# Chapter 4.2

## Peripheral Nerve and Muscle Stimulation

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Abstract
In this chapter we focus on technology to activate electrically peripheral motor nerves. Two important concepts are stressed; 1) the closer the electrode is to the target tissue the easier it is to isolate the applied electric field to a smaller region and 2) the affect of the applied electric field is, generally speaking, always the greatest on the largest myelinated axons experiencing the applied electric field. . These concepts are applicable to other neural systems.

Motor nerves can be activated through electrodes placed on the surface of the skin, on the surface of the muscle, in the muscle, on the motor nerve or in the motor nerve. All electrodes must satisfy the requirements of material compatibility, mechanical compatibility and the ability to transfer the required electrical charges without tissue or material deterioration. The choice of electrode materials and geometric design are determined by these factors and by the intended location on the nerve or muscle. Specific designs, tissue reactions and applications are described herein. Electrodes placed on muscles produce single muscle activation. Nerve electrodes can have the advantage of activating multiple muscles. Selective stimulation of peripheral nerve fibers for effecting specific muscle activation or specific motor function is discussed in the section on nerve electrodes.

### 1. Introduction

The material presented in this section will focus on electrodes that can be used to activate motor nerves electrically. There are three basic locations where electrodes are applied for this purpose, on the surface of the skin (surface electrodes), on or in the muscle (epimysial or intramuscular electrodes), and on, in or adjacent to a nerve trunk (these are often thought of as nerve cuff electrodes). The reason for choosing the motor system and

muscle as the target organ is the simplicity of the system and the fact that the output of the motor system is easily measured.

At the peripheral level, the motor system is comprised of a nerve fiber, one highly efficient synapse per muscle fiber, and the set of muscle fibers ("motor unit") that connects to tendon and bone, and to which force and position transducers can be easily applied to measure the behavioral response. Because of the highly efficient nerve-muscle synapse, a single evoked propagating action potential will result in a measurable force when the motor axon is excited.

Other behavioral systems that could be and should be of interest are those controlling sensory perceptions, such as visual and auditory, or even feelings such as pain and emotional distress. Unlike the peripheral motor system, these systems usually involve multiple synapses between the activated nerve and the behavioral response, the synapses in these systems are not as efficient, and the behavioral response, a perception or feeling, is not easily measured or quantified. In these non-motor systems a single evoked propagating action potential may not result in a detectable response. Even though the target organ in this presentation is muscle, the concepts are applicable to other body systems that present similar nerve-tissue-electrode environments but where the evoked response is something other than a measurable force or movement.

## 2. Basic Concepts

A rule of thumb to keep in mind is that the effects of an applied electrical field are always greatest on the larger diameter axons and the axons closest to the electrode. The effect can be either depolarization or hyper polarization.

*Nerve Depolarization/Excitation:* When the transmembrane potential is decreased to a level that a sufficient number of voltage gated sodium ion channels are switched from the resting-excitable state to the active state it causes a propagated action potential to be initiated (see Chaps. 1.1 and 2.1). This state change occurs when the net transmembrane current is positive, flowing from the inside of the cell to the outside of the cell, and is usually caused by the application of a cathodic stimulus applied near the site of excitation.

*Nerve Hyperpolarization:* When the transmembrane potential is increased from the resting state, the voltage gated sodium ion channels are less likely to be gated into the active state and the population of voltage gated ion channels that were previously inactivatable can be switched to an activatable state. This state change occurs when the net transmembrane current is negative, flowing from the outside of the cell to the inside of the cell, and is usually caused by the application of an anodic stimulus applied near the site of hyperpolarization.

*Virtual Cathode:* A site that is some distance from the actual electrode, usually the electrode designated as the anode, where the net transmembrane current is positive,

positive charge flows from the inside to the outside of the membrane, the transmembrane potential is lowered, and nerve excitation can occur (Fig. 1).

*Virtual Anode:* A site that is some distance from the actual electrode, usually the electrode designated as the cathode, where the net transmembrane current is negative, positive charge flows from the outside to the inside of the membrane, the transmembrane potential is increased, and nerve hyperpolarization can occur (Fig. 1).

*Motor Point:* A site, usually on the surface of a muscle, but can also be used to indicate a position on the skin or a point within the muscle, where the amplitude of the stimulus required to fully activate the muscle is at a minimum. Physically, this is a site where all of the motor nerve fibers are closest to the stimulating electrode.

*Denervated Muscle:* A muscle that has lost its motor neuron innervation. The mechanism by which nearly all motor prostheses work is by electrically activating the motor nerves that in turn synaptically activate the muscle fibers of each motor unit served by the activated motor nerve. If the muscle fibers were to be activated directly from the applied stimulus, the externally applied field would have to be sufficient over all muscle cells for all to be activated. Without the benefit of nerve fibers distributing the action potential and the amplification effects of the nerve-muscle synapse, the applied stimulus may cause injury to the cells close to the electrode before the electric field in the region of the most distant fibers was above threshold in all but the smallest muscles of the body. The strength-duration curves for indirect, via motor nerve, and direct muscle activation are shown in Fig. 2 [44].

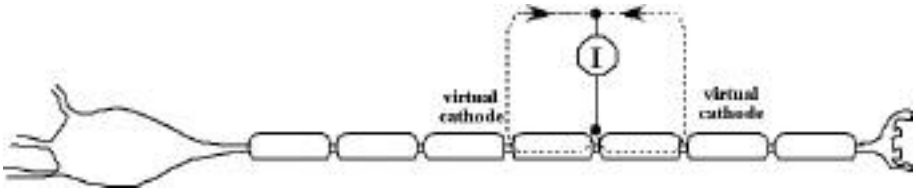


Fig. 1. Schematic representation of nerve and an external stimulator with an electrode positioned on a node of Ranvier. The stimulus shown is anodic. Positive charge enters the nerve under the electrode and exits the nerve at adjacent nodes. Current exiting the nerve membrane gives rise to membrane depolarization. Current exiting the nerve membrane at a site removed from the actual electrode is termed a virtual cathode. Current entering the nerve membrane, causing hyperpolarization, at a site removed from the actual electrode is termed a virtual anode.

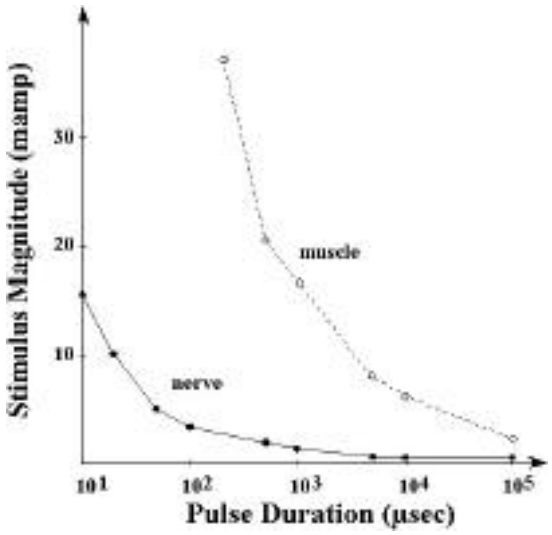


Fig. 2: Strength-Duration curve for nerve and muscle tissue. Data were acquired with intramuscular electrodes placed in cat tibialis anterior muscle. The evoked muscle response was constant throughout the tests at a submaximal level. Curare was administered to achieve the direct muscle activation response. After Figure 20 in Mortimer (Mortimer 1981)

*Activating Function:* When an extracellular stimulus is applied to excite a nerve, mathematical models predict that the second difference quotient of the extracellular field is the driving force to cause membrane depolarization or hyperpolarization (see Chap. 2.1). In the simplest form the following equation applies to a myelinated nerve fiber with it long axis along the "x" axis [41].

$$\frac{V_{e,n-1} - 2V_{e,n} + V_{e,n+1}}{\Delta x^2} \tag{1}$$

Where $V_{e,n}$ is the extracellular potential at the $n_{th}$ node of Ranvier, $V_{e,n-e}$ is the extracellular potential at the node immediately to the left of node "n", and $V_{e,n+1}$ is the extracellular potential at the node immediately to the right of node "n". This equation indicates that the driving function is greatest in regions where the potential gradient is the steepest.

*Electric Potential in Tissue Medium:* To a first approximation, the stimulating electrode is considered to be a point source, the tissue medium is homogeneous and isotropic and the electric potential at any point in the tissue medium can be calculated from:

$$V_e = \frac{\rho_e I_{stim}}{4\pi r} \tag{2}$$

Where “r” is the distance from the point electrode to the point in tissue space of interest.

*Perineural Membrane:* The perineural membrane is an extension of the dura in the spinal cord and surrounds or bundles axons coursing in the periphery. This membrane helps to maintain an extracellular medium surrounding the axons that is different from that found in other tissue in the peripheral portions the body.

*Anodic Break Excitation:* A nerve appears to self-generate an action potential following the release of a hyperpolarizing (anodic) pulse. The effect of the hyperpolarizing pulse is to elevate the excitability of a nerve by activating previously inactivated voltage gated sodium ion channels or in terms of the “m” and “h” parameters of the Hodgkin-Huxley model of a nerve, “h” is increased from ~0.6 to values at or close to 1.0. Increasing “h” reflects a larger percentage of the sodium ion channels have been put into the inactive-activatable state that were in that state under resting conditions. When a large number of these channels become active just after the release of the stimulus, sufficient current can flow to induce a propagated action potential.

## 3. Electrodes Placed on the Skin Surface

### *3.1. Introduction*

Surface stimulation was used for the earliest applications of electrotherapy. The Roman physician Scribinius Largus is said to have advocated the electrical discharge from the Torpedo fish for relief of pain [40]. In the eighteenth and early nineteenth centuries, surface electrical stimulation was applied to alleviate various ailments [28], reinforcing any mystical beliefs one might have about electricity.

Electrodes applied to the surface of the body usually consist of a metal plate with an electrolytic gel to maintain contact. Common materials are stainless steel, silver-silver chloride, platinum or gold plated surfaces. These electrodes are often discoid in shape, but other geometries, conforming to the body contour, are also in use. Many electrodes are self-adhesive or are strapped onto the body surface. Suction electrodes, similar to ECG electrodes are also used. Flexible electrodes made of carbon filled silicone rubber or conductive polymers are also available.

Changes in the surface conditions of the skin and differences in positioning of electrodes can lead to variability in stimulation characteristics. As a non-invasive means for temporary electrotherapy, these electrodes provide ease of application and do not need extensive operator skills.

### *3.2. Applications to the motor system*

### *3.2.1. Lower Limb*

Surface electrodes have been used to assist ambulation for paralyzed subjects. A number of different systems have been developed for clinical use. WalkAid was designed at the University of Alberta, for the management of foot-drop, where subjects are not able to make their toes clear the ground during the swing phase of walking. WalkAid is adjusted by a tilt sensor, which determines threshold angles for turning stimulation on and off [78]. The Odstock Dropped Foot Stimulator (ODFS) was developed in Salisbury, UK between 1989 and 1995. It is a single channel stimulator for drop-foot correction during walking using self adhesive skin surface electrodes placed on the side of the leg. A two channel stimulator O2CHS was later used. The devices are controlled by a foot switches to synchronize stimulation [13, 70]. MikroFES was an orthotic stimulator for correction of drop-foot in paralyzed subjects designed at Lubjiana, Slovenia, [6].

Surface stimulation has been used in conjunction with orthoses for assisted walking. The HAS (Hybrid Assist System) applied surface stimulation with an externally powered brace [55]. The RGO system is a walking device that uses surface electrodes and passive bracing [67]. By way of historical credit, Liberson [36] developed the first drop foot brace and Kantrowitz [32] was the first to report paraplegic standing

### *3.2.2. Upper limb*

Surface electrodes have been used to restore grasp in upper extremity paralysis. The Handmaster was initially developed as an exercise device in Israel for activation of the hands of subjects with C5 spinal cord injury. It uses surface electrodes in a forearm-wrist splint to stimulate the paralyzed muscles [66]. It uses a push button switch and a sliding resistor to adjust hand position. The BGS (Belgrade Grasp System) was developed by Popovic to provide for hand grasp and arm reach. It used a separate channel to activate the triceps muscle to provide shoulder reach. The Bionic Glove was designed for subjects who have active control of wrist flexion-extension. It uses a position transducer mounted on the wrist for stimulation control [54, 56]. A similar device controlled by EMG from wrist extensors has also been described [61]. By way of historical credit, Long was the first person to report electrically induced hand grasp [37].

