MODELING INTERFASCICULAR INTERFACES FOR PERIPHERAL NERVES

by

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Abstract

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Stimulation electrodes with higher levels of selectivity than currently available are required to restore limb function, especially in the upper extremity. One strategy to increase the selectivity of an electrode is to move it closer to the target axons. A balance between selectivity and invasiveness can be made with interfascicular electrodes. We hypothesized that through Finite Element Method (FEM) models we could show that directed interfascicular electrodes placed within the nerve can achieve levels of selectivity equal to that of intrafascicular contact without penetrating the perineurium.

A simplified FEM model of a nerve was created of two cylindrical fascicles placed within a cube of epineurium. Using this model we showed that the contact-fascicle distance had a larger impact on the selectivity of a directed interfascicular contact than the relative diameter of the fascicles when the contact is less than 50 µm from the surface of the perineurium. When the contact is greater than 50 µm from the surface of the perineurium, the relative sizes of the fascicles have a more significant impact on the selectivity of the electrode. As the contact is placed closer to the surface of the perineurium, specifically within 50 µm, the surrounding fascicles have
a reduced impact on the overall selectivity. Additionally, we have shown that interfascicular electrodes can achieve levels of subfascicular selectivity greater than that of intrafascicular electrodes even when placed 50 µm off the surface of the perineurium.

A bio-inspired FEM model was created to compare the selectivity of interfascicular and intrafascicular electrodes in a more realistic environment. In each simulation, directed intrafascicular electrodes placed directly on the surface of the perineurium were able to achieve selectivity levels equal the intrafascicular electrodes. The results of the previous model were also corroborated, as the interfascicular contact-fascicle distance increased, the selectivity of the interfascicular contact decreased and the diameters of the neighboring fascicles had an increasingly significant effect. These results suggest furthering the exploration and development of directed interfascicular contacts with the primary goal of placing the contacts within 50 µm of the target fascicle.
Chapter 1: Introduction

This chapter presents background information relating to interfascicular stimulation. First, spinal cord injuries and functional electrical stimulation are explained. Next, the basic anatomy and properties of peripheral nerves are introduced. Current electrodes, along with their respective advantages and disadvantages, are introduced with a focus on their relation to interfascicular stimulation. The electrodes are grouped by their level of invasiveness and include extraneural, interfascicular, and intrafascicular electrodes. Finally, a more detailed look at existing interfascicular designs is performed with an emphasis placed on the differences between the interfascicular designs.

Spinal Cord Injuries

Each year, over 11,000 people in the United States experience a Spinal Cord Injury (SCI) (Wyndaele and Wyndaele 2006). Injuries of the spinal cord cause a disruption of the nervous system. The disruption interrupts the communication between the brain and the peripheral muscles and often leads to significant loss of muscle function for the patient, including complete paralysis (McDonald and Sadowsky 2002).

Functional Electrical Stimulation

One strategy for restoring muscle function after a SCI is through interfacing with residual nervous system below the injury to activate the functioning muscles. The
field of functional electrical stimulation (FES) is focused on achieving this interface through electrical means. A common implementation of the electrical interface is through a system of electrodes which stimulate and record from the peripheral nervous system.

The stimulation selectivity of an electrode, often simply referred to as selectivity, is a measure of the ability to activate only the intended target muscles. Selective activation is difficult in neural stimulation because of many factors including the properties of the electrodes, the anatomy of the PNS, and the electrical properties of the PNS. For example, in healthy and normally functioning nerves, the smallest fibers are activated first (Stephens, Garnett, and Buller 1978). This allows fine motor control and a smooth increase in force as larger axons and motor units are recruited last. With many current methods of electrical stimulation, however, larger axons are activated first. The reverse recruitment order of electrical stimulation makes achieving fine levels of motor control very difficult with FES.

The overall goal of any interface systems is to gain access to information from sensory afferents, selectively stimulate multiple nerve fibers, and to provide graded control of muscle force without damaging the nerve and surrounding tissues (A. Branner et al. 2004). In general, more invasive electrodes are more selective. The trade-off between invasiveness and the level of selectivity must be carefully considered and matched with the target application of the electrode interface system.
Electrical stimulation has found clinical application in restoring various functions including pain reduction (Chae and Hart 1998), ventilatory assistance (Chervin and Guilleminault 1997), control of hand movements (Bhadra, Kilgore, and Peckham 2001), lower extremity activation (Triolo et al. 1996), and micturition (Boger, Bhadra, and Gustafson 2008).

Peripheral Nerve Anatomy

The anatomy of the peripheral nervous system drives the design of interfacing electrodes. The cell bodies of the efferent axons of the peripheral nervous system are located in the spinal cord while the cell bodies of the afferent axons are in the dorsal root ganglion (Mazurek and Shin 2001). The afferent nerves receive stimuli from specialized receptor cells in both muscles and skin (Mazurek and Shin 2001). There are many stimuli of importance for FES including temperature and pressure from skin receptors and mechanical force from muscle receptors. The afferent nerves in the PNS tend to be of a smaller diameter than efferent nerves, from 2-20 µm, and can either be myelinated or unmyelinated (Matloub and Yousif 1992). Efferent motor nerves transmit motor signals and originate in the spinal cord anterior horn. There are two types of motor nerves, alpha-fibers which transmit motor control signals to the skeletal muscles of the body and gamma-fibers which innervate the smooth muscles of the body (Mazurek and Shin 2001). Efferent nerves are often myelinated and typically have a larger diameter than afferent nerve fibers (Enoka and Fuglevand 2001). Nerves are
collections of these various nerve fiber types and the relative proportion of each type of nerve fiber varies with the location and function of the nerve.

All peripheral nerves have the same basic architecture (Figure 1.1). Each nerve contains four distinct tissues: the epineurium, the perineurium, the endoneurium, and the nerve fibers (Mazurek and Shin 2001). The main function of the outermost layer, the epineurium, is to provide a blood supply to the nerve. It consists of loose connective tissue and contains many blood vessels (Sunderland 1965). Individual nerve fibers are bundled into groups within the nerve called fascicles. Fascicles are present throughout the length of the nerve, but their size and structure changes throughout the nerve due to various fascicles splitting and recombining down the nerve (Sunderland 1946).

