Rodríguez et al., 2000)* when used as cuff and regenerative-type electrodes. Silicone elastomer is still the material of choice for encapsulation of cables and also as additional coating for hermetically sealed electronic circuits *(Stieglitz et al., 2004)*.

Choice of fabrication technology

Most of the neural implants in clinical practice that have obtained FDA approval or CE mark have been made by means of precision mechanics. The long experience over decades with helically wound cables, standardized plugs, titanium and ceramic housings for microelectronic components, and the use of medically approved materials such as special silicone elastomers allows the combination of materials in implants reducing time- and cost-intensive evaluation procedures. Because a new application of a neural interface or implant is a long procedure, many new implants rely on the experience from pacemaker and neuromodulation experience *(Rijkhoff, 2004)* and combine established components and materials for new products, for example, Neurodan Inc. uses silicone rubber-based cuff electrodes and a ceramic housing for a new implantable foot-drop system. The devices are robust, stable, and reliable but suffer from a low spatial resolution and low selectivity of the electrodes as well as from a quite large size.

If anatomy limits size, and a high number of electrodes seems to be mandatory for adequate performance, for example, for vision prostheses that stimulate the retina with an implant in the eye *(Meyer, 2002)*, microsystem technology has to be chosen. Flexible substrate and electronic circuits can be assembled to flexible implants. Polymer coatings with parylene C as insulation material and silicone elastomer as encapsulation are under investigation *(Schneider and Stieglitz, 2004; Stieglitz, 2004)*. Even though first chronic results from pilot experiments showed that these combination layers were stable over more than 1 year *in vivo* *(Stieglitz et al., 2003)*, significant numbers of devices in long-term tests have to be assessed before microsystems will gain a remarkable segment of implantable peripheral nerve interfaces in clinical applications.

Bioelectronic interfaces

Apart from the neuro-technical interfaces, some approaches combined cells and technical devices a priori and tried to establish a more biologically inspired interface to the nervous system *(Thomas et al., 1972)*. These approaches are called bioelectronic or biohybrid interfaces. Many basic research investigations have been carried out to couple single-nerve cells or nerve cell networks to technical recording equipment via electrodes or electronic components. A manifold of micromachined neuron probes is described *(Rutten, 2002)*. The structure's topology (e.g., the width of grooves) has an important impact on the growth of the cultured cells *(Wilkinson et al., 1987; Clark et al., 1990; Connolly et al., 1992)*. Fromherz *et al.* *(1991b)* could demonstrate the guided growth of nerve cells from leeches on a laminin-coated substrate. In further experiments, they obtained a current-free measurement of the membrane potential of a single neuron of a leech by direct coupling to the gate of a field effect transistor (FET) *(Fromherz et al., 1991a)*. A multielectrode array for a network of cultured neurons will be possible using an array of FETs. Usually metallic electrodes are used for bidirectional information exchange with nerve cell cultures for recording and stimulation. The activity of embryonic spinal cord cells of mice has been recorded simultaneously over a period of several months on a planar glass substrate with 64 iridium tin oxide electrodes *(Droge et al., 1986)*. Autonomous signals, generated from the cultured neural networks without forcing them in predefined surface topologies, could also be examined *(Gross and Kowalski, 1991)* and used for qualitative and quantitative drug detection. Having surface topologies on the substrate, axonal outgrowth of embryonic nerve cells from rats was observed and electrical activity was recorded in a microstructure with 16 electrodes that were connected with grooves *(Jimbo and Kawana, 1992; Jimbo et al., 1993)*.

If implantation of cells in microstructures should be successful, the migration of the host cells out of the technical device must be prevented. In some investigations, silicon micromachining was used to create wells with gold electrodes on the bottom and a grillwork at the top *(Tatic-Lucic et al., 1993)*, and the cells were seeded into the wells. The grillwork prevented the neurons from migration. Pine *et al.* *(1994)* managed to place single hippocampus cells of the rat into a 3D silicon structure, which was termed 'cultured neuron probe.' They could demonstrate that the transplanted cells inside the microcompartments retained their capacity for axonal outgrowth and that nerve action potentials could be directly recorded extracellularly from the soma of the cells. However, the transfer of the cultured cells from the *in vitro* environment into the brain remained difficult. Another bioelectronic interface was introduced as 'cone electrode' *(Kennedy, 1989)*. Here, a piece of a rat sciatic nerve was placed into a cone of 1.5 mm length and 100–200 μm diameter. After implantation in the brain of a rat, neurite ingrowth was observed and stable recordings were obtained over 6 months. Neither approach has been investigated in the PNS.