### *3.2.3.* Scoliosis

Surface stimulation has been investigated as a treatment for scoliosis (lateral curvature of the spine [4, 11]. Paraspinal muscles were activated, typically during the night, for curvature correction. Retrospective studies appear to show that the outcomes with electrical stimulation were not significantly different than the natural progression of the

spinal curvatures. It was not found to be effective in preventing curve progression for idiopathic scoliosis in a group of 30 adolescents [22]. A prospective study comparing the outcomes of bracing and electrical stimulation with untreated patients did not show improved results with those treated by electrical stimulation [46].

## 4. Electrodes Placed In or On the Muscle

Electrodes placed beneath the skin can be positioned closer to the target motor nerves than an electrode on the surface of the skin, and uncomfortable sensations that are associated with activating cutaneous sensory fibers can usually be avoided. Positioning the electrode close to the target muscle also lessens the likelihood of spillover excitation, i.e., activation of non-target muscles. Two classes of electrodes are considered under this heading, intramuscular electrodes and epimysial electrodes. Both electrode types are in direct contact with the muscle but separated by muscle tissue from the motor nerves innervating the muscle.

Considering that the excitatory potential decreases inversely with the separation between the electrode and motor nerve, the electrode should be positioned at a point that is close to the region of the muscle where the major portion of the motor nerve fibers are located. This position or point is often referred to as the “motor point”. At the “motor point”, the stimulus amplitude required to fully activate the muscle is at its lowest value. In the case of the epimysial electrode , the motor point can be identified by moving a stimulating electrode across the surface of the muscle to locate the surface position that requires the least amplitude to fully activate the muscle. In the case of the intramuscular electrode, a fine needle probe might be used by itself or in conjunction with a surface probe; the “motor point” for an intramuscular electrode is usually just below the muscle surface at the “motor point” position identified with a surface electrode.

For most if not all practical neural prostheses, muscle activation, is through electrical depolarization of the motor nerve and not direct depolarization of the muscle membrane. Even though muscle cells contain voltage gated ion channels, generate propagating action potentials, and are electrically excitable, the stimulus amplitude required to activate a muscle directly is very much greater than that required to activate muscle indirectly, through its nerve supply (see Fig. 2).

In skeletal muscle, as opposed to cardiac muscle, muscle cells are activated, directly by the applied stimulus or through their nerve supply rather than by propagation from adjacent muscle cells. Therefore, for direct muscle activation the stimulus level must be sufficient to activate all muscles fibers of interest, which is usually all of the muscle cells in the muscle. Because the electric potential decreases inversely to the separation between the electrode and target cell, very large stimulus amplitudes are required to activate directly muscle cells only a few millimeters away from the electrode. These amplitudes can easily be in excess of values considered to be noninjurious for all but the

smallest muscles. For this reason, motor prostheses are considered practical only for muscles that retain their motor innervations.

### *4.1. Intramuscular electrodes*

#### *4.1.1. Introduction*

Intramuscular electrodes are relatively easy to implant, particularly those having a percutaneous lead that can be inserted with a hypodermic needle. These electrodes first made their appearance in the later part of the 1960's as an extension of intramuscular recording electrodes [7]. The recording electrodes were insulated straight wires, usually in the 25 to 50 μm diameter range, with short deinsulated portions at or near the ends of the wires to sense the potential changes caused by propagating action potentials in the muscle. The electrodes were loaded into a hypodermic needle with only a bent tip outside the needle to act as a barb that would catch in the tissue when the needle is withdrawn.

These electrodes had a life expectancy of a few hours to a couple of days. The failure mode of these electrodes was mechanical fatigue resulting from repeated bending as the muscle moved during contraction. A recording electrode was easily converted to a stimulating electrode by replacing the external recording amplifier with a current or voltage pulse generator. To extend the life expectancy of these intramuscular electrodes the straight wire was coiled into a helix, which transforms a bending force on the electrode into a torsional force on the wire [15]. In the helical configuration the life expectancy of these electrodes were extended to about one month.

Longevity of these electrodes was further extended when the electrodes were fabricated with stranded, insulated wire, usually seven strands with each strand in the 30 μm diameter range. The insulated stranded wire was wound into a helix with the tip deinsulated and bent to construct a barb that would catch in the muscle tissue, holding the electrode in place when the hypodermic needle was withdrawn. These electrodes had a life expectancy of a year or so. Subsequent modifications to the barbed helically wound intramuscular electrode design have been to wind a pair of stranded wires in tandem. The open helix configuration was preserved in the Peterson version [53] and a closed helix version was created (helix enclosed in silicone rubber tubing), known as the Memberg electrode [43]. Both of these versions exhibit life-times that appear to be twice or more that of an electrode wound from a single stranded wire (personal communication and [57]. A review of intramuscular electrodes and their development can be found in the first chapter of Bhadra's master's thesis [8].

### *4.1.2. Materials and Construction*

The strength, flexibility and tolerance of mechanical deformation are important considerations in the design of intramuscular electrodes. The stimulating surface and the lead sections of these electrodes are often one continuous metal. They are usually fabricated by stripping off the insulation from an insulated wire to provide for the stimulation interface. The whole wire is then formed around a wire mandrel to fabricate a stimulating tip and lead in one operation. These electrodes are usually implanted in the body of the muscle using a hypodermic needle as a carrier for the electrode with the body of the electrode loaded in the hypodermic needle prior to implantation. The electrode is usually unloaded from the hypodermic needle when a barb, attached to the electrode, remains outside the hypodermic needle, catches in the tissues as the hypodermic needle is withdrawn. Scheiner et al, [63] used a small rod in the center of the electrode rather than a barb to unload the intramuscular electrode.

The "barb", for many of the electrodes that have been used, is a portion of the wire bent backward that forms the stimulating tip and the lead. Exceptions to this "barb" configuration include polypropylene barbs used with the Peterson and Memberg electrodes and metal wire barbs were used with the Scheiner electrode [9]. The "barb" serves as an aid to unload the electrode from the hypodermic needle and more importantly to stabilize the electrode in the implanted position until the fibrous tissue encapsulates the electrode. The data illustrating the withdrawal force required to dislodge four types of intramuscular electrodes are shown in Fig. 3.

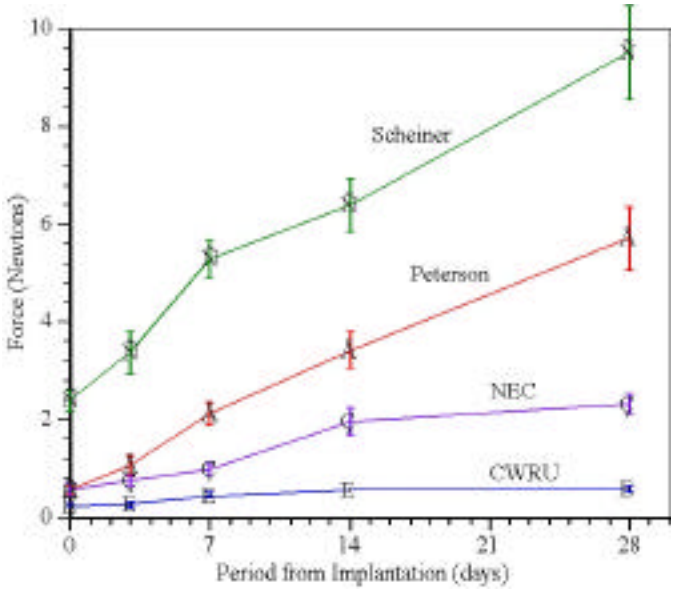

Fig. 3 : Mean and S. E. of the peak force at dislodgement (PFD) for the four types of electrodes in the five implantation periods common to them. The electrode types are described in (Bhadra 1993).

From Fig. 3 it can be seen that the force require to dislodge an intramuscular electrode increases with time after implant, which is attributed to the development of fibrous tissue encapsulation. The fibrous encapsulation does not appear to provide restraint from movement until after the seven days following implantation [9].

The most common metal used in the fabrication of intramuscular electrodes is 316 LVM stainless steel (low carbon, vacuum melt). Because the metal has an amorphous structure, the likelihood of mechanical failure is reduced at grain boundaries, where high stress concentrations can develop and in very small wires cause conduction failure. The main problem to worry about is corrosion of the electrode if the potential across the electrode-solution interface becomes more positive than +400 mV, referenced to a Saturated Calomel Electrode (SCE) [45]. Platinum is more resistant to corrosion than stainless steel but is more prone to mechanical failure because platinum tends to form "grains", crystals that can become the size of the wire, in the range of 25 μm. Adding iridium to platinum can reduce the grain size but usually the resulting strength of Pt/Ir is below that of stainless steel. Caldwell [14], described a dispersion hardening process and reported that Platinum-Iridium with Thorium added ($ThO_2$) showed a 50% improvement in yield strength, a value that comparing well with that of 304 stainless steel.

### *4.1.3. Applications to the motor system*

Intramuscular electrodes have been employed in a number of devices where a muscle is the target organ. They have been used to activate paralyzed muscles that retain a functional motor neuron in the muscles of the upper extremity [51], lower extremity [39], and diaphragm [52]. They have also been used to activate muscles to cause the evoked muscle force to perform functions other than moving a limb. For instance, muscles of the back have been moved to inside the chest and wrapped to form structures that can aid in pumping blood (see Chap. 4.1) [16], and muscles of the leg have been moved and wrapped to perform as a sphincter for maintenance of bowel continence [5] and urinary continence [31] (see Chap. 7.4). Muscles have also been stimulated to correct spinal deformity in the treatment of scoliosis [30]. Such electrodes are able to activate segments of muscles, particularly the deeper ones, in a way that may be difficult to achieve with other kinds of electrodes.

### *4.1.4. Tissue reaction considerations*

The coiled wire intramuscular electrode has been found to be tolerated well by body tissues, in the subcutaneous tissues, and at the sites where the electrode exits the skin,

when the electrode is used as a percutaneous electrode. The tolerance is attributed to the materials used in fabrication and the physical configuration of the electrode.

Figure 4 shows a Peterson electrode. The diameter of the wound insulated portion is approximately 800 µm. The materials used in the fabrication of these electrodes are:

- 316 LVM stainless steel wire forms the conducting lead and the stimulating tip. The wire is stranded from seven strands of wire each strand is 40 µm in diameter.
- Perfluoroalkoxy (PFA) insulation 50 to 75 µm in thickness.
- Polypropylene suture material, 5-0 gage or diameter, forms the barb and center core of the electrode assembly.

The subcutaneous tissue reaction to the Peterson type of electrode is shown in Fig. 5. The tissue was cut in a plane that is parallel to the axis of the electrode [19]. In the left hand panel, the area appearing as an oval hole is the space occupied by the insulated helix portion of the electrode lead. The long oval space in between the oval holes is the space occupied by the polypropylene core. In the right hand panel is the tissue reaction around the stimulating tip/barb portion of the electrode. A higher power view of the region between two windings, indicated by the box in the left hand panel is shown in Fig. 6.

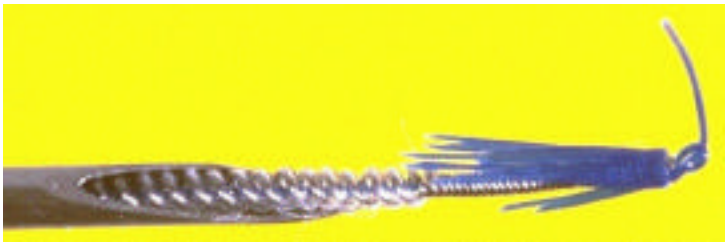

Fig. 4. Photograph of Peterson type electrode. The diameter of the insulated helical portion of the lead is approximately 800 µm. The electrode is shown partially loaded into a hypodermic needle, on the left hand side of the figure.