The fascicle is surrounded by a membrane known as the perineurium. The perineurium is a tough, electrically anisotropic layer made up of both collagen and perineurial cells (Matloub and Yousif 1992). The perineurium is responsible for the tensile strength and endoneurium fluid pressure within each fascicle. In addition to the mechanical structure provided by
the perineurium, it acts a diffusion barrier within the nerve (Olsson and Kristensson 1973).

In naturally controlled muscles, the motor control signal is sent from the central nervous system into the efferent nerves of the peripheral nervous system (Hennig and Lømo 1985). Each motor nerve is terminated at a muscle junction and innervates multiple muscle cells. The nerve fiber and the muscle cell which it innervates are termed a motor unit. Control of a motor unit is a binary system; the units are either activated or inactivated. In natural control, graded muscle force is controlled by the number of motor units which are recruited and activated during a motion (Milner-Brown, Stein, and Yemm 1973). The smallest motor units are usually activated first, while larger motor units are only activated when extra force is required. Recruiting the smallest fibers first resists fatigue and provides fine control of the force exerted by each muscle (Enoka and Fuglevand 2001).

**FES Electrodes**

FES can be applied at the skin surface, muscle, and nerves within the body. Surface and muscle electrodes are selective to the muscles over which they are placed. These electrodes are affixed in or on the skin or the muscle and have been successfully used in restoring standing and reducing foot-drop in patients following a stroke (Daly et al. 2001). They cannot selectively stimulate deep or small muscles and require at least one electrode for each activated muscle (Guiraud et al. 2006). To achieve coordination in the large numbers of muscles in the upper extremity,
surface and muscle based electrodes would require a very large, and potentially impractical, number of electrodes.

Nerve electrodes are able to activate a large number of muscles with a single electrode. There several techniques to deliver FES at the level of the nerve. An important feature which distinguishes electrode designs is their location with respect to the nerve. Achieving a balance between invasiveness and selectivity has led to different designs including extraneural, interfascicular, and intrafascicular electrodes.

**Extraneural Electrodes**

*Epineural electrodes*

Epineural electrodes are implanted with a surgical procedure which sutures the electrode to the epineurium sheath of the target nerve (Thoma et al. 1989). The surgery is delicate and high tensile forces can pull the electrode from nerve. This limits their use in limbs which experience a lot of motion such as the arm (Girsch et al. 1991). Modern microsurgery techniques can attach multiple electrodes to the nerve to allow for bipolar stimulation. Epineural electrodes are used for the stimulation of the phrenic nerve for breathing control and for foot-drop improvement (Mayr et al. 1993).

*Circumneural Helical Electrodes*
Helical electrodes use a platinum ribbon wrapped around the nerve to ease the surgical procedure when compared to epineural electrodes because of their self-sizing ability. The design confirms the nerve into a circular shape which maximizes the volume of the nerve which is stimulated, but reduces the spatial selectivity. One drawback of the design is the open nature of the shape allows current to escape and therefore requires higher stimulation amplitudes and reduces selectivity. Helical electrodes are used for stimulating the vagus nerve which is used in the treatment of intractable epilepsy, sleep apnea, and the treatment of depressive syndromes (McLachlan 1997).

**Cuff Electrodes**

Cuff electrodes are constructed of an insulating sheath with imbedded electrodes (Navarro et al. 2005). The sheath surrounds the nerve in a similar manner to the helical electrode, but it is completely enclosed. This allows it to have many of the benefits of the helical design such as relatively simple surgical implantation with the added benefit of requiring an order of magnitude lower stimulation amplitudes (Loeb et al. 2001). Another difference between cuff electrodes and the helical electrode is that the contacts in a cuff
electrode are discrete instead of a continuous ribbon (Travers and Jackson 1992). Discrete contacts enable cuff electrodes to achieve more selective stimulation than helical electrodes (Loeb et al. 2001).

*Spiral Electrodes*

Different cuff geometries have been developed to ease implantation and increase selectivity. Similarly to helical electrodes, spiral electrodes are designed to be self-sizing and hold the nerve in a cylindrical shape (Naples et al. 1988). In contrast to helical electrodes, the spiral cuff electrodes contain discrete contacts which are placed circumferentially around the nerve. The inclusion of discrete contacts allows for the selective activation of fascicles within a nerve. The cylindrical shape of the electrode makes the selective activation of deep fascicles difficult to achieve with a standard pulse train. The electrodes have been implanted in both cats and humans. In cats, the electrode has been shown to be selective in the sciatic nerve (Tarler and Mortimer 2004; Tarler and Mortimer 2007). In humans, a spiral cuff was placed on the femoral nerve and used cuffs have been implanted on the deep peroneal nerve for nearly 30 years (Strojnik et al 1987, Polasek et al. 2007).

*Flat Interface Nerve Electrodes (FINE)*
Another cuff electrode design is the Flat Interface Nerve Electrode (FINE). This cuff electrode configuration applies a force to reshape the nerve into a flatter, more rectangular shape. The flat nerve provides better access to the individual fascicles to increase fascicular selectivity by bringing fascicles which are in the center of a cylindrical nerve closer to the surface (Tyler and Durand 2002). Additionally, the shape brings the fascicles closer to the contacts reducing the contact-fascicle distance which increases the selectivity. The FINE has been implanted in rats, cats, dogs, non-human primates, and humans. The electrode has been shown to be selective on the sciatic nerve of cats, the hypoglossal nerve of dogs, and the femoral nerve of humans. (Tyler and Durand 2002; Yoo, Sahin, and Durand 2004, Schiefer 2010).

Several studies have investigated the safety of the reshaping force from the FINE (Tyler and Durand 2003; Leventhal, Cohen, and Durand 2006). When implanted in rats, pressures of less than 60 mmHg did not produce statistically significant paw spreading or Wallerian degradation. When the pressure exceeded 60 mmHg, increased paw spreading was observed for 7 days, but disappeared after 14 days (Tyler and Durand 2003). To prevent nerve injuries, a set of equations guiding the design of the FINE have been developed. Implantations of
the FINE in cats have corroborated the results of the rat implantations (Leventhal, Cohen, and Durand 2006).

**Intraneural Electrodes**

Intraneural electrodes are more invasive than extraneural electrodes and are implanted within the nerve, either in the epineurium or the endoneurium. Intrafascicular electrodes penetrate both the epineurium and the perineurium of the fascicle, while interfascicular electrodes only penetrate epineurium of the nerve (Navarro et al. 2005). These electrodes require very little power to activate the nerve fibers and multiple contacts can be implanted in one nerve to provide independent stimulation of multiple fascicles (Ken Yoshida and Horch 1993). Several designs have been developed for both stimulation and recording.