In the PNS, bioelectronic interfaces are in an early and experimental stage. A traumatic lesion of a peripheral nerve leads to Wallerian degeneration of the distal nerve, and healing of such a lesion occurs only under favorable conditions involving sprouting of axons from the proximal nerve stump, outgrowth along the distal nerve stump, and reinnervation of target tissues. Recovery is usually delayed and limited if the lesion site is very proximal. As a consequence, muscle atrophy prevents the formation of new neuromuscular junctions at a later time point when regenerating nerve fibers may reach the muscle. To study the problem, researchers have developed an animal model for a biohybrid approach to cure flaccid paralysis that involves embryonic spinal cord cell transplantation into a container adapted to the distal nerve stump to restore skeletal muscle function *(Katsuki et al., 1997; Thomas et al., 2000; Klinge et al., 2001b)*. The container consisted of a 10-mm-long piece of autologous femoral vein *(Katsuki et al., 1997)* that was sutured on one side to the distal nerve stump and closed with sutures on the other side. Reinnervation of the gastrocnemius and tibialis muscles via the distal stump of the sciatic nerve was observed after a few weeks, although there was no communication with the CNS. A regenerative electrode was introduced as a bioelectronic interface *(Stieglitz et al., 2002)* between the sprouting embryonic neurons and the peripheral nerve to allow neural stimulation for controlled muscle excitation to prevent atrophy and restore some function. Instead of a vein, a technical compartment has also been implanted that contained purified motoneuronal embryonic cells. Functional regeneration was proven but the number of surviving cells tremendously decreased from the 10,000 that had been injected to some tens that finally innervated the muscle *(T. Stieglitz, 2004. The neuron micro probe project, personal communication)*. Further basic investigations are necessary to obtain long-term survival of the transplanted cells. Finally, the issue of using cells should be scientifically and ethically addressed at a very early point of time to develop strategies to transfer results from animal experiments into human patients.

Control of Neuroprostheses and Hybrid Bionic Systems Using PNS Interfaces

Bioelectrical signals recorded by means of interfaces are amplified, filtered, and fed into a signal processing unit for prosthesis control. The different approaches to use information recorded from PNS interfaces that control neuroprostheses and hybrid bionic systems are briefly summarized in this section.

EMG-based control of neuroprostheses and hybrid bionic systems

EMG signals recorded using surface electrodes (often named as sEMG) are considered an important source of information to allow human beings to control robotic prostheses. sEMG signals are easy to record and provide an important access to the neuromuscular system of the user. In the recent past, several architectures have been developed and tested to control different robotic platforms: artificial prostheses aimed at substituting parts of the body (e.g., hands or upper extremities); exoskeletons aimed at augmenting or restoring reduced human capabilities; tele-operated robots able to carry out tasks in environments where the access of human beings is not possible.

It is important to point out that for the implementation of an EMG-based control algorithm, the second and third types of application are very similar if the remotely controlled robotic device presents a human-like structure (typically the upper extremity). In fact, in both these cases, the different joints of the prosthesis can be controlled by the 'homologous' muscles (e.g., the extension of the wrist by using the extensor carpi radialis or ulnaris muscles). On the contrary, the control of prostheses (or the tele-operation of not-human-like robots) is complicated by the need for coding the different actions of the robot. For example, the extension of the fingers of a prosthetic hand must be coded using different muscular activities such as the ones of upper arm or forearm. Similarly, residual EMG signals recorded from a paretic muscle can be used for the control of stimulation of the same muscle or of a different muscle in FES systems. For these reasons, in this section the different architectures for EMG-based control are divided into two main classes: (1) control of non-homologous muscles and (2) control of homologous muscles. One case study is presented for each class: EMG-based control of hand prostheses and EMG-based control of exoskeletons.