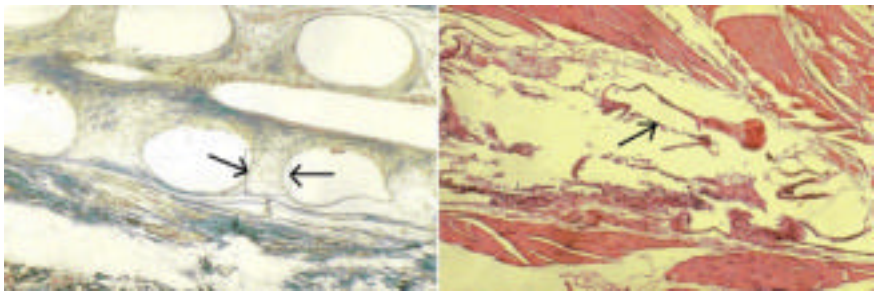

Fig. 5. High power magnification of the tissue encapsulation between two windings of the helically wound lead of the Peterson electrode. At the interface between the electrode insulation and the tissue a compact group of cells forms a barrier between the implant and the interstitial space, indicated by arrows. This barrier layer is in

the range of three to four cell layers thick. The space between the barrier walls contains a loose connection of cells and collagen. From (Corey, 1990).

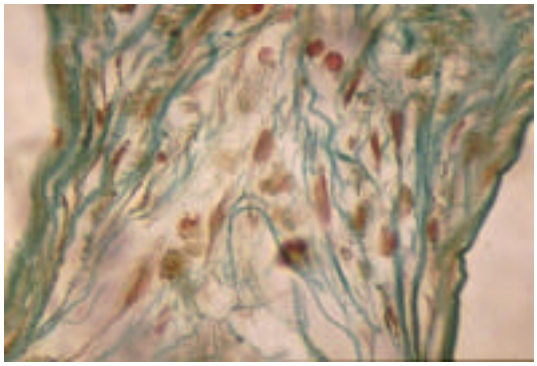

Fig. 6. Higher magnification view of the encapsulation tissues occupying the space between two coils of the lead wire (left panel of Fig. 5). Adjacent to the insulated lead is a thin layer of cells that are closely packed and believed to for a barrier bacteria. The majority of the connective tissue lying between the two coils is loose connective tissue dominated by collagen fibers.

The tissue reaction to the helically wound lead provides insight into the reasons why these percutaneous electrode leads are so well tolerated in the body and as they traverse the skin. The compact cell layer provides a barrier that suppresses bacterial entry into the tissue spaces and a barrier to nutrients required to sustain bacterial growth in the area occupied by the wound lead. The “open” helix and the lose connective layer permit the lead to extend and compress under axial loads without a piston like action as would occur with a closed cylinder lead under similar loads. A sliding motion between the tissue encapsulation and the lead is believed to irritate the encapsulating cells and discourage the formation of a barrier layer.

Examination of the tissue reaction at the skin exit site shows that the epidermal layer extends down about 3 mm to form a well with a diameter of approximately 1.0 mm, slightly larger than the wound lead. At about 3 mm below the surface of the skin tissue encapsulation begins to form with the characteristic compact layers and lose connective tissue layers. Experience suggests that when the compact layer is disrupted, the tissues become vulnerable to bacterial invasion and infection. Microscopic particulate matter, adhering to the implanted device, will antagonize the formation of the compact cell layer barrier, because of the presence of a chronic inflammatory response to an otherwise sterile implant. To reduce the likelihood of implanting a lead with particulate matter adhering to the surface, a thorough cleaning procedure (see §7) is recommended prior to implantation, and the electrode should be kept immersed in sterile water or saline prior to implantation whenever possible. It is important to keep in mind that a clean polymer surface is often hydrophobic and that particulate matter it comes into contact with will cling to it and possibly be carried into the tissue space at the time of implantation.

Removal of a percutaneous intramuscular electrode, or open helix lead, by pulling on it, involves rupturing the encapsulation tissue layers with little if any disruption of muscle tissue [8]. As the lead is pulled, individual turns of the helix uncoil by tearing the encapsulation layer (Fig. 7). The tearing of successive encapsulation layers continues until the barbed end of the electrode gives way, usually including a few undisturbed coils of the helix. The tearing to the tissue layers usually does not involve muscle tissues. It is important to recognize that if the force applied to the lead wire exceeds the yield strength of the material, the lead will mechanically fail, often below the skin. Further, it is likely that the fractured end is no longer coiled and therefore that uncoiled portion is not as compliant as a coiled helix to axial loads.

Experiments in animals [45] indicate that the tissue reaction to stimulation is not statistically different from what would occur with a passive implant, provided the charge injection is below 20 μC/cm$^2$ for cathodic monophasic stimuli and 40 μC/cm$^2$ for balanced charge biphasic stimuli. The 40 μC/cm$^2$ for balanced charge biphasic stimuli, cathodic phase first, limit is set by corrosion that can occur during the anodic phase of the stimulus pulse. When imbalanced biphasic stimuli are applied, less charge in the anodic phase than in the cathodic phase, a much larger charge can be injected before evidence of tissue injury is observed [62].

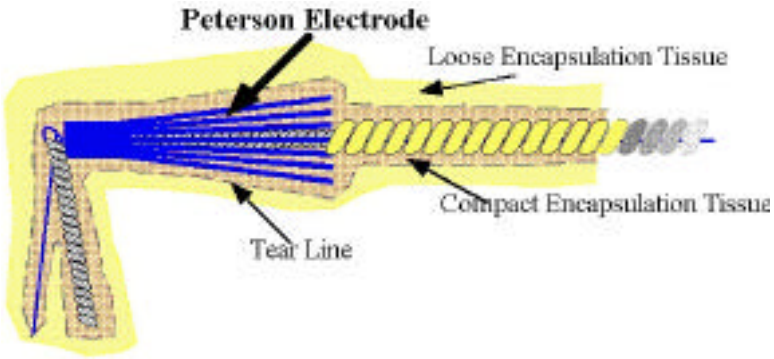


Fig. 7. Schematic drawing of Peterson type electrode, encapsulation tissues and muscle, into which the electrode had been implanted. The lead was pulled to the right for removal (Bhadra 1993).

### *4.1.5. Side effects*

Percutaneous intramuscular electrodes can fail. Evidence of failure is usually gleaned when a stimulus, applied to the terminal end of the electrode lead, fails to result in a physiological response, e.g., muscle contraction. When this occurs within days or a few weeks following implantation the cause is usually electrode movement away form the “motor point” area, but could also be due to a mechanical failure in the lead causing a break in the conduction pathway. If the stimulus current and voltage can be measured, an

open circuit can be distinguished from electrode displacement by excess voltage or a reduced current flow detected upon application of the stimulus pulse. Loss of the stimulus response after weeks or months after implantation is almost always a result of a break in the electrical conduction pathway.

Percutaneous intramuscular electrodes/leads can be removed after long periods of implantation, but care must be taken not to exceed the yield strength of the wire, which is usually the strongest component of the lead. Tension applied to the lead will cause the coiled helix to uncoil, which means that the tissue encapsulation that has formed around the lead tears. When this encapsulation layer has been disrupted, any pathogen barrier that it provided will be lost and the skin exit site is venerable to infection. Therefore, it is important to keep the site "free" of bacteria at the time of lead withdrawal and until the site heals, typically several days. If the lead breaks beneath the skin during removal, it is very likely that a portion of the coiled lead will straighten. The straightened portion of the lead may not be as compliant as the coiled portion and unable to compress or extend when the surrounding tissues move relative to each other. Under these circumstances, the straightened portion of the lead may cause continued irritation of the surrounding tissues due to relative movement. This continued irritation of the cells adjacent to the straightened section of the lead may not allow a tight cell layer barrier to develop around the lead. Further, it is possible that the continual relative motion of the straightened lead and surrounding tissues may cause the straightened portion to erupt through the skin. The erupting portion of the lead will not have a well-formed tight cell barrier and will be vulnerable to bacterial invasion and infection. Reddening and slight swelling at the impending eruption site will precede often eruption. If proper caution is not taken to address the erupted portion of the lead, infection may ensue.

Four groups have reported on their clinical experience with percutaneous electrodes. Knutson and colleagues [33] employed electrodes that were of an open helix design and fabricated from multi-filament (7 or 10 strand), FEP Teflon®-insulated, type-316L stainless steel wire with a diameter of approximately 200 μm. The wire was wound around an arbor into a coil, forming an electrode lead with a diameter of approximately 580 μm. They report on 858 electrodes implanted over a period between 1978 and 1998. Their data show that 95% of the electrodes were functional at six months, 91% of the electrodes were functional at twelve months and that 78% of the electrodes survived both the *in situ* period and were extracted whole at six months and 57% survived after twelve months of implantation. Some 16% of their subjects experienced infection or a granuloma at the lead exit site. Knutson and colleagues [33] state "All incidents were localized, non-systemic occurrences and were resolved by administering antibiotics, cleaning the implant site, removing electrodes, cauterizing with silver nitrate, or excising electrodes or granulomas." Smith [65] and colleagues reported on their experience with similar electrodes used in adolescents with tetraplegia. They report that 75% of the electrodes survived six months and 51% survived one year.

The second group, Prochazka and Davis [57], reported on their experiences with a "single wire" electrode that was similar to that used in the Knutson, et al. study and with one that was similar to the Peterson electrode, which is wound with two separate wires and has a Prolene® central core. They reported that five of eleven "single wire" leads failed within eight months. They found that the "Peterson type" electrodes had a longer survival period. Of seven implanted electrodes, four were still functioning after 4.75 years.

The third group, Handa and colleagues [29], have reported that their experience with a "hard" 316L stainless steel wire had a lower failure rate than when they used a "soft" 316 stainless steel base material. Their "hard wire" electrode was fabricated using a "rope" with nineteen strands of 25 μm wire wound into a helix. They report an average failure of less than 2% over a period ranging from eleven to fifty weeks.

The fourth group, Scheiner and colleagues [63], reported on a percutaneous intramuscular electrode wound with a compound helix, which they called a double helix. They reported on 775 electrodes over a five year period. Sixty-five percent (453) served the intended purpose. Seventy-four (10%) of their electrodes failed due to mechanical failure, usually with the first year of service and four (0.5%) were removed because of infection.

### *4.2. Epimysial electrodes*

#### *4.2.1. Introduction*

Epimysial electrodes are electrodes positioned on the surface of a muscle, below the skin and not in the muscle. These electrodes are usually secured to the muscle by sutures or staples and are insulated on one side to direct the stimulus current away from non-target tissues, e.g., sensory nerve fibers in the skin or adjacent muscles. A perceived advantage of epimysial electrodes over intramuscular electrodes is that they (electrode and lead) are less prone to mechanical failure and less likely to move in the hours/days immediately following implantation.

When using epimysial electrodes there are two important points to consider: electrode location relative to the motor nerve, and movement of the electrode relative the underlying tissues when the muscle changes length. Grandjean and Mortimer [26] reported on work carried out in the calf muscles of cat. The results of this work indicated that when a monopolar epimysial electrode was closest to the motor nerves:

- Threshold stimulus amplitude was lower;
- The gain was the highest, that is differences between the threshold levels of activation and full activation were small;
- The selectivity was the greatest in that a larger portion of the target muscle could be activated before the amplitude was sufficient to activate nearby muscles;

- Length dependent recruitment was minimized, that is the percent of the muscle activated at a given stimulus magnitude changed the least as the muscle lengthened from the shortest to the longest muscle length.

When a bipolar epimysial electrode is used rather than a monopolar electrode with a distant return electrode, the stimulus current is constrained to regions closer to the two electrodes. Compared to the results with the monopolar electrode:

- Threshold was increased;
- Relative gain decreased;
- Greater selectivity was found in the range closer to threshold and poorer selectivity was present in the stimulus range closer to maximum activation of the muscle.