**Fine Wire Penetrating Electrodes**

Longitudinally implanted intrafascicular electrodes (LIFEs) can achieve subfascicular selectivity by activating subsets of nerve fibers within a fascicle (Micera et al. 2008). These electrodes are constructed of thin insulated wires with a short exposed section. The wires are typically constructed of conducting polymer materials because of the relative flexibility of the polymer wires when compared to the flexibility of metal wires (K. Yoshida et al. 2000). The electrodes are implanted longitudinally into the fascicle by means of a thin needle. The hollow needle is inserted into the endoneurium in a parallel fashion to the direction of nerve travel until the barbed portion of the wire is centered within the
fascicle (Micera et al. 2008). These electrodes have shown fascicular selectivity and graded muscle contractions in acute animal trials (Micera et al. 2008). The selectivity and ability for these electrodes to elicit sensation in sensory nerve fibers make them a candidate for closing the feedback loop in current myoelectric prosthetics. The major drawback to LIFE electrodes are their difficult implantation procedure. Threading multiple LIFE electrodes into several different fascicles within one nerve is a difficult task.

**Microneedle Arrays**

Another type of intrafascicular electrode is the penetrating microelectrode such as the Utah Electrode Array. Microneedle arrays such as the Utah Array are constructed of a flexible substrate from which sharp contact protrude into the fascicles within the nerve (Figure 1.2) (Almut Branner and Normann 2000). In acute studies, both fascicular and subfascicular selectivity was reported without disturbing nerve function. The University of Utah has developed an insertion device which has been reported to insert microneedle arrays within the nerve without significantly disrupting nerve function (Almut Branner, Stein, and Normann 2001). However, chronic studies using the Slanted Utah Electrode Array and pneumatic insertion device reported a decrease in axoplasmic cross sectional area and an increase in the number of thinly myelinated axons within the fascicle (A. Branner et al. 2004). An additional concern with the use of microneedle arrays is the potential chronic damage associated with the stiff microneedles in limbs which have a large range of motion. Tethering forces and surgical implantation procedures can induce
damage and reduce the stability of the electrodes in chronic implant (A. Branner et al. 2004). One advantage of microneedle array electrodes is a physiological recruitment pattern (McDonnall, Clark, and Normann 2004).

**Interfascicular Electrodes**

A balance between the high selectivity of intrafascicular electrodes and the low invasiveness of extraneural electrodes can be obtained with interfascicular electrodes. The contacts of interfascicular electrodes are placed inside the epineurium of the nerve, but outside of the perineurium of the individual fascicles. Placing the contacts within the epineurium of the nerve allows for the contacts to get much closer to the target axons. One barrier placing stimulation contacts close to the target axons is the perineurium which surrounds the individual fascicles within a nerve. This membrane plays an important role in sustaining the health of the nerve and from as early as 1918 there has been speculation that puncturing the perineurium may cause damage to axon health (Sunderland 1946). The perineurium is a tightly packed sheath of connective tissue which acts as a diffusion barrier and is responsible for maintaining endoneurial pressure (Olsson and Kristensson 1973). The potential for chronic damage to the nerve provides motivation to develop electrodes which do not penetrate the perineurium.
Interfascicular disk electrodes were first simulated in 1989 (Veltink et al. 1989). Since, the late 80’s, interfascicular designs have undergone feasibility studies in silico. In 1989, Veltink performed simulations analyzing the effect that electrode-axon distance had on selectivity (Veltink et al. 1989). He looked at distance in relatively crude steps, comparing extraneural, interfascicular, and intrafascicular electrode designs. Veltink’s simulations used relatively simple disk electrodes in all three locations. He also did not look at parameters which affect the selectivity within each of the electrode locations.

**SPINE**

The Slowly Penetrating Interfascicular Electrode (SPINE) was designed to place several contacts within the epineurium of the nerve (Tyler and Durand 1997). This electrode featured penetrating elements which contained disk electrodes and were inserted in between fascicles of the nerve. These planes effectively divided the nerve into smaller sections with many fewer fascicles within each section. Histology confirmed that the penetrating elements of the SPINE electrode were able to alter the fascicular geometry of the nerve. The SPINE was able to achieve greater functional selectivity than comparable extraneural electrodes. Additionally, this study showed that

![Figure 1.7: The Slowly Penetrating Interfascicular Electrode](image)
varying the depth and location of the interfascicular contact resulted in different levels of selectivity. The fascicular selectivity of the SPINE interfascicular electrode was partially due to the insulating plane of the penetrating elements which was able to isolate the stimulating field to a subset of the total fascicles (Tyler and Durand 1997).

**Multigroove Electrode**

Around the same time that the SPINE was developed, Verloop reported another new interfascicular electrode design called the multigroove electrode (Koole et al. 1997). This electrode contained several mostly complete circular tracts of silicone. Inside these tracks were small contacts. The tracts were open at the top to allow for the insertion of fascicles. Using the multigroove electrode as an interfascicular electrode is invasive because it requires the dissection of the epineurium of the nerve and manually placing each fascicle within the grooves of the electrodes (Koole et al. 1997). This procedure nearly surrounds the fascicle and constrains the electric field from each contact to one fascicle. Verloop validated the design with both simulation and experiments. The multigroove electrode was able to achieve fascicular selectivity in both the simulation and acute animal experiments. Verloop investigated the effects of
placing both a cathodic and anodal contact within each fascicle tract (Koole et al. 1997). The simulations and the experiments resulted in a diminished inverse recruitment order when compared with extraneural stimulation. This is consistent with Veltink’s simulation results of intrafascicular electrodes which noted a decreased inverse recruitment order as the contact-axon distance decreases (Koole et al. 1997).

**Flexible Penetrating Electrode**

Stieglitz developed a flexible penetrating electrode using BIOMEMS materials. (Stieglitz and Gross 2002) Two conceptual electrodes were presented in the literature, one penetrating probe with a shape similar to a cortical probe and a penetrating “nerve plate”. The nerve plate was conceptualized as penetrating through the perineurium of the nerve and having contacts on both sides. The processes for creating these double sided flexible electrodes were described and the electrical properties of the electrode were documented, but no experiments or simulations of the use of the electrodes have been presented.