EMG-based control of hand prostheses

In this case, it is usually not possible to use the 'homologous' muscles to control the movements of the prosthetic device, and the development of a complex algorithm exploiting the potentialities of using advanced pattern recognition techniques is required. In many cases, the formal scheme for the acquisition and analysis of EMG signals for the control of prosthetic devices is composed of several modules *(Zecca et al., 2002)*: (1) signal conditioning, pre-processing, and detection of onset movement *(Micera et al., 1999)*; (2) feature extraction; (3) dimensionality reduction; (4) pattern recognition; and (5) off-line and on-line learning.

Because of this pattern recognition procedure, it is important to identify the correct onset of the movement in order to extract significant features from the sEMG signals. Due to the stochastic characteristics of the sEMG, the onset detection is a challenging task, especially when the response is weak. Several methods and algorithms have been proposed in the literature, but little is known about their reliability and accuracy. The generalized likelihood ratio (GLR) method seems to be more robust than other methods especially when muscle activity is weak *(Micera et al., 2001b)*.

Several approaches have been used to extract meaningful features from the EMG. From the first works by Graupe and colleagues *(Graupe and Cline, 1975; 1982; Graupe et al., 1982)*, the EMG signal was modeled as the amplitude-modulated Gaussian noise whose variance is related to the force developed by the muscle. As a consequence, most commercial EMG-based algorithms used in prosthetic control are based only on one dimension of the EMG signal, the variance or mean absolute value. However, the parameters that can be extracted using this global steady-state approach (e.g., variance, mean absolute value, Fourier spectrum, and median frequency) are often not sufficient to distinguish between more than two classes of movement. Later investigations showed that useful information can be found in the transient burst of myoelectric signal *(Hudgins et al., 1993)* immediately after the onset of contraction and that transient EMG signals have a greater classification capacity than steady-state signals. Several features can be extracted in both time and frequency domains *(Zardoshti-Kermani et al., 1995; Englehart, 1998; Pattichis and Pattichis, 1999; Sparto et al., 2000)* that increase the possibility of controlling more than two degrees of freedom of the prosthesis when used in combination with advanced classification algorithms *(Kelly et al., 1990; Christodoulou and Pattichis, 1999; Micera et al., 1999; Han et al., 2000; Santa-Cruz et al., 2000)* and on-line learning techniques *(Nishikawa et al., 1999; 2000)*.

However, by using this approach, the user must initiate all the contractions to control the prosthesis from rest, making it difficult to switch from one class to another and increasing the response time of the user when dealing with unexpected situations. To avoid these problems, recent research tried to implement a continuous classifier able to quickly switch from one state (i.e., hand task) to another *(Englehart and Hudgins, 2003; Carrozza et al., 2004)*. This approach seems promising for the development of EMG-based controlled hand prostheses although the use of EMG signals seems to be limited to prosthesis with a few degrees of freedom (probably no more than four). A possible solution to overcome the limits of the EMG-based approach is to implement interfaces between the PNS and the artificial device to record and stimulate peripheral nerves in a selective manner.

EMG-based control of exoskeletons

The sEMG signals have been also used in the recent past for the control of upper and lower extremity exoskeletons. In this application, sEMG signals are used to determine the force/torque to be produced by the actuators moving the different joints. This means that, for example, the sEMG signals recorded from (some of) the flexor/extensor muscles of the wrist are used to control the actuator moving the artificial wrist joint. This approach is supported by biomechanical studies *(Hof, 1997; Onishi et al., 2000)* showing that under isometric contractions the relationship between force and EMG can be considered linear. However, the use of EMG for this purpose under dynamic conditions (as in the case of exoskeleton control) presents several problems because of muscle dynamics and possible prostheses *(Rainoldi et al., 2000)*. Different complex algorithms have been developed to extract force/torque information from sEMG signals that address these limitations, although in some cases good results have been achieved using a simple proportional control law *(Gordon and Ferris, 2004)*. Two main types of strategies have been implemented: (1) soft-computing algorithms such as neural networks or fuzzy systems and (2) biomechanical models.