### *4.2.2. Applications to the motor system*

Epimysial electrodes have been used by Hunter Peckham and colleagues for a number of years in their development of an upper extremity assist device for C5 or C6 adult subjects with tetraplegia, which became know as the "FreeHand System™" produced by NeuroControl Corporation in Cleveland, Ohio, [50]. This device used epimysial electrodes and Memberg type intramuscular electrodes. The grasping function provided by the device was shown to offer them an improved level of independence and the device is considered reliable with most of the subjects using it at home on a regular basis (see Chap. 6.2).

### *4.2.3. Tissue reaction considerations*

Two groups have reported on the nature of the tissue encapsulation surrounding epimysial electrodes. Akers et al. 1997 [2] reported on an epimysial electrode, formed with a platinum disk embedded in silicone rubber, that is sutured to the surface of the muscle in the leg of canine and one that is like those used in the "FreeHand System". Their results indicated a mean thickness for the encapsulation layer of 0.179 mm with the encapsulation layer thickening when the attachment sutures were not in place. Schmit and Mortimer [64] reported somewhat different results for their experiments carried out with epimysial electrodes stapled to the abdominal surface of the canine diaphragm. The tissue capsule forming on the back side of the electrode, a silicone rubber surface facing away from the muscle, was quite thin or not detectable. On the surface between the stimulating surface and the muscle the encapsulation layer had a mean thickness of 1.24 mm. This layer exhibited two subregions, a collagen outer layer and a layer of granulation tissue adjacent to the electrode surface. The nature of the granulation tissue layer suggested the cause was a chronic mechanical irritation brought about by relative

movement between the contracting (shortening) muscle tissue and the non-compressible silicone rubber of the electrode carrier.

#### *4.2.4. Side effects*

Schmit and Mortimer reported that relative movement between the contracting (shortening) muscle tissue and the non-compressible silicone rubber of the electrode carrier could result in a transient loss of induced muscle contraction [64]. As the muscle was induced to shorten, the electrode carrier would accommodate the change in space between the two stapled portion by buckling, pulling the recessed disk away for the muscle tissue and subsequent loss of contact. The outward manifestation of this phenomenon was like a brief hiccup with each electrically induced muscle contraction. Replacing the recessed metal disk with a protruding hemisphere solved the transient loss of electrical contact problem.

## 5. Electrodes Placed On or In the Nerve

Positioning the stimulating electrode on or in the nerve opens opportunities for a degree of selective activation that is not possible with electrodes that are placed in or on muscle or on the skin. Further, the stimulation contact is closer to the target tissues, which means that threshold stimulus currents can be lower, the activating function is greater, and there is a lower demand on the power requirements of the stimulator. Two electrode configurations will be considered; the first utilizes electrical contacts placed on the surface of the nerve, outside the perineural membrane and housed in a silicone rubber carrier, commonly referred to a cuff electrodes, and the second utilizes contacts placed below the perineural membrane, commonly referred to as intrafasicular electrodes.

### *5.1. Cuff electrodes*

#### *5.1.1. Introduction*

Cuff type electrodes hold the stimulating contacts in close proximity to the nerve trunk. Holding the target tissues close to the stimulating contacts offers opportunities for power efficiency and improved selectivity. Power efficiency is improved because less power is spent on electrical conduction through the space between the electrode and target tissues. Improved selectivity is possible because the electric potential gradient is larger when the spacing between the stimulating contact and the target tissue is the least. Further, cuff type electrodes are less likely to move in relationship to the target tissues after implantation. In order to take full advantage of these opportunities, it is important that

the electrode assembly be in close contact with the nerve trunk. However, when the cuff is in close contact with the nerve at the time of implantation, there is a risk that blood flow can be compromised and/or the nerve fibers can be mechanically traumatized.

### *5.1.2. Cuff diameter to nerve diameter ratio*

Prior to the 1990s, cuff electrodes were rigid cylinders containing metal contacts embedded in silicone rubber or a similar material, see Naples *et al.* [49] for a review of cuff electrodes. The dogma that persisted in the neural prosthesis community was that the internal cuff diameter should be 50% larger than the external diameter of the target nerve, (CNR = 1.5). Implicit in this statement is that the nerve has a round cross-section. This conclusion was based on nerve repair studies performed on transected nerves in the 1960's [21]. The results of the study indicated that nerve fiber regeneration success was better for nerves that were rejoined when the two ends of the nerve were held in place by a cylinder, with an internal diameter that was 50% larger than the nerve. The perceived importance of the larger diameter was that a cuff with a CNR of 1.5 could accommodate swelling without occluding blood flow in the region of the cuff.

In the 1980's the Huntington helix [1] was introduced as an alternative design to the rigid cylinder. The concept of the Huntington Helix is illustrated in Fig. 8. Shown here is an early version, which has more wraps than those that are now in use. Stimulating contacts are exposed metal sections along the internal diameter of the helix. The open helix design can accommodate some swelling without constraining blood flow, allowing axial flexibility and compressive/tensile loads. A version of the Huntington Helix electrode is used on the vagus nerve stimulating device marketed by Cyberonics™ (www.cyberonics.com). The recommended CNR for the Huntington Helix electrode is a loose fit such that the lumen of the electrode and the diameter of the nerve are a close match with no constriction of the nerve (personal communication with D.B. McCreery). Installation of the helical configuration can be perceived as demanding for the surgeon. The task is made less demanding by reducing the number of wraps. With fewer wraps there is a risk that the helix will come off of the implanted nerve during body movements; so suturing the helix to the epineurium has been used to reduce the likelihood of accidental displacement in the time immediately following implantation.

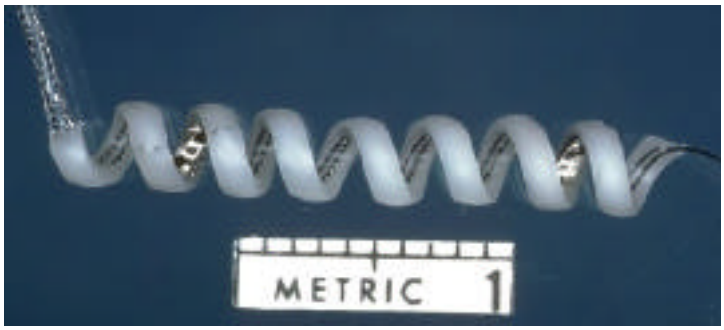


Fig. 8. Photograph showing an early version of a bipolar Huntington helix electrode. Subsequent designs use fewer wraps and a straight section, rather than wraps, between the stimulating contacts. Stimulating contacts can be seen between the ends of the first and second wraps, counting from the left hand side, and the sixth and seventh wraps.

The self-sizing spiral cuff (Fig. 9) also appeared in the 1980's as an alternative to the rigid cylinder [48]. The spiral configuration is achieved by laminating two sheets of silicone rubber together, with one of the layers stretched in relationship to the other. The stretched layer forms the internal aspect of the cuff. Increasing the relative stretch produces a cuff with a smaller internal diameter. Stimulating contacts are embedded between the outer, unstretched, layer and the inner, stretched, layer prior to lamination. Experiments in cats indicate that these cuffs can accommodate CNR between 0.6 and 2.0 [3].

Fig. 9. Photograph of the self-sizing spiral cuff electrode. The spiral configuration can open or close to accommodate a range of different diameter nerves.

Cuoco and Durand [20] reported that the measured compressive forces, developed by self-sizing spiral cuff electrodes, were not sufficient to occlude nerve blood flow inside the cuff. The estimated occlusion pressure is estimated to be ~27 cm $H_2O$. These studies were carried out in cuffs that contained no contacts or wire. Care must be taken when routing the lead wire to this electrode to avoid placing a load on the cuff that is sufficient to pull the cuff off of the nerve following implantation. It might be tempting to think of tying a suture around the cuff to avoid accidental displacement, but this would defeat the self-sizing property of the configuration. It can be argued that if the routing of the lead would result in a force applied to the cuff sufficient to displace the cuff from the nerve, it would be better for it to be displaced rather than cause injury to the nerve by mechanically loading it.

Tyler, 1999, [71] reported on an alternative electrode configuration where the effort was to flatten the peripheral nerve. The intent was to align fascicles into a single layer of nerve bundles spaced cross sectional area of the electrode (Fig. 10). The idea, which was considered daring at the time, grew from an experiment where fascicles were found to have been accidentally divided when a self-sizing spiral cuff was displaced after the implant site had been closed [3]. The results show that the "flattening" effect of the electrode can be tolerated provided the flattening is not too extreme. The upper limit to "flattening" seems to correlate with forces that are great enough to flatten single fascicles.

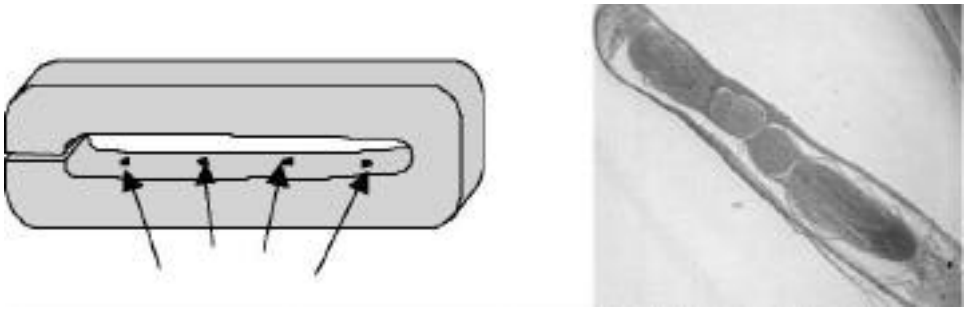

Fig. 10. Schematic drawing of FINE electrode and photograph of rat sciatic nerve after implantation of FINE electrode. The arrows on the left hand figure call your attention to the stimulation contacts, which may be in a position to activate only a single fascicle (Tyler 1999).

### *5.1.3. Tissue reaction considerations*

Tissue reaction considerations include trauma to axons as well as the nature and extent of the encapsulation tissue surrounding the implant. Traumatized axons may not conduct propagating actions potentials and thick encapsulation layers degrade electric field gradients by increasing the separation between the electrode contacts and target axons.

Trauma to axons can be a direct result of mechanical trauma or a secondary effect of loss of blood flow, ischemia [60]. . Rydevik and colleagues make a strong point of the effects of compression and stretching on occlusion of blood flow in the vascular bed associated with peripheral nerves. Naples *et al.* [49] point out that signs of past trauma are often observed in nerves that have received cuff type electrodes. The typical histolologic signs take the form of crescent shaped regions containing thinly myelinated axons, which are believed to be remyelinated axons, and greater space between axons occupied by connective tissue. Most of these data come from animal experiments and observable evidence of axon trauma in these studies apparently is rarely noted. Human subjects, who have undergone surgical procedures that involved mobilization of a peripheral nerve, not uncommonly report transient alteration of tactile sensation or muscle weakness. The transient loss of neural function and remyelinated axons are presumed to be characteristics of a transient loss of nerve conduction due to loss of myelin subsequent to a transient episode of localized ischemia. Data acquired by these authors combined with data reported by the group at HMRI indicate that there is a 30% chance that the process of dissecting the nerve free of surrounding connective tissue will cause a transient loss of conduction. The cause of conduction loss appears to be demyelination of axons, believed to be secondary to a transient loss of blood flow that was induced during dissection. When the demyelinated axons are remyelinated, the thickness of the myelin is thinner and conduction returns. These findings are consistent with the report by Larsen *et al.*, 1998, [34] where it was concluded, “their implanted cuff electrode may cause an initial loss of axons with subsequent complete structural regeneration”.