**Nielsen Electrode**

More recently, Nielsen et al. published a new interfascicular electrode design. (Nielsen, Sevcencu, and Struijk 2012) This design consisted of four silver contacts spaced by 1mm on a nylon tube. A suture is used to pull the electrode through the epineurium of the nerve. The interfascicular electrode was implanted at the bifurcation of the sciatic nerve in nine rabbits with two contacts facing the
peroneal fascicle and two contacts facing the tibial fascicle, the only two fascicles in the nerve. The electrode was able to selectively activate both fascicles at 100 and 98% selectivity. The electrode design was well suited for the two fascicle nerve and it has not demonstrated that the electrode design will translate to other locations.

**Peripheral Nerve Modeling**

The increased availability of computing power has made simulation an increasingly leveraged tool in electrode design. The dynamics of axon activation were first described by Hodgkin and Huxley. While the sub-threshold response of the model has been well described as an RC circuit, accurate models of the non-linear supra-threshold activation response have been more difficult to develop. Several assumptions, such as a consistent fiber diameter and the perfect insulating properties of myelin have been shown to be inaccurate and have been addressed in models developed after Hodgkin and Huxley's dynamics. Early models have assumed that myelin is a perfect insulator even though observations did not support this assumption. Subsequent models treated myelin as a highly resistive, but not perfectly resistive, insulator (Frankenhaeuser and Huxley 1964; Goldman and Albus 1968). Models which take into account the resistive nature of myelin, Nodes of Ranvier, and the periaxonal space have been more accurate in representing the activation dynamics of axons (Stephanova and Bostock 1996; McIntyre, Richardson, and Grill 2002). One of most accurate models, developed by McIntyre, Richardson,
and Grill, represents many of the non-linear dynamics of axons, but is computationally expensive to solve (Richardson, McIntyre, and Grill 2000; McIntyre, Richardson, and Grill 2002).

One area of focus in improving the effectiveness of simulation has been in the development of a fast and accurate approximation method. Several attempts have been made to linearize the non-linear activation function for axons. Warman, Grill, and Durand developed a method which used the second derivative and a linearized activation function to approximate axon activation (Warman, Grill, and Durand 1992). This method had good results when the contact was close to the axon, however, as the contact was moved further from the axon the accuracy of the activation approximation quickly decreased. Peterson, Izad, and Tyler developed a method which modified the driving function from a second derivative to a discretized second difference (Peterson, Izad, and Tyler 2011). Additionally, instead of linearizing the activation function, they used the nonlinear McIntyre, Richardson, Grill (MRG) model to calculate the activation with respect to pulse width and the spatial second difference of the voltage field (Peterson, Izad, and Tyler 2011). These calculations resulted in look-up tables with pre-calculated activation thresholds for various pulse widths. Since the activation approximations were calculated with the MRG model, they were robust for contact-axons distance. Peterson, Izad, and Tyler extended their method by calculating a multinode approximation by taking into account the weighted sum of the nodes along the axon. In the simulations presented here, both the single and the multinode methods will be used.
As computations become faster and cheaper, the use of Finite Element Models (FEM) to construct bio-inspired and electrically accurate models has increased. These models have been used to investigate the influence of various physical properties and electrical waveforms on activation (McNeal and Bowman 1985; Veltink et al. 1989; Lertmanorat and Durand 2004; Hennings, Arendt-Nielsen, and Andersen 2005; Schiefer, Triolo, and Tyler 2008). FEM’s have continued to become more accurate and have a finer resolution. One common assumption in the nerve FEM’s is that all fascicles have the same diameter. It has been shown that fascicle diameter varies and that the thickness of the highly resistive perineurium is 3% of the diameter of the fascicles (Gustafson et al. 2005; Grinberg et al. 2008; Gustafson et al. 2009). As the perineurium is the most resistive tissue, the fascicle diameter plays an important role the electric field within a nerve. A simplified nerve model will be used in these simulations to investigate the effects of fascicles with different diameters on the selectivity of the electrode.

**Research Motivation**

The restoration of upper extremity functions to those who suffer from an SCI requires more selective electrodes than are currently available for implantation in humans. For current electrodes, as the selectivity increases, so does the invasiveness. While high selectivity is needed to coordinate the movements of the many upper extremity muscles, a balance must be reached between selectivity and chronic stability. Functional electrodes must have minimal chronic effects on the
nerves. The highly invasive and selective electrodes have not been able to demonstrate the chronic stability needed for human implants.

A balance between the selectivity and invasiveness can be achieved with interfascicular electrodes. By placing the electrodes within the epineurium of the nerve, the contacts can be closer to the target axons than is possible with extraneural electrodes.
Chapter 2: Specific Aims

Aim 1: To determine the key design parameters which affect the selectivity of a directed interfascicular electrode.

The design parameters which influence the performance of the directed interfascicular electrode will be determined using finite element model (FEM) simulation. A simplified nerve will be constructed consisting of the tissues of the nerve including epineurium, perineurium, and endoneurium. The fascicles will be designed to approximate human fascicle size in both electrical properties and size. The simplified nerve will be surrounded by a simulated saline bath to simulate the volume conduction of the body. The directed interfascicular electrode will be constructed as two nested cubes sharing one adjacent face. The larger cube will have the electrical properties of silicone while the inner cube will have the electrical properties of platinum. Maxwell Ansoft (Ansys, V12) will be used to construct the mesh and perform the electrical simulations. The voltage field generated from the FEM models will be analyzed with MATLAB (V2010b) using activation approximation methods developed by Izad, Peterson, and Tyler.

The effect of the contact-fascicle distance on selectivity will be simulated. This simulation will be performed by moving a non-target fascicle with a diameter of 60% the target fascicle. The non-target fascicle will be moved
along a grid pattern. This process will be repeated as the contact is moved away from the surface of the target fascicle. The amplitude of a monophasic stimulus pulse will be increased until the target fascicle is fully activated. This process will be repeated for each position along the grid. A contour plot will be generated by demarking areas where the electrode was able to achieve the same levels of selectivity. The minimum contour where 100% selectivity was achieved will be determined for each contact-fascicle distance. A similar procedure will be used to determine the effect of the fascicular geometry of the nerve on selectivity. A similar simplified nerve will be generated, but in this case the size of the non-target fascicle will be varied and the contact-fascicle distance will be held at 50 µm. The non-target fascicle diameter will range from 10% to 100% of the target fascicle diameter. For each non-target fascicle size and each location along the grid, the amplitude of the monophasic stimulation pulse will be increased until the target fascicle is fully activated. The same contour and activation approximation which was used for the contact-fascicle distance will be used to determine the minimum contour where 100% selectivity was achieved.