In the first case, a neuro-fuzzy network was used to predict torque information from the sEMG of upper extremity muscles and from the kinematic trajectories of the different joints to control a shoulder exoskeleton *(Kiguchi et al., 2001; 2003)* (Fig. 15). The initial fuzzy if-then control rules of the architecture were designed based on the analysis of biomechanics and motor control strategies implemented by different subjects during preliminary experiments. Moreover, an on-line learning algorithm was developed to deal with the change of the physiological conditions of the human subject (e.g., because of muscular fatigue) in order to minimize the amount of muscle activity and motion error. Using this approach, it was possible to control the different degrees of freedom of the shoulder reducing the muscular effort of the subjects.

Another possibility of extracting force/torque information from the sEMG signals is to develop biomechanical models starting from results achieved in neurophysiology and motor control *(Zajac, 1989; Krylow et al., 1995)*. Rosen et al. *(2001)* developed a 'myoprocessor' based on the Hill model of muscular activation to extract force/torque information from muscle information. Using this schemea one-degree-of-freedom exoskeleton has been controlled using a multiple-feedback approach: (1) dynamic feedback – the moments generated at the interfaces between the human arm, the external load, and the exoskeleton structure; (2) kinematic feedback – the joint angular trajectories recorded using encoders, and the angular velocity and acceleration calculated by finite differences; and (3) physiological feedback – the operator used his/her natural sensors (vision, proprioceptors, and joint receptors). Experimental tests have shown that the use of sEMG significantly improved the mechanical gain of the system (i.e., the possibility of augmenting capabilities and/or reducing human muscular efforts to carry out the different tasks) while maintaining natural control of the system.

Although sEMG signals have been used so far with very promising results in controlling exoskeletons, many different issues have to be addressed to develop effective hybrid systems to be used for the restoration of human handicaps. These issues include the possibility of simultaneous control in real time of several degrees of freedom, the possibility of developing