Thick layers of encapsulation (connective) tissue may degrade the electric field gradient (the activating function), which decreases the possibility of selectively activating small regions of the nerve inside the cuff. Connective tissue forms around an electrode and usually fills all available space. Therefore, loose fitting electrodes will have thicker layers of connective tissue between the cuff and the nerve. A second cause of thick encapsulation is mechanical irritation caused by continued relative motion between the cuff and the surrounding tissues. Sustained mechanical irritation can cause injury to delicate capillaries forming in connective tissues, which can exacerbate connective tissue thickening. To minimize the likelihood of sustained mechanical irritation, the cuff and the nerve should be bound closely together. So-called half-cuffs, cuff configurations that do not completely enclose the nerve, are prone to having thicker layers of connective tissue ingrowth between the nerve and the electrode than do cuffs that completely encircle the nerve. An example of the tissue encapsulation found surrounding a “half-cuff” is shown in Fig. 11.

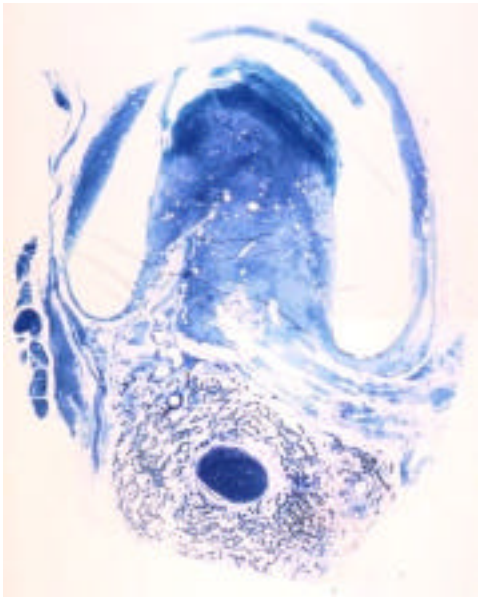

Fig. 11. Cross-section of the connective tissue formed around a “half-cuff”. The horseshoe shaped region in the upper part of the photograph, which is absent tissue, is the space previously occupied by the “half-cuff”. The oval shaped region in the lower part of the figure is the nerve, which has been pushed out of the cuff. Close inspection of the upper portion of the connective tissue on the inner aspect of the cuff reveals layers, like rings on a tree trunk. These layers of connective tissue are presumed to have developed in response to mechanical irritation between the cuff and the local tissues.

### *5.1.4. Selective activation techniques*

#### 5.1.4.1 Introduction

Ordinarily, when a short duration stimulus pulse is applied to an axon, action potentials propagate from the site of stimulus in both the orthodromic and the antidromic directions (Fig. 12). Cuff type electrodes can be used to effect a degree of selective activation, selectivity, that is not achievable with other configurations. Specifically, action potentials can be created that propagate in only one direction from the site of their initiation, antidromically or orthodromically, and the relative excitability of large an small diameter neurons can be manipulated. The factors that play a key role in cuff electrode selectivity are the fact that the target tissues are bundled as a group with a known orientation to the cuff, and the fact that the cuff is usually constructed of an insulating material, which acts to constrain current flow.

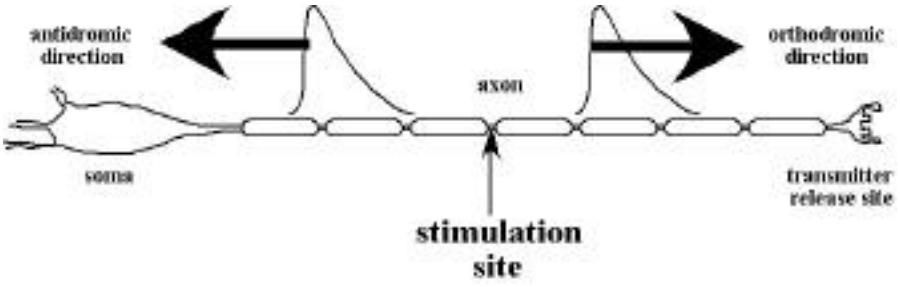


Fig. 12. When a suprathreshold stimulus is applied to an axon, action potentials are created that propagate in both the antidromic and orthodromic directions, starting from site of stimulation.

### 5.1.4.2 Unidirectional propagating action potentials

Action potentials propagating in only one direction from the site of initiation can be generated by arresting the stimulus initiated action potential that is propagating in the other direction. Depolarization of an axon, in the middle portion of its length, gives rise to two action potentials traveling in opposite directions from the site of initiation (Fig. 12). The orthodromically propagating action potential will result in the release of neurotransmitters from the presynaptic terminal and the antidromically propagating action potential will propagate in the opposite direction. It is generally assumed that the antidromically propagating pulse will have no effect on the cell or receptor end; this may or may not be the case. Unidirectionally propagating pulses can be useful in blocking unwanted neural activity [74] or creating afferent neural activity without generating efferent activity or conversely creating efferent activity without causing afferent activity.

Van den Honert [74] described a technique to effect unidirectionally propagating action potentials. The technique involved stimulating the axon to create two propagating action potentials, moving in opposite directions, and then arresting the one propagating in the unwanted direction. In principle, the two propagating action potentials were created at the cathode and the unwanted action potential arrested at the anode, both contacts inside the same cuff electrode.

To arrest a propagating action potential the anodic currents from the electrode must be sufficient to counter the depolarizing action potentials of the invading action potential. The depolarizing currents from the invading action potential are greater than required to reach threshold depolarization and persist for approximately 300 μs. Therefore, the anodic current supplied by the stimulator must be sufficient to counter these depolarizing currents. However, currents of the required magnitude can be sufficient to create axon excitation at virtual cathode sites, illustrated in the upper panel of Fig. 13.

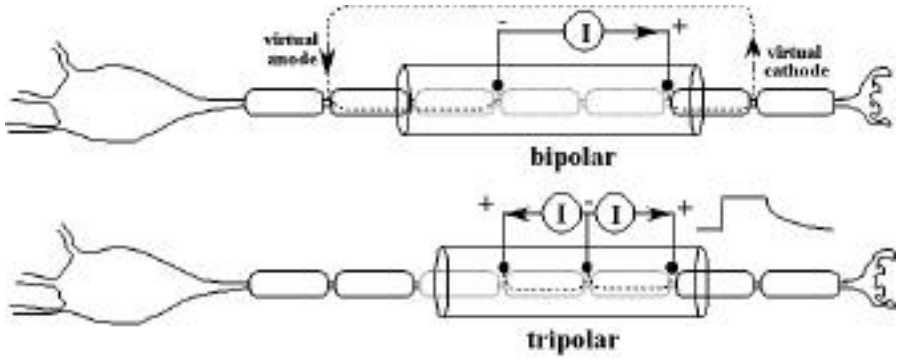


Fig. 13. Stimulation currents entering the axon at the anode can arrest the depolarizing currents of an invading action potential, but in a bipolar configuration currents can exit at a virtual cathode site and initiate a propagated action potential. The propagated action potential created at the virtual cathode site negates the arrested action potential at the anode. The external pathway for current to create a virtual cathode can be eliminated by adding a guard anode, to create a tripolar electrode configuration, at the opposite end of the cuff electrode, as illustrated in the lower panel.

The original technique required an asymmetric tripolar cuff electrode with three contacts, anodes at each end and a cathode placed closer to the arresting anode and further from the escape end of the cuff. To arrest a propagating action potential, a hyperpolarizing, anodic stimulus was applied to nodes at the same time an invading action potential is arriving at that node. For an activating cathode and an arresting anode spaced closely together, the activating stimulus and the arresting pulse could be the same pulse originating from the same stimulator. This assumes that the average delay per node is in the range of 15 to 20 μs. The effect of the hyperpolarizing pulse is to counter the depolarizing effect of the invading action potential and thus arrest further propagation. The depolarizing currents arising from a preceding depolarized node act on the adjacent node for 300–400 μs. Therefore, the hyperpolarizing pulse must be of a similar duration and amplitude. The net effect is that the arrest pulse waveform must have a pulse duration of ~350 μs and the amplitude must be greater than what would be required to create an action potential.

Subjecting a nerve to this type of arrest pulse has three effects. At the cathode the stimulus is well above that required to activate many if not all of the smallest fibers. At the anode, the long duration anodic pulse can result in “anodic break” excitation and/or virtual cathode excitation by depolarizing currents arising at the edge of the cuff, close to the anode contact. The “anodic break” excitation can be avoided by using an exponentially decaying lagging edge on the anodic, arrest, stimulus [75]. The resulting stimulus waveform is called a quasitrapezoidal pulse (Fig. 14).

Fig. 14. Quasitrapezoidal waveform required to effect arrest of an invading action potential. The plateau phase is typically 350 to 400 μs in duration and the time constant of the exponentially falling lagging edge is 500 μs.

The virtual cathode was suppressed by placing a second anode at the escape end of the cuff to discourage flow of current outside the cuff. In this three-electrode configuration two stimulators were required; the two cathodes were connected to the middle contact, the cathodic current into the electrode contact was the sum of the currents from the two stimulators and the anodic current to the anode at the escape end of the cuff was less than that applied to the arrest anode. The current to the arrest anode was adjusted to yield arrest of the action potential generated at the cathode. The current to the escape anode was adjusted to just suppress the virtual cathode current arising from current flowing outside the cuff from the arrest anode to the cathode, but not to a level where the incoming action potential was arrested. The separation between the middle cathode and the arrest anode is smaller than the separation between the middle cathode and the escape anode. The need for two stimulators was viewed as a complicating factor to this design.

Ungar [73] reported on a monopolar cuff configuration that was a significant simplification of the tripolar design of van den Honert. Unger used a single stimulator with the cathodic terminal connected to a ring contact inside the cuff and the stimulator anode was positioned in the interstitial space some distance from the cuff. The contact was placed 5 mm from the arrest end of the cuff and the overall length of the cuff was 40 mm (Fig. 15). The Unger design takes advantage of the two virtual anodes created at the ends of the cuff to create the arrest anode and to reduce the likelihood of action potential arrest at the escape anode. The 35 mm cuff length between the cathode and the escape end of the cuff creates resistance inside the cuff to make anodic current flow in that direction less than that toward the arrest end, which allows an escape window. The required 40 mm overall length of the cuff is viewed as a drawback for some applications.

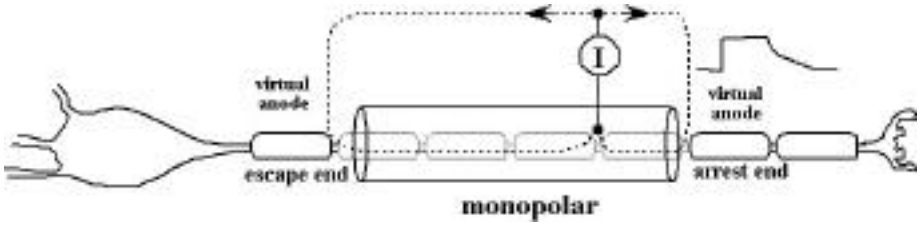


Fig. 15. Schematic drawing of a monopolar cuff configuration developed to effect unidirectionally propagating action potentials. The design utilizes the virtual anode as the arrest site and has no virtual cathodes. In this arrangement, unidirictionally propagating action potentials would be moving in the antidromic direction, toward the cell body.

Sweeney [68] described a bipolar electrode configuration that could produce unidirectionally propagating action potentials and that had a length that was less than half of the Ungar design (Fig. 16). Lifting the contact at the arresting anode away from the nerve reduced the virtual cathode effect stemming from at the current flowing from the arrest anode around the outside of the cuff back into the escape end of the cuff.

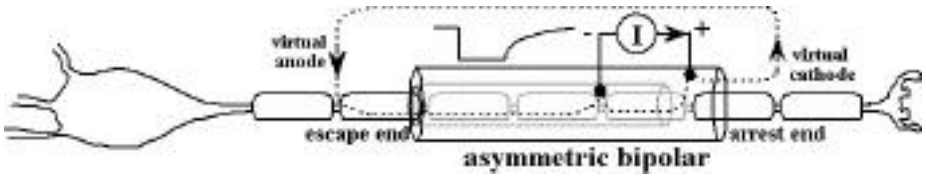


Fig. 16. Schematic drawing of a bipolar cuff configuration that was developed to effect unidirectionally propagating action potentials traveling in the antidromic direction. Elevating the arrest anode away from the nerve suppresses the virtual cathode effect at the arrest end of the cuff.