**Aim 2: To compare both the fascicular and subfascicular selectivity of the directed interfascicular electrode with that of an intrafascicular electrode.**

To compare the selectivity of the directed interfascicular electrode and an intrafascicular electrode and FEM of an anatomically realistic nerve will be created. The histological slice of a human radial nerve will be traced and
digitized using ImageJ (NIH, Bethesda, M.D). The two dimensional nerve slice will be extruded into a three dimensional slice within Maxwell Ansoft. The electrical properties of the nervous tissue will be assigned and a directed interfascicular electrode or intrafascicular electrode will be placed within the simulated nerve. The interfascicular electrode will be either placed directly on the surface of the perineurium or placed some distance off the perineurium. The intrafascicular contact will be placed as close to the interfascicular contact as possible while staying within the endoneurium of the fascicle. A monophasic stimulus amplitude will be used to activate the axons. The amplitude of the axon will be increased over a range based upon the diameter of the target fascicle. The voltage field generated from the FEM will be exported into MATLAB and the fascicles will be populated with axons according to the anatomical distribution of size, location, and offset. An approximation method developed by Izad, Peterson, and Tyler will be used to approximate the activation of the axons within the model (Peterson, Izad, and Tyler 2011).

Additionally, a simplified model will be created within Maxwell Ansoft to simulate the subfascicular selectivity of the directed interfascicular contact and the intrafascicular contact. The model will consist of a nerve with one fascicle of realistic size for a human radial nerve. The nerve will contain the epineurium, perineurium, and endoneurium of the nerve. The nerve will be placed in a saline bath to represent the volume conduction of the body. Two
directed interfascicular contacts and two intrafascicular contacts will be placed within the nerve. The directed interfascicular contacts will be placed 50 µm off the surface of the perineurium. The intrafascicular contacts will be placed as close to the interfascicular contacts as possible while staying within the endoneurium of the simulated fascicle. The voltage field generated from the FEM will be exported into MATLAB for activation approximation and selectivity calculation. The subfascicular selectivity definition from Leventhal and Durand will be used to determine the number of independently activated axons within the nerve (Leventhal and Durand 2003).
Chapter 3: Modeling Interfascicular Interfaces for Peripheral Nerves

Abstract

Interfascicular electrodes provide a balance between the high selectivity of intrafascicular electrodes and the low invasiveness of extraneural electrodes. Using FEM modeling techniques, this study describes the parameters which affect the performance of the directed interfascicular electrode. The directed interfascicular contact is sensitive to both the contact-fascicle distance and the relative diameters of the target and non-target fascicles. A sensitivity analysis was performed and the selectivity of the directed interfascicular contact is more sensitive to the contact-fascicle distance than the relative diameters of the target and non-target fascicle when the contact is within 50 µm of the target fascicle. The directed interfascicular contact was able to achieve 87% subfascicular selectivity when located 50 µm off the surface of perineurium while the intrafascicular contact was able to achieve 76% subfascicular selectivity. When the directed interfascicular contact is placed directly on the surface of the perineurium it was 100% selective for each fascicle modeled, equaling the results of the intrafascicular contact. The directed interfascicular contact can achieve high levels of selectivity when placed within 50 µm of the target fascicle. When the contacts are placed on the surface of the target fascicle, the directed interfascicular contacts can achieve levels of selectivity, at both the fascicular and subfascicular level, similar to intrafascicular electrodes without penetrating the perineurium. Directed interfascicular contacts achieve a balance
between invasiveness and high levels of selectivity which will add function to existing neural interfaces.

**Introduction:**

There is a tradeoff between the degree of selectivity that a peripheral nerve electrode can achieve and its level of invasiveness (Navarro et al. 2005). One strategy for increasing the selectivity of neural electrodes is to get close to the target axons without disturbing the function of the nerve. Interfascicular electrodes are placed within the nerve, but outside the perineurium of the fascicles within the nerve. This level of invasiveness lies between intrafascicular electrodes and extraneural electrodes.

Intrafascicular electrodes achieve high levels of selectivity by penetrating the perineurium, a sheath of connective tissue which acts as a diffusion barrier and is responsible for maintaining endoneurial pressure (Stewart 2003). Example interfascicular designs, such as the Utah Slant Electrode Array (USEA) and Transverse Intrafascicular Multielectrode (TIME), contain contacts which are inserted perpendicularly to the nerve. In other designs, such as in the Longitudinal Intrafascicular Electrode (LIFE), the contacts are threaded into the fascicles along the length of the axons (Bowman and Erickson 1985; Almut Branner, Stein, and Normann 2001; Meier, Rutten, and Boom 1995;
Extraneural electrodes do not penetrate the nerve. They have been designed to ease implantation and minimize the effects of the distance between the contacts and the axons. Designs include helical, self-sizing spiral, and reshaping Flat Interface Nerve Electrodes (FINE) (Tyler and Durand 2002; Choi, Cavanaugh, and Durand 2001); (Sweeney, Ksienki, and Mortimer 1988).

A balance between the high selectivity of intrafascicular electrodes and the low invasiveness of extraneural electrodes can be obtained with interfascicular electrodes. The contacts of interfascicular electrodes are placed inside the epineurium of the nerve, but outside of the perineurium of the individual fascicles (Figure 3.1). Placing the contacts within the epineurium of the nerve allows for the contacts to get much closer to the target axons.

Several interfascicular designs have been proposed. The Slowly Penetrating Interfascicular Nerve Electrode (SPINE) electrode contained both extraneural and interfascicular contacts (Tyler and Durand 1997). Recently, Nielson et al. showed fascicle level selectivity using an interfascicular electrode in the sciatic nerve of a cat. (Nielsen, Sevcencu, and Struijk 2012) Both of these designs, however, include a large insulating plane as part of the interfascicular portion of the electrode. This effectively divided the nerve into compartments. The question addressed in this work is whether or not a hemi-point source could selectively activate portions of a peripheral nerve. The secondary question was how the recruitment of interfascicular placement compares with intrafascicular placement.
The simulations in this paper consider a new interfascicular electrode design, the directed interfascicular electrode. The contact in this design is embedded within an insulating plane which creates an asymmetric electric field. The asymmetric field can then be directed toward the target fascicle to increase selectivity.