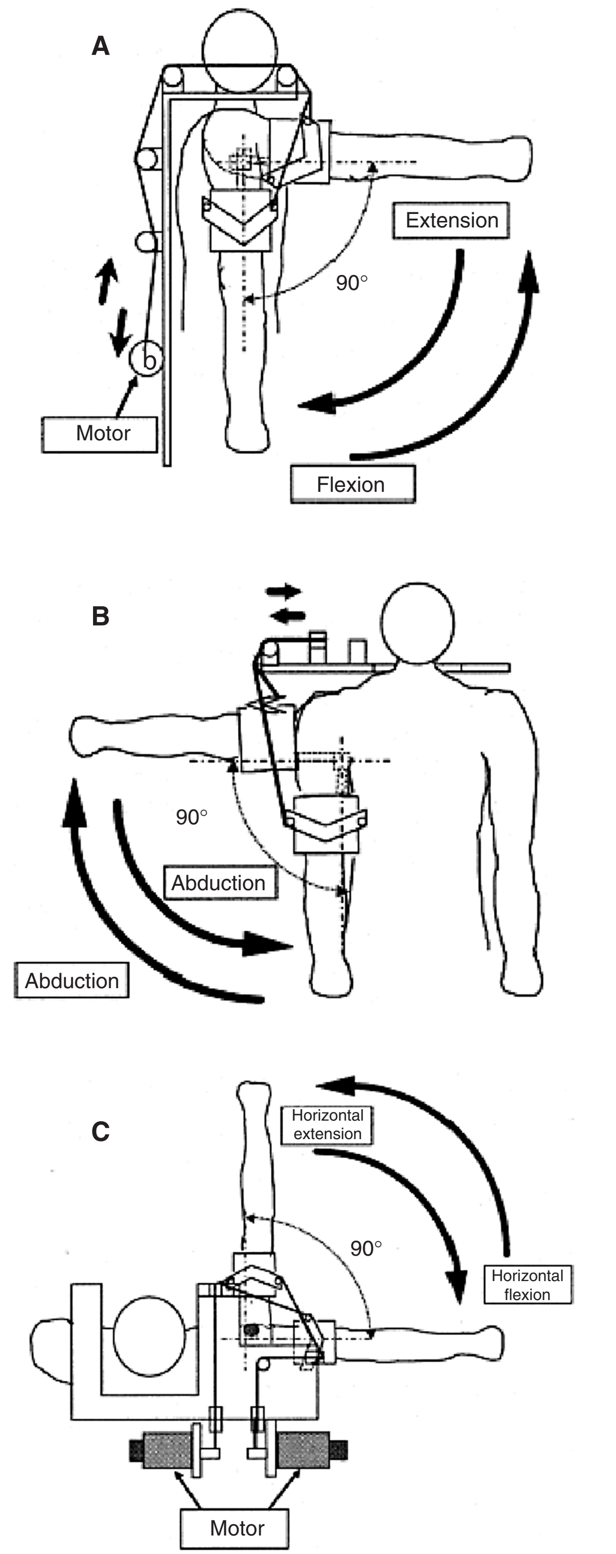

Figure 15. Scheme of an exoskeleton for the different degrees of freedom *(from Kiguchi et al., 2003, with permission).*

effective control algorithms avoiding to increase the computational load reducing the efficacy while facing the previous issue, and the possibility of modifying in real time the parameters of the algorithms in order to address different situations (e.g., muscular fatigue).

ENG-based control of neuroprostheses and hybrid bionic systems

The signals recorded using different neural interfaces have been used in the past to extract useful sensory information to improve the performance of FES systems. In fact, the non-linear and time-variant characteristics of the neuromuscular system ask for the use of closed-loop control algorithms to develop effective and usable systems that require feedback information about the executing motor task. Despite the promising results that have been achieved using artificial sensors *(Castro and Cliquet, 2000; Carpaneto et al., 2003; Cavallaro et al., 2005)*, the extraction of information from natural sensors in the body by processing afferent nerve signals is very challenging *(Johnson et al., 1995)*.

In most instances, ENG signals are used to detect an event such as slippage during grasping or heel contact. In these applications, ENG signals are band-pass filtered, rectified, and bin-integrated. This new signal is then compared with a threshold in order to detect a particular event. For example, for hand grasp neural prosthesis, a cuff placed around the palmar digital nerve recorded the activity from mechanoreceptors when a grasped object was slipping to regulate the force of grasping *(Haugland and Hoffer, 1994; Haugland et al., 1994; Inmann and Haugland, 2004)*. In other cases, such as heel contact with the floor detected from a cuff electrode on the sural nerve, more advanced statistical techniques are used to improve the detection performance *(Upshaw and Sinkjaer, 1998)*.

Similarly, ENG signals recorded from muscle spindles have been used in animal models to extract kinematic trajectories. Recorded ENG signals using cuff electrodes allowed the prediction of ankle movements in an animal model *(Micera et al., 2001a; Jensen et al., 2002; Cavallaro et al., 2003)* with the idea of using this information for the closed-loop control of standing in paraplegic subjects. For this purpose, the ENG, after band-pass filtering, rectification and bin-integration, is further processed by using advanced techniques. Neuro-fuzzy models seem the most adequate because of their model-free structure. Recently developed algorithms using this approach allow the extraction of useful kinematic information mimicking the actual trajectories *(Cavallaro et al., 2003)* (Fig. 16).

Recently, LIFE electrodes have been used to control a hand prosthesis using the ENG signals recorded from peripheral nerves of amputee subjects *(Dhillon et al., 2004)*. The subjects involved in the study were able to control a cursor on a PC screen, indicating that ENG signals can be used to achieve more than a simple