5.1.4.3. Selective activation of large and small diameter axons

The capacity to selectively and controllably activate axons of different diameters in a trunk carrying mixed populations can enhance the performance of a neural prosthesis. This facility makes it possible to target a specific population and to avoid activation of other populations that may cause undesirable side effects. For example, consider electrically activating a motor nerve having axons that serve both large and small motor units. Recall that large diameter axons preferentially innervate large motor units. These motor units characteristically supply muscle fibers that have poor fatigue characteristics, whereas small motor units usually contain fatigue resistant muscle fibers (see Chap. 1.5). When conventional stimuli, pulse widths of 100 μs ± 50 μs, are applied to the motor nerve, the resulting muscle force will be dominated by the force and fatigue characteristics of the easily fatigable population. Similarly, for some applications it may be desirable to preferentially activate large diameter fibers. In this section, our focus will be on ways to enhance the possibility of exciting a particular population of large or small diameter axons.

Noticing that the effect of an applied electric field was greater on large diameter axons than on the smaller diameter axons, Fang [25] surmised that the technique developed to arrest action potential propagation would arrest propagating action potentials in the larger diameter fibers at lower stimulus amplitudes than would be required to arrest a propagating action potential in smaller diameter axons when both large and small diameter axons were present in the same nerve trunk. The task was to then show that an action potential traveling on a large diameter axon would be arrested before an action potential traveling on a small diameter axon, thus creating the illusion that the small

diameter fiber would be recruited without activating the large diameter axons. A symmetric tripolar stimulating electrode was employed which would effect arrest at both ends of the cuff. Simulations predicted that larger diameter axons were blocked at lower current levels than smaller diameter axons (Fig. 17).

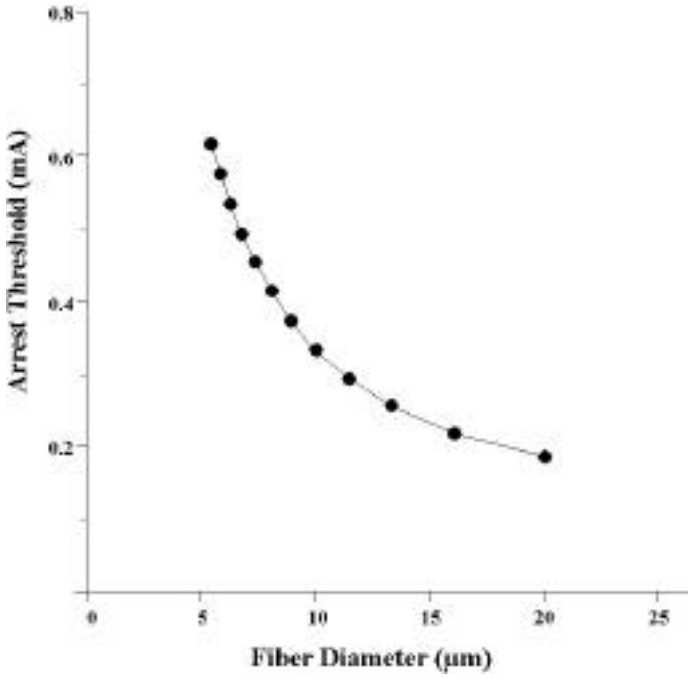


Fig. 17 Arrest threshold as a function of fiber diameter predicted by a analog model analysis (Fang and Mortimer 1991b).

These predictions were confirmed in animal experiments where evoked action potentials were recorded in ventral roots from an electrode placed on the medial gastrocnemius nerve of cat. The gastrocnemius nerve carries both large diameter α motor axons and small diameter γ axons. The larger diameter fibers have a faster conduction velocity, measured as a shorter latency as compared to longer latency for small diameter axons. With narrow rectangular pulse stimulation the largest motor axons were recruited at the lowest stimulus threshold and when the stimulus amplitude was increased to a level that would activate the smallest diameter axon, the larger was also activated. These results are shown in Fig. 18.

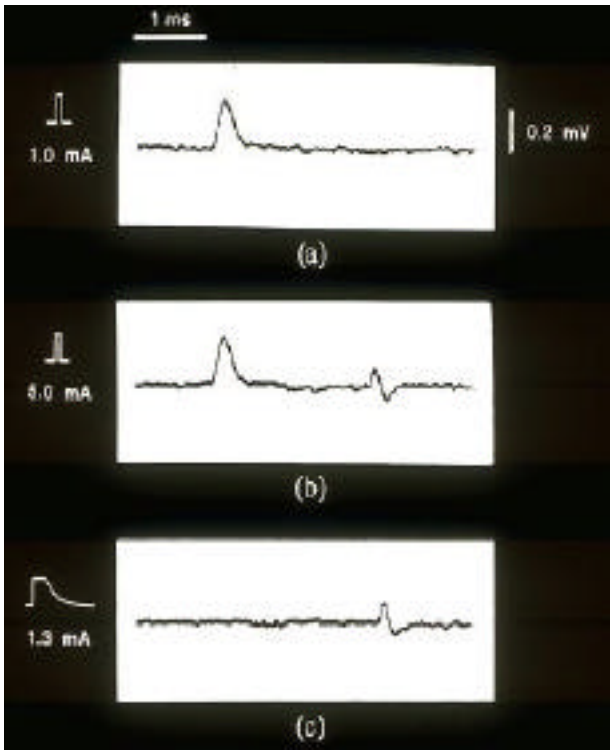


Fig. 18. Single fiber action potentials recorded from a ventral root filament containing one active alpha fiber (120 m/s) and one gamma fiber (40 m/s). Conventional narrow pulse stimuli were applied in the experiments for the results shown in the top two panels, showing that at amplitudes sufficient to activate the small diameter axon the large diameter fiber was recruited at a lower stimulus amplitude. In the lower panel, a 350 μs quasitrapezoidal was applied at an amplitude that was sufficient to arrest propagation in the large α motor neuron but not sufficient to arrest propagation in the small γ motor neuron. The same result was demonstrated for α motor neurons of slightly different diameters (Fang and Mortimer 1991b).

Fang [24] employed the selective arrest technique to demonstrate that small diameter motor axons, innervating fatigue resistant muscle fibers, could be selectively activated without activating large diameter motor axon innervating the large motor units, which are made up of muscle fibers that fatigue in a few tens of seconds. In another report, Fang [23] reported on an experiment where large diameter motor axons were preferentially activated with every other stimulus pulse, by stimulating with a 10 μs wide pulse and the alternate stimulus pulse preferentially activated small diameter motor axons using a 350 μs quasitrapezoidal stimulus. The net effect was to create a two motor unit muscle, activating each motor unit separately and alternatively.

Grill and Mortimer [27] described a way to manipulate the excitability of large and small diameter axons closer to and further away from the stimulating electrode by using a "pre-pulse". A "pre-pulse" is a subthreshold stimulus with a duration that is usually

several hundred microseconds in duration and precedes the depolarizing stimulus pulse. The technique takes advantage of the fact that the effects of an electrical stimulus are greatest on large diameter nerve fibers and nerve fibers that are closest to the stimulating electrode. These facts apply to hyperpolarizing stimuli as well as depolarizing stimuli.

The effect of the "pre-pulse" is directed at the so-called "h" parameter, which describes the proportion of the voltage gated sodium ion channels in the inactive-activatable state (see Chap. 2.1). Under resting conditions roughly 40% of the sodium ion channels are in the inactivated-inactivatable state ("h" ~ 0.6). A subthreshold depolarizing pre-pulse will increase the relative number of voltage gated sodium ion channels in the inactivated-inactivatable state, making the patch of nerve membrane that experiences the field created by the pre-pulse less easily excitable or raises the magnitude of the stimulus required to initiate an action potential. A subthreshold hyperpolarizing pre-pulse has the opposite effect, e.g., it increases the relative number of voltage gated sodium ion channels that are inactivated-activatable state, ("h" >0.6), making the patch of nerve more easily excitable.

The results of pre-pulse simulation experiments are shown in Fig. 19. In panel **A**, when a 500 μs cathodic pulse was delivered; the 20 μm axon required a lower stimulus amplitude to initiate a propagated action potential, increasing with increased electrode-nerve separation, and the threshold current was least for the large diameter axon. In panel **B**, a 500 μs depolarizing pre-pulse increased the activation threshold for axons closer to the electrode more than for those spaced further from the electrode, meaning that fibers further away from the electrode had a lower threshold than did fibers closer to the stimulating contact, indicated by the region highlighted in yellow. Panel **C** is shows the results when a two step subthreshold pre-pulse was applied.

Two effects stand out. First, the region where distant axons have a lower threshold than closer axon is extended from that shown with the single step pre-pulse (region highlighted in yellow). Second, the small diameter fibers have a lower threshold as compared to the threshold for the larger diameter fibers (stippled region). These results are accounted for by the fact that the inactivating effects of the depolarizing pre-pulse are greater on larger diameter fibers than on small fibers and are greater on axons closer to the electrode than on those more distant.

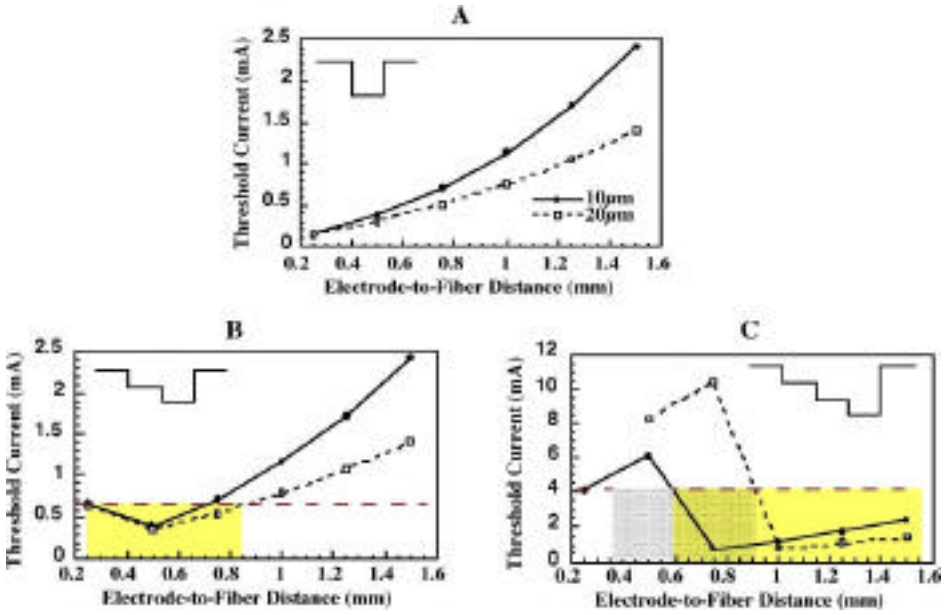


Figure 19. Graphs depicting the threshold stimulus current required to cause a propagating action potential in nerve fibers of two different diameters as a function of separation between the axon and stimulating electrode. These data were collected using a simulation paradigm similar to that described by McNeal (McNeal 1976). The duration of each phase of the stimulus pulse was 500 μs. Panel **A** is a graph of the results for a single depolarizing pulse. Panel **B** is a graph of the results when a single depolarizing pre-pulse was applied. In the yellow highlighted region the fiber more distant to the electrode had a lower threshold compared to fibers close to the electrode. Panel **C** is a graph of the results when a two step depolarizing pre-pulse was applied. In the yellow highlighted regions fibers further from the electrode had a lower threshold that fibers closer to the electrode. In the stippled region, small diameter fiber had a lower threshold than did the larger diameter fibers (Grill and Mortimer 1995).