Modeling a directed interfascicular contact in a simplified nerve model using Finite Element Methods (FEM) will allow us to determine the effects of the fascicle-contact distance on selectivity. Using the same model, we will analyze the effects of the relative diameter of non-target fascicles. A bio-inspired FEM model will also be developed to test and compare both the fascicular and subfascicular selectivity of the directed interfascicular contact and an intrafascicular contact. A sensitivity analysis will show that the contact-fascicle distance will be a more important design parameter than the relative diameters of the fascicles. Additionally, directed interfascicular contacts can achieve high levels of fascicular and subfascicular selectivity.

**Methods:**

Finite Element Method (FEM) models of a realistic human radial nerve cross-section and a simplified nerve (Figure 3.2) were analyzed. The simplified model (Figure 3.3) was constructed in Maxwell Ansoft (Ansys, V12) and consisted of two fascicles with both an endoneurium and a perineurium inside of a...
simulated epineurium. The entire nerve was contained within a cube of saline to represent the volume conduction of the body. The model was extruded to be a length of 60 mm to approximate an infinite nerve. (Schiefer, Triolo, and Tyler 2008)

The endoneurium of the anatomically realistic nerve was traced in ImageJ (NIH, Bethesda MD) and transferred into a three-dimensional FEM using Maxwell Ansoft (Ansys, V12). The perineurium was created in Ansoft as a tissue layer with a thickness of 3% the diameter of each fascicle. (Grinberg et al. 2008) The entire nerve was contained within a cube of saline to represent the volume conduction of the body. The model was extruded to be a length of 60 mm to approximate an infinite nerve. (Schiefer, Triolo, and Tyler 2008)

The directed interfascicular contact and insulation were modeled as nested cubes sharing one exposed face. The larger cube was modeled as insulation with the conductivity of silicone while the inner cube was modeled as a platinum contact. The contact was placed within the epineurium of the nerve. For comparison, an intrafascicular contact was also modeled. The intrafascicular contact was modeled as platinum cube with sides of 5 µm. The extraneural stimulation electrode was modeled as a FINE electrode with a silicone body and platinum contacts which were positioned around epineurium of the nerve.

The electrical properties of the materials used in both the simplified and anatomically realistic simulations can be found in Table 1 (Choi, Cavanaugh, and Durand 2001).

<table>
<thead>
<tr>
<th>Material</th>
<th>Conductivity (S/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x-direction (transverse)</td>
</tr>
<tr>
<td>Endoneurium</td>
<td>0.083</td>
</tr>
<tr>
<td>Perineurium</td>
<td>0.002</td>
</tr>
<tr>
<td>Epineurium</td>
<td>0.083</td>
</tr>
<tr>
<td>Saline</td>
<td>2.000</td>
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All voltage fields were imported into MATLAB (Mathworks, R2010). Two methods were used to analyze the activation of axons within the field. When a discrete value of selectivity was required, 100 axons were randomly placed within each fascicle. The distribution of the axon diameters followed the distribution of axons within the Ulnar nerve as described by Stewart. The Nodes of Ranvier of each of the axons were uniformly distributed within the internodal length as determined by the diameter of the specific fiber (Stewart 2003). A linear approximation method as described by Peterson, et al. 2011 was used to determine the activation threshold of the axons within the fascicles (Peterson, Izad, and Tyler 2011). To visualize the activation, a second method was used based on the probabilistic model described by Peterson. Axons were uniformly distributed throughout the space within each fascicle. The probability of each potential nodal position and axon diameter was compared with the second spatial difference of the voltage field to determine the overall probability of activation at each axon location. The collection of probabilities at each axon was interpolated to create a continuous probability density function of activation for each fascicle.

To gain a detailed view of the selectivity achieved with interfascicular stimulation, we developed a stringent definition of selectivity (Equation 1), where RB is the Recruitment Benefit, RC is the Recruitment Cost, A is the number of activated axons within a fascicle and N is the total number of axons within a fascicle.
The Recruitment Benefit is defined as the number of activated axons within the target fascicle. The Recruitment Cost is the number activated axons within a non-target fascicle multiplied with a proportionality factor. The proportionality factor weights the recruitment cost of non-target fascicles based on the percentage activated to take into account the functional consequence of a highly activated non-target axon. This value is calculated for each nontarget fascicle and then summed to give a total Recruitment Cost.

Each fascicle, whether target or non-target, can report a maximum recruitment benefit or recruitment cost of 100. In this study, the choice of target fascicle and the contact location are based on the experiment being performed.

Once a target fascicle is chosen, all other fascicles in the nerve are by definition non-target fascicles. Since typical nerves contain more non-target fascicles than target fascicles, this definition can lead to counterintuitive negative values of selectivity. A negative value of selectivity occurs when the sum of the recruitment cost for each non-target fascicle is greater than the recruitment benefit from the target axon.

\[
S_j = RB_j - \sum_{i=1}^{\# \text{Fascicles}} RC_i \quad i \neq j
\]
\[
RB_j = A_i \quad RC_i = A_i \times \frac{A_i}{N_i}
\]

Equation 1

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probabilistic mapping can be used to visualize the activation and the selectivity
definition is used to quantify the activation (Figure 3.3).

Subfascicular studies were performed by placing contacts on opposing sides of the
target fascicle. Subfascicular selectivity was then calculated using Equation 2 where
$A_1$ represents the axons activated by contact 1, $A_2$ represents the axons activated by
contact 2, and $A_{total}$ represents the total number of axons within the fascicle.

$$S_{sub} = \frac{A_1 \cup A_2 - A_1 \cap A_2}{A_{total}}$$  

Equation 2

Subfascicular selectivity is defined as the percentage of axons activated within a
fascicle by only one of the two contacts. A higher percentage of independantly
activated axons is desirable as it indicates a higher level of control over which axons
are activated and may allow for independent activation of multiple muscle groups
within a single fascicle fascicle.