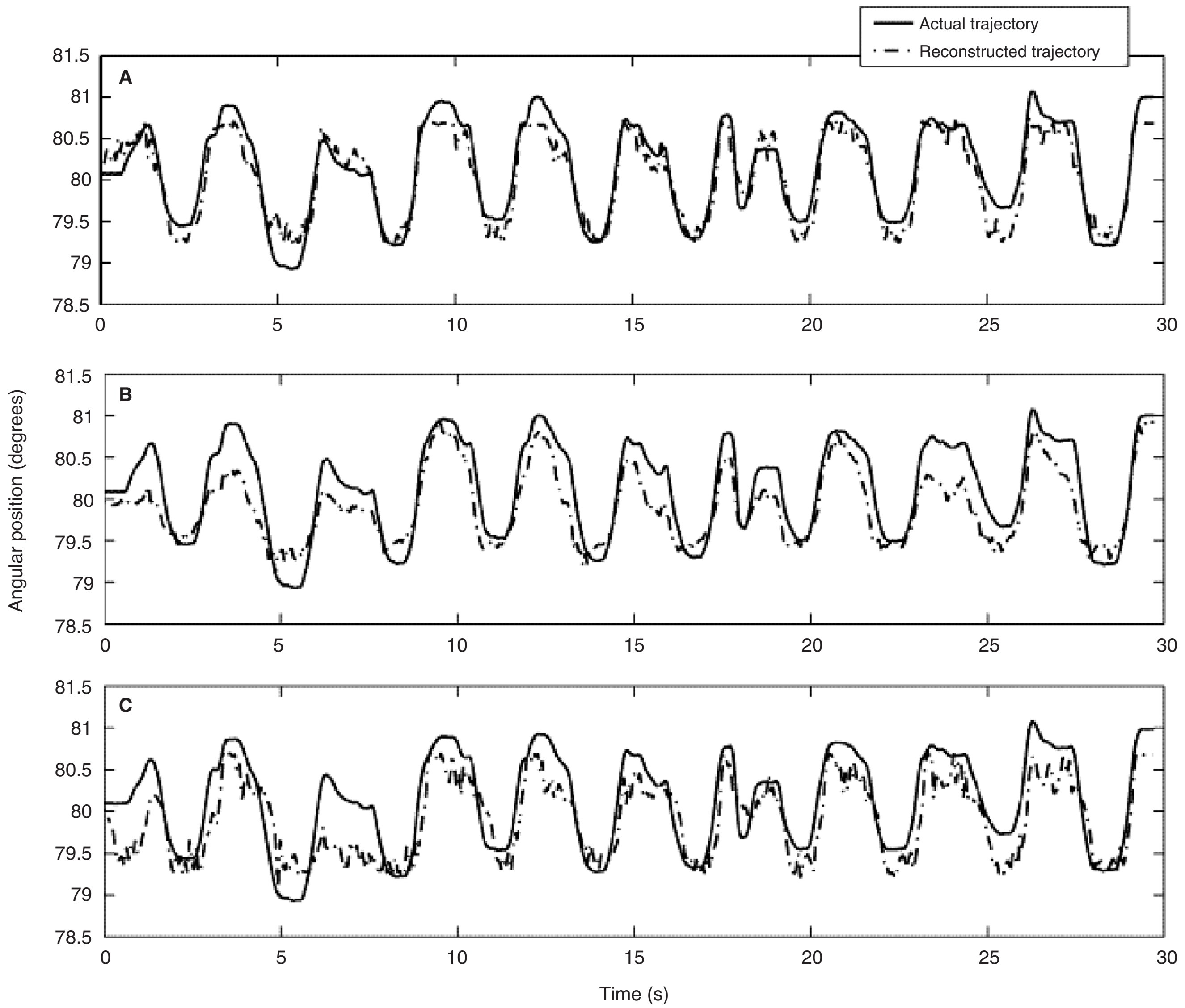

Figure 16. Results with simulated standing movements obtained with a neuro-fuzzy algorithm *(from Cavallaro et al., 2003, with permission)*.

on-off control and that neural signals could solve some of the problems of the EMG-based control of hand prostheses for amputees. In addition, it was possible to elicit adequate sensory feedback to the users by stimulating the afferent nerves through the LIFEs.

Conclusion

There are several approaches in the use of electrodes to establish contact with the PNS and through this interface to promote the use and control of prostheses. At the moment, there is no universal best choice for all possible uses of the described interfaces, which must be used carefully according to the capabilities and specifications of the neuroprosthesis. This review has hopefully provided a concise and critical evaluation of the field on which further advances will be made.

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