### 5.1.4.4. Selective activation of axons in peripheral nerve fascicles

Axons in specific fascicles of a peripheral nerve can be selectively activated, particularly if the stimulating contact is in close proximity to the fascicle containing the target axons. McNeal and Bowman [42] hand-placed stimulating electrodes over the target fascicles to achieve selective activation. Under implant conditions it is not possible to align a stimulating contact with each particular fascicle in a nerve bundle. Therefore, under implant conditions it would be desirable to be able to "tune" the electrode by "steering" the applied fields to create a virtual excitation site at or in the target fascicle. Chintalacharuvu, [17, 18] studied the effects of the simultaneous application of currents to more than one contact in a model of a peripheral nerve with a close fitting cuff electrode

and the electrodes aligned along the long axis of the axons. The simulation results showed that:

- Steering currents applied from contacts placed on opposing sides of the nerve or from contacts that were adjacent to each other on the outside surface of the nerve could alter the region of the nerve where extracellular potentials were at or above threshold. "Field steering" improved the selectivity.
- Longitudinal tripolar configurations were more selective than monopolar configurations. A longitudinal tripolar configuration utilizes three in-line contacts, aligned with the long axis of the nerve, with the center contact providing depolarizing or hyperpolarizing currents and the flanking electrodes acting as the return electrodes. A monopolar configuration has no flanking electrodes and uses a remote return electrode.
- Threshold currents for excitation were greater for tripolar configurations than for monopolar configurations.
- Snug fitting cuffs were more selective than loose fitting cuffs.

A major consideration for the tripolar electrode is manufacturing the electrode/lead assembly. Designs currently in use employ four radially placed contacts, one for a monopolar and three for the tripolar configuration. Four radially placed monopolar electrodes requires four independent leads while four radial placed tripolar electrodes will require at least eight or twelve independent leads.

A lead assembly containing eight or twelve independent conductors, disregarding a connector with this number of conductors, is difficult to construct and is much less compliant than a four conductor lead. This concern provided an impetus for Tarler [69] to explore the consequences of using a monopolar cuff configuration rather than a tripolar configuration. Experiments were carried out on cat sciatic nerve, which is approximately 3 mm in diameter and contains four major motor fascicles, to quantify the selectivity that was achievable with self-sizing spiral cuff electrodes containing four monopolar and four tripolar radially placed contacts. The results of these experiments showed that ankle torque, in three dimensions and over a range from threshold to full motor axon recruitment, elicited with monopolar and tripolar electrodes was statistically indistinguishable. Therefore, even if a tripolar configuration is the "gold standard", monopolar configurations in a self-sizing spiral cuff , to a first approximation, can be expected to work reasonably well

### 5.1.4.5. Tunable electrodes

When multicontact cuff electrodes are placed around a peripheral nerve, contacts may not necessarily be aligned with a target fascicle. A remedy could be either to add more

contacts to the electrode assembly or develop a means to "tune" the electrode. With multiple contacts available, virtual excitation sites can be created by superimposing the electric fields generated by simultaneous application of currents to two or more contacts in the electrode assembly.

Tarler has explored "field steering" as a technique to creating virtual excitation sites that are different from the physical location of an actual stimulating contact [69]. These experiments were carried out with self-sizing spiral cuff electrodes, containing four radial contacts, implanted on cat sciatic nerve. The cat sciatic nerve is ~3mm in diameter and contains four major motor fascicles. Tarler found that, by random chance, about two-thirds of the time one of the four contacts was positioned to excite selectively and controllably one of the four motor fascicles in the sciatic nerve. In one of the nine animals, all four contacts could selectively and controllably activate a single fascicle. In those cases where a single contact could not activate a target fascicle, field steering was shown to be an effective means of creating a virtual excitation site confined to a target fascicle. Figure 20 shows the results of an experiment performed by Tarler where "field steering" was demonstrated [69].

In the experiments shown in Fig. 20, three of the four motor fascicles could be selectively activated, MG, LG and Tib, by contacts 90˚, 180˚ and 0˚, respectively. Contact 270˚ resulted in coactivation of Tib and CP. Selective activation was assured by comparing the torque resulting from stimulation applied to the isolated nerve branch to the CP, MG, LG, and Tib, with the torque recorded when stimuli were applied to each electrode contact. When an anodic stimulus was applied to contact 0˚, while a cathodic stimulus was applied to contact 270˚, a virtual excitation site was created for the CP fascicle.

Two additional observations can be made from the results depicted in Fig. 20. First, if an electrode contact is reasonably close to a fascicle, it appears to be fairly easy to isolate the stimulus to that fascicle. Under these conditions, which have occurred quite often over the last decade in our laboratory, it is possible to recruit all of the motor fibers from threshold to full recruitment before axons in adjacent fascicles were activated. Second, when looking at the recruitment characteristics of the tibial nerve, there is a hint that subfascicle selectivity may be possible. The tibial nerve serves several muscles that operate around the ankle joint, with two groups dominating the torque profile. The two groups form the sides of a parallelogram (shaded in Fig. 20). When stimulus currents are applied to contact 0˚, the group producing predominately medial rotation is activated first followed, at higher stimulus levels, by the component producing more plantar flexion. On the other hand, when stimuli are applied to the contact on the tibial branch, the order in which the fascicles are recruited is reversed. There is a strong indication here that motor axons serving a specific muscle are collected together rather than being randomly placed in the fascicle.

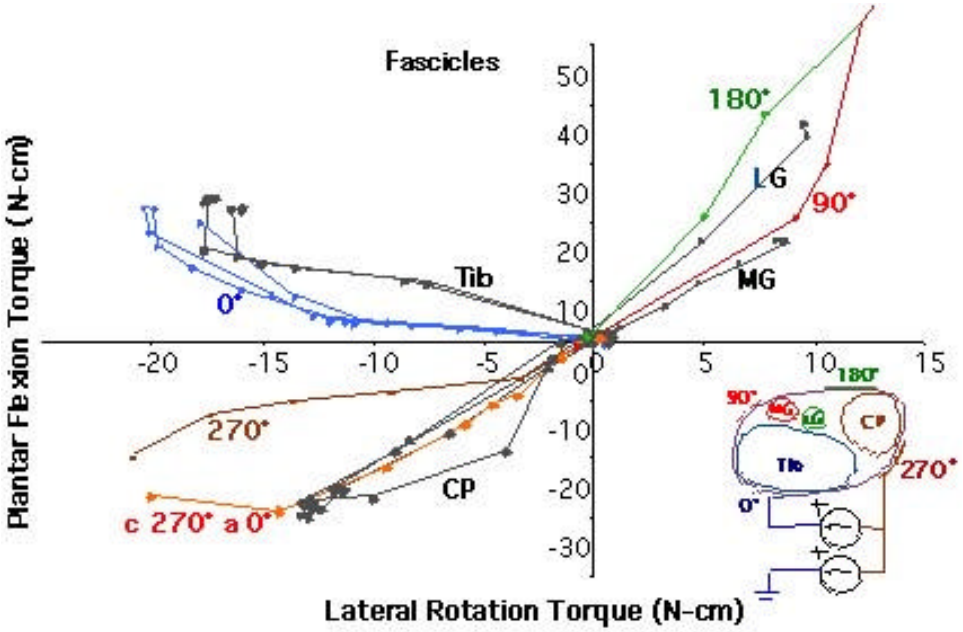


Fig. 20. Data reported by Tarler showing that "field steering" techniques can be used to create virtual excitation sites or tunable electrodes. The coordinates of the plot are ankle torque in two dimensions, Planter Flexion/Dorsi-FlexionData and Medial/Lateral Rotation. Data shown are for evoked ankle torque resulting from stimulation applied to various contacts within the self-sizing spiral cuff electrode. Also included on this graph are torque measurements recorded when stimuli were applied to each of the four isolated motor nerves, labeled Tib, CP, MG and LG. The drawing, shown in the lower right hand portion of the figure, provides an approximation for the nerve anatomy relative to the position of the four electrode contacts labeled O˚, 90˚, 180˚ and 270˚. A schematic of the stimulator configuration used to apply current for the multiple contact electrode is also shown. Single dots represent data collected a different stimulus levels. In this experiment, the Mg, the LG and the Tib branches were selectively activated over the full range by contacts 90˚, 180˚ and 0˚ respectively. Stimuli applied to the 270˚ contact appeared to activate both the tibial and common peroneal fascicles. Anodic steering (designated c270˚a0˚), anodic current applied to contact 0˚ made it possible to activate selectively only the CP fascicle from the self-sizing spiral cuff electrode {NB: this doesn't correspond to what is on the figure} (Tarler 2000).

### 5.4.1.6. "Simultaneous" activation of more than one target group of axons

Consider the challenge of producing a motor response that is the sum of torques produced by simultaneous electrical activation of two motor axon populations, each serving a different muscle acting around a common joint. If the stimulating contacts are sufficiently far apart, the stimulation induced fields do not interact. However, if the contacts are sufficiently close together, the induced electric fields can overlap to effect

depolarization of a larger number of axons than the sum of the axons activated when stimuli are applied separately.

For example, when axons in fascicle Tib are activated by a cathodic stimulus applied to contacts 180˚ and an anodic stimulus applied to 90˚ ((c180˚a90˚), Fig. 21), a torque is measured as shown in Fig. 22. Similarly, when a stimulus is applied to contact 0˚ Torque (c0˚) torque is measured,.

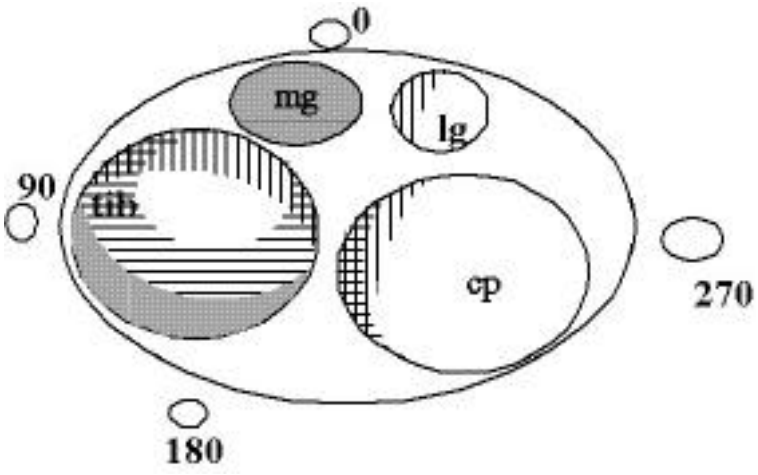


Fig. 21. Schematic representation of cat sciatic nerve containing four motor fascicles, tibial (tib), medial gastrocnemius (mg), laterial gastrocnemius (lg) and common peroneal (cp). Electrode contacts in the self-sizing spiral cuff electrode are labeled 0˚, 90˚, 180˚, and 270˚. Grayed areas represent axon populations activated when stimuli (c180˚a90˚) and (c0˚) are separately applied. The vertically hatched areas depict axons stimulated to subthreshold levels by (c0˚), and horizontal hatched areas depict axons stimulated to subthreshold levels by stimuli (c180˚a90˚). Regions where the two subthreshold regions overlap to create suprathreshold excitation have overlapping horizontal and vertical hatched areas.

The grayed area in Figure 21 depicts the axons that are depolarized by the stimulus when stimuli are applied to activate only one of the two populations of axons. The vertical hatched area depicts axons that have been partially depolarized by stimuli applied to the 0˚ contact and remain hyperexcitable for a period of time following the application of the stimulus. The horizontal hatched region represents the axons that have been partially depolarized by stimuli applied to contacts 90˚ and 180˚ and remain hyperexcitable for a period of time following the application of the stimulus.

When stimuli are applied at the same time to contacts 0˚, 90˚ and 180˚, the hyperexcitable regions overlap and the torque produced by these axons is added to that produced by the axons in the grayed regions. Under these circumstances the resulting torque is not a linear sum of the torques produced by axons in the grayed regions. A linear sum of the two torques would be a torque in the area of the upper right hand portion of the graph shown in Fig. 22 (circle labeled “Expected torque sum”). Instead of

the torque that was desired, a torque in the left hand portion of Fig. 22 was recorded (circle labeled "Combined stimulation with 20 μs delay").