As selectivity calculations are highly dependent on the location of non-target
fascicles near the target fascicle, a contour plot was used to visualize the selectivity
when the non-target fascicle is in a variety of locations. The contour plot shows the
locations of a non-target fascicle when 100% selectivity, or full activation of the
target fascicle and no activation in the non-target fascicle, is achieved. To analyze
the effect of contact distance, a non-target fascicle with a diameter 60% of the target
fascicle was moved across a grid surrounding the target fascicle. Fascicles with
smaller diameters have thinner layers of perineurium, which makes them easier to
activate. In the simplified model the non-target fascicle was given a diameter of
60% to conservatively represent the case of smaller target fascicle than non-target fascicle, as fascicle diameters can vary widely. (Saxod et al. 1985)

**Results:**

_Simplified Nerve Model_

To investigate the effects of electrode-fascicle distance, a simplified nerve model was constructed with two fascicles. First, the effect of the distance between the perineurium and the contact was investigated. Using this method, it was determined that the minimum distance that full activation can be achieved with a directed interfascicular contact 10 µm off the target perineurium is when the non-target fascicle is 300 µm away from the target fascicle (Figure 3.4). Using the same procedure it was found that the farthest non-target fascicle to target fascicle distance for full activation when the contact is off the target perineurium by 60 µm, 100 µm, and 250 µm are 650 µm, 700 µm, and 850 µm, respectively. These distances are the maximum of the limit of full selectivity (Figure 3.4). The minimum distance is lower directly behind the target fascicle, even when the contact is 100 µm away from the perineurium. The limit of full selectivity is only 100 µm from the perineurium of the target fascicle and is nearly on the perineurium when the contact is 10 µm off the perineurium. These results highlight the large effect on selectivity that the
fascicular geometry can have on extrafascicular methods of stimulation such as interfascicular and extraneural stimulation.

In addition to the location of the non-target fascicle and the distance between the contact and the surface of the perineurium, the relative diameters of both the target and non-target fascicles have a large effect on the selectivity of the directed interfascicular contact. As the relative diameter of the non-target fascicle is increased, the distance for full selectivity is decreased (Figure 3.5). If the target and non-target fascicles have an equal diameter the maximum distance for full activation is 450 µm and the minimum distance is 25 µm. The maximum selectivity when the non-target fascicle is 60%, 30%, and 10% of the target fascicle diameter is 625 µm, 790 µm, 845 µm, respectively. The corresponding minimum distances for full activation are 35 µm, 75 µm, 80 µm. The distance limits for full selectivity change as the diameter changes because of varying perineurium thickness. The thickness of the perineurium can be estimated at 3% of the diameter of the nerve. Since the perineurium is the most resistive tissue in the nerve, varying the relative sizes of the target and non-target fascicles varies the effective resistance of the target and non-target fascicle. When the target fascicle is near a very small non-target fascicle, high levels of selectivity are difficult to achieve. The thickness of the perineurium is the most resistive membrane within the nerve and is its thickness is a function of the fascicle diameter. As the fascicle
diameter gets larger, the perineurium gets thicker and the resistance of the fascicle increases. The lower resistivity of smaller fascicles makes them easier to stimulate than the more resistive larger fascicles. Penetrating the epineurium and placing a contact within the nerve may be able to achieve high levels of selectivity because of its ability to go within the nerve and get very close the target fascicle. The proximity of the contact to the target fascicle will allow the contact to avoid activating smaller non-target fascicles and achieve high levels of selectivity.

A sensitivity analysis was performed to determine the effect on selectivity of both electrode distance and non-target fascicle diameter (Figure 3.6). The electrode-fascicle distance sensitivity curve has two distinct regions of sensitivity which are sharply divided at an electrode distance of 50 µm. The sensitivity curve was bounded at 250 µm to represent the maximum distance between neighboring fascicles in the radial nerve from which the nerve model was based. A sample of 6 histological nerve slices and 39 fascicles from the radial nerve used to derive the realistic nerve model resulted in an average fascicle diameter of...
separation of 114 ± 57 µm. Between 2 µm and 50 µm, each micron of electrode-fascicle distance results in an additional 8.99 µm between the non-target and target fascicle for full selectivity. Between 50 µm and 250 µm, each additional micron of contact-fascicle results in a 1.02 µm increase of the distance between the non-target and target fascicles. The sensitivity of the selectivity to the size of the non-target fascicle was consistent throughout the range analyzed. The diameter of the non-target fascicle ranged from 10% of the target fascicle to 100% of the diameter of the target fascicle to represent the most difficult case of selectively activating a target fascicle with a smaller diameter than the non-target fascicle. Over this range, each one percentage decrease in the non-target diameter results in a 4.5 µm increase in distance between the non-target and target fascicles for full selectivity. The selectivity of a directed interfascicular electrode is most sensitive to the electrode-fascicle distance when the electrode is close to the fascicle. As the electrode is moved further than 50 µm away from the target fascicle, the relative diameter of the neighboring fascicle begins to dominate the selectivity of the sensitivity. The shift in selectivity sensitivity dominance has implications for electrode implantation within a real nerve. The simplified models predict that high levels of selectivity can be achieved if the contact is placed within 50 µm of the target fascicle. If the contact is further than 50 µm from the target fascicle, the relative diameters of the non-target fascicles will play an increasingly dominant effect on the selectivity, and high levels of selectivity will become more difficult to achieve.

Realistic Nerve Model
Stimulations from intrafascicular and interfascicular electrodes were simulated on three fascicles within the realistic nerve model (Figure 3.2). The three fascicles were chosen to represent varied diameters of both the target and neighboring non-target fascicles. The interfascicular contact used in this simulation was directly adjacent to the perineurium of the target fascicle. The intrafascicular contact was placed within the epineurium of the fascicle, just inside the internal surface of the perineurium. The intrafascicular and interfascicular contacts were able to achieve 100 percent selectivity on all three target fascicles (Figure 3.7). The maximum selectivity achieved by both the interfascicular and intrafascicular electrodes was not dependent on the size of the target fascicle or the size of the surrounding non-target fascicles.

It is unclear whether placing a contact directly to the perineurium is experimentally feasible, so the effect placing a directed interfascicular contact near, but not in contact with, the perineurium was investigated. The effect of the distance between the directed interfascicular contact and the perineurium of the target fascicle was investigated by modeling the selectivity as the contact was moved away from the perineurium of the target fascicle. The directed interfascicular contact at increasing
distances from adjacent to the perineurium, 10 µm, 50 µm, and 100 µm away from the perineurium achieved decreasing selectivity (Figure 3.8). There is a large reduction in selectivity when the contact is moved off the perineurium, even when that distance is as small as 10 µm. When the contact is 100 µm off the perineurium, it is only able to achieve 20% of the selectivity of an adjacent contact. As the distance between the contact and target fascicle increases there is greater activation in the non-target fascicles which leads to lower selectivity.