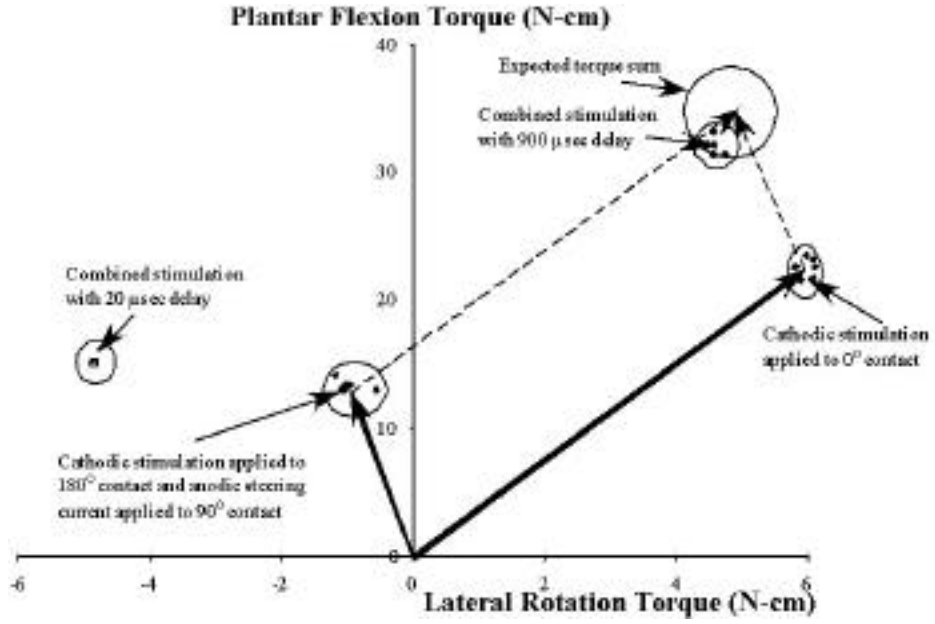


Fig. 22. Graph of torque measured when stimuli were applied to effect activation of two separate populations of motor axons. The bold lines represent the torque measured when separate stimuli were applied. When the stimuli were applied with a separation of 20 μs, which is essentially with no delay between the stimuli, the resulting torque was that shown circled in the left hand portion of the graph. When the stimuli were applied with a 900 μs separation between the pulses, the resulting torque was a linear addition of the separately evoked torques (Tarler 2000).

Excitation of axons in the subthreshold-hyperexcitable regions can be avoided if a delay is introduced between the time a stimulus is applied to effect activation of one set of axons (e.g. grayed area in the tibial fascicle and the other set of axons, the grayed population in the medial gastrocnemius fascicle). The delay must be sufficiently long to allow the axon membranes to recover from a hyperexcitable state and sufficiently short to avoid a physical response that appears as two separate responses, i.e., contractions. Tarler found that a delay of 700 to 900 μs was long enough to enable full recovery from the hyperexcitable state and still be within the refractory period of all axons [69]. Stimuli applied to two motor nerves separated by 700 to 900 μs appears at the joint as if the stimuli were applied simultaneously. Experimentally, when a 900 μs delay was added between the stimuli to the two populations, Tarler recorded a torque that was a linear addition of the torque vectors when stimuli were applied separately (upper right hand portion of Fig. 22).

### *5.2. Intraneural electrodes*

Many of the neuronal structures targeted for stimulation are embedded in surrounding neural tissue, particularly in the central nervous system. To gain electrical access to these structures without excitation of intervening cells gave impetus to the exploration of electrodes that penetrate into the neural tissue. There is a trade-off between specificity of stimulation with lower current usage on one hand and some damage to the penetrated tissue on the other. This approach has also been applied to peripheral nerves, to closely approach a nerve fiber for stimulation or recording. It was thought that to selectively stimulate any particular nerve fiber, an electrode had to be applied close to the fiber inside the nerve. Intraneural electrodes are positioned to penetrate the epineurium around the nerve trunks. Subsets of these electrodes are meant to enter the perineurium around the fascicles and go between the nerve fibers and are called intrafascicular electrodes. Intraneural electrodes, which do not enter the fascicles, have also been termed *inter*-fascicular electrodes.

An early method used coiled wire electrodes inserted into the nerve [10] Electrodes were implanted in rabbit tibial nerve and no significant changes in nerve conduction velocities were observed up to 9 weeks post-implantation. There was little change in motor current threshold beyond 10 days post-implantation. The nerves were reported to show little histologic demyelination or denervation in most specimens. Platinum and Platinum-Iridium, bipolar wire electrodes have been implanted intraneurally in experimental animals for recording nerve activity [35, 38, 47].

Veltink et al. published a modeling study of nerve fascicle stimulation of small monofascicular rat common peroneal nerve and multifascicular human deep peroneal nerve [77]. They also used intrafascicular and extraneural electrodes on rat common peroneal nerve. They reported that recruitment was more stable for intrafascicular electrodes than for extraneural electrodes with a lesser overlap of recruited motor unit groups with intrafascicular than for extraneural electrodes [76]

Pairs of Pt-Ir intrafascicular wire electrodes have been implanted in cats to determine if these could selectively activate separate subsets of axons in a single fascicle. An average overlap of activated nerve fibers was reported to be 5.5% between fascicles and 27% within a fascicle [81]. They also found a reduction in fatigue with the intrafascicular electrodes in cat gastrocnemius muscle; using interleaved dual channel stimulation [80].

Micro-machined electrodes exploited the feasibility of multiple electrodes in the dimensions suitable for approaching nerve axons. These electrodes were first fabricated with three or four shanks, each with active sites with area between 400 to 1600 $\mu m^2$ [79]. Electrodes were subsequently developed with greater numbers of active sites. It was thought that the electrodes should lie on a grid with a distance between electrodes based on the distances between the nodes of Ranvier. A linear 12-electrode array was used to

study selectivity of stimulation in the peroneal nerve of the rat [58]. Selectivity was found to be highest when two electrode sites were separated by 200–250 μm [59].

An intraneural electrode was developed to slowly penetrate the fascicle in order to lower the trauma of acute insertion. This slowly penetrating interfascicular nerve electrode (SPINE) was reported to penetrate the nerve within twenty-four hours without evidence of edema or damage to the perineurium and were showed functional selectivity in majority of experimental trials [72].

A silicon-based array of microelectrodes, which contained 25 to 100 electrodes, was used on the cat sciatic nerve, using a high velocity insertion technique. Currents at 10 μA range evoked muscle twitches and were stable for up to 60 h. [12].

Since the mid 90's, research and development in micromachined stimulating electrodes and microelectrode arrays have been carried out under the 'Neural Prostheses Program' funded by the National Institute of Neurological Disorders and Stroke, National Institutes of Health. The results of these and other electrode development projects have been detailed in the progress reports by the individual research teams (see Reference).

## 6. Summary

Muscles can be activated by electrodes placed on the surface of the skin, on the surface of the muscle, in the muscle, on the motor nerve or in the motor nerve. Each position of the electrode carries different attributes that should be taken into account when designing a motor prosthesis. Electrodes placed on the surface of the skin require the largest relative stimulus amplitude to activate muscle and result in a diffuse stimulus field that may give rise to unwanted movements and/or sensations. Placing stimulating electrodes closer to the target tissues by implanting them under the skin reduces the stimulus magnitude required to activate the nerve fibers and improves the likelihood that the stimulus will not cause activation of non-target neural tissue.

The effect of an applied electric stimulus is greater on large diameter axons than on small diameter axons and greater on axons that are closer to the electrode than on axons that are farther from the electrode. This means that if a stimulus is applied to effect axon depolarization, the larger axons close to the electrode will be activated at the lowest stimulus currents. Similarly, if a stimulus is applied to effect axon hyperpolarization, the larger, closer axons will be the most affected at the lowest stimulus currents. This finding opens opportunities to activate select neuron populations.

In skeletal muscle, as opposed to cardiac muscle, muscle cells are activated either directly by the applied stimulus or through their nerve supply rather than by propagation from adjacent muscle cells. Therefore, for direct muscle activation the stimulus level must be sufficient to activate all muscles cells of interest, which is usually all of the muscle cells in the muscle. Because the electric potential that results from an applied stimulus decreases inversely to the separation between the electrode and target cell, very

large stimulus amplitudes are required to directly activate muscle cells only a few millimeters away from the electrode. These amplitudes can easily be in excess of values considered to be noninjurious for all but the smallest muscles. For this reason, motor prostheses are considered practical only for muscles that retain their motor innervations.

Intramuscular electrodes are relatively easy to implant, particularly those having a percutaneous lead. They can be inserted with a hypodermic needle. The coiled wire intramuscular electrode is tolerated well by body tissues, in the subcutaneous tissues and at the sites where the electrode exits the skin, when the electrode is used as a percutanteous electrode. The compact cell layer formed around implanted devices provides a barrier that suppresses bacterial entry into the tissue spaces and a barrier to nutrients required to sustain bacterial growth in the area occupied by the wound lead. The "open" helix and the lose connective layer permit the lead to extend and compress under axial loads without a piston like action as would occur with a closed cylinder lead under similar loads. Piston like actions are believed to induce cell trauma and hence a chronic inflammatory response.

Cuff type electrodes can be used to effect a degree of selective activation, selectivity, that is not achievable with other configurations. Specifically, action potentials can be created that propagate in only one direction from the site of their initiation, antidromically or orthodromically, and the relative excitability of large and small diameter neurons can be manipulated. The factors that play a key role in cuff electrode selectivity are that the target tissues are bundled as a group with a known orientation to the cuff and that the cuff is usually constructed of an insulating material, which acts to constrain current flow.

Axons in specific fascicles of a peripheral nerve can be selectively activated, particularly if the stimulating contact is in close proximity to the fascicle containing the target axons. When multicontact cuff electrodes are placed around a peripheral nerve, contacts may not necessarily be aligned with a target fascicle. The simultaneous application of stimuli from more than one contact, "field steering", creates excitatory fields that are positioned at sites different than the individual electrode contact, "virtual electrodes."

The most recent technology to come on the scene involves electrodes inserted into the peripheral nerve. These contacts are in close proximity to many of the target fibers, which means that the stimulus threshold would be lowest of all the electrode configurations presented in this chapter.

## 7. Addendum: Electrode Cleaning Instructions

### *7.1.* Objective

The cleaning process is carried out on components and fabricated parts and devices to ensure a product that is maximally free of extraneous surface contaminants.

### *7.2. Consumables*

Ultra pure water (Resistivity ~18Mohms-cm)
Freon TMS-167 (Freon may not be available and a suitable substitute would need to found)
Safezone TMS-197 (Miller-Stephenson, Morton Grove, IL 60053, www.miller-stephenson.com)
Ethanol
Liquinox detergent (Alconox, Inc., White Plains, NY 10603, www,alconox.com)
Clean gloves.

### *7.3.* **Equipment**

Ultrasound bath
Clean glass container for storing electrodes

### *7.4. Preparation*

1. Prepare liquinox detergent solution by mixing with ultrapure water in the ratio of Liquinox: UPW = 1:10.
2. Check to ensure that there is sufficient water in the ultrasound bath to partially immerse the container used, without overflow onto the devices.
3. Place items to be cleaned in glass container.

### *7.5. Precautions*

Silicone containing products are NOT to be cleaned in either Freon or Safezone (both are used as degreasers) because these chemicals can cause mechanical distortion of devices using silicone rubber. Start process at Step 3 (below) for those products containing silicone rubber. Do not touch cleaned items without wearing clean gloves that are free of particulate matter (e.g., talc).

### *7.6. Procedure*

1. Sonicate in Freon (TMS-167) for 5 minutes.
2. Sonicate in Safezone (TMS-197) for 5 minutes.
3. Sonicate in prepared Liquinox/UPW mixture for 5 minutes.
4. Pour out solution and rinse in ultra-pure water.
5. Sonicate in ultra-pure water for 5 minutes.
6. Sonicate in ethanol for 5 minutes.
7. Sonicate in ultra-pure water for 5 minutes
8. Remove from bath and allow to dry on clean surface.

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http://npp.ninds.nih.gov/ProgressReports/

This is the URL to the web page with the Neural Prosthesis Program, Progress Reports and are a valuable resource because results appear in these reports that do not appear elsewhere.

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