Subfascicular Selectivity

The subfascicular selectivity of both interfascicular and intrafascicular contacts was simulated. The interfascicular contacts were placed on opposite sides of the target fascicle 50 µm away from the surface of the perineurium. No non-target fascicles were included in this model. The intrafascicular electrodes were placed just inside the surface of the perineurium to minimize the spatial differences between the
interfascicular and intrafascicular contacts. The directed interfascicular contacts achieved a maximum subfascicular selectivity of 86 and the intrafascicular contacts achieved a maximum selectivity of 76 (Figure 3.9). At the stimulation amplitude which had the highest selectivity for the intrafascicular contacts, the intrafascicular contact had a lower selectivity than the interfascicular contacts. At this stimulation amplitude, the intrafascicular contacts activated more axons with both contacts while leaving more axons non-activated than the interfascicular contacts (Figure 3.10).

**Discussion:**

Finite element model simulations on both realistic and idealized nerves have shown that directed interfascicular electrodes...
can achieve a high degree of both fascicular and subfascicular selectivity. If the
directed interfascicular contact is placed directly on the surface of the perineurium
the level of the selectivity is equivalent to the selectivity achieved with
intrafascicular selectivity. As the directed interfascicular contact is moved off the
perineurium, the levels of selectivity decrease. These simulations have shown that
there are many factors that influence the selectivity of directed interfascicular
electrodes including the distance of the contact from the perineurium, the fascicular
geometry of the nerve, and the number of interfascicular electrodes present. The
simulation data presented can help drive the development of directed
interfascicular electrodes by identifying key design parameters.

To isolate the key design parameters such as contact to perineurium distance and
relative target fascicle size a simplified nerve model was created. The results of this
model have demonstrated the dependence of the maximum selectivity on the
relative size and location of neighboring non-target fascicles within the nerve.
Additionally, as the contact is placed further from the surface of the target fascicle,
non-target fascicles must be farther from the target fascicle to achieve the same
level of selectivity. This intuitive result highlights the importance of contact-fascicle
distance in interfascicular selectivity. More specifically, the selectivity of the
directed interfascicular contact is highly sensitive to the electrode-fascicle distance
when the contact is within 50 µm of the target fascicle. As the contact is moved
beyond 50 µm of the target fascicle, the relative diameters of the neighboring
fascicles, have an increasingly dominant effect on the selectivity which can be
achieved. These results suggest that interfascicular electrodes can be provide a functional increase in selectivity over existing electrodes, especially if the contact is placed close to the target fascicle. The distances between the contact and the surface of the perineurium are potential hurdles for achieving high levels of selectivity from extraneural electrodes. Solutions such as bipolar stimulation pulses and optimization algorithms have been implemented to help overcome the reduced selectivity caused by the large distance of the extraneural electrodes. If these solutions were applied to arrays of electrodes placed within the epineurium of the nerve, even higher levels of additional selectivity will be possible.

The simplified nerve model simulations have highlighted the dependence of interfascicular stimulation on fascicular geometry. As fascicular geometry cannot be determined ahead of implants, solutions overcoming this dependence must be general for any fascicular anatomy. The effects of non-target fascicle diameter may be minimized by placing the contacts within 50 µm of the target fascicle surface. Both the realistic and simplified models presented suggest that high levels of selectivity can be achieved with individual interfascicular contacts which are placed near the target fascicles.

Interfascicular stimulation is able to achieve high levels of subfascicular selectivity, even when the contact is not in contact with the perineurium. The high subfascicular selectivity of directed interfascicular contacts may make it possible to activate separate muscle groups within a single fascicle. Alternatively, two contacts
could be placed on opposite sides of the target fascicle and each contact would activate only 50% of the axons within the fascicle for full activation. This would reduce the maximum distance of a non-target fascicle required for full activation.

In these models, directed interfascicular contacts have been able to achieve levels of fascicular selectivity equal to intrafascicular contacts without penetrating the perineurium. The selectivity of the interfascicular stimulation is highly dependent on the distance between the contact and the target perineurium as well as the surrounding fascicular geometry of the nerve. Placing the directed interfascicular contact within 50 µm of the target fascicle will reduce the effects of the non-target neighboring fascicles. Utilizing arrays of interfascicular electrodes placed within 50 µm of the target fascicle may leverage the subfascicular selectivity of the directed interfascicular electrode in order to increase the selectivity of the interface and provide a functional benefit over existing electrode designs.

Chapter 3: Discussion

Designing FES systems which can restore high levels of function requires more selective peripheral nerve interface systems. In current electrode designs, there is a correlation between the level of invasiveness and the level of selectivity. As contacts are placed closer to the target axons both the selectivity and the invasiveness increases. In any electrode design, a balance must be achieved between the selectivity and invasiveness. Electrode designs such as extraneural, intrafascicular,
and interfascicular electrodes each achieve a different balance between selectivity and invasiveness. Extraneural electrodes do not penetrate the tissues of the nerve and implanted onto the surface of the nerve. Interfascicular electrodes are placed within the epineurium of the nerve, a loose translucent tissue which is responsible for holding the fascicles together (Matloub and Yousif 1992). Intrafascicular electrodes penetrate both the epineurium as well as the perineurium of the nerve. Penetrating these tissues minimized the resistance between the contact and the target axons. An additional factor for the design of peripheral interfaces is the ease of electrode placement. Balancing the selectivity and invasiveness of peripheral nerve electrodes has motivated the development of interfascicular electrodes.

Investigating properties such as the effect of contact distance and fascicular geometry with simulations allows for tight control of the nerve and experimental design. For this study, a simplified nerve was created to isolate the effects of fascicular geometry and contact-fascicle distance. The results of the simplified and well controlled nerve simulations were validated with anatomically accurate simulations. The anatomically accurate simulations were performed to validate the results of the simplified model and provide for a comparison between the selectivity of intrafascicular and the directed interfascicular contact. Finally, simulations were performed to investigate the subfascicular levels of selectivity achieved by both intrafascicular and interfascicular contacts. The results of these simulations can be used to drive design decisions as the directed interfascicular contact is developed.
Selectivity Definition

The high levels of selectivity achieved by both interfascicular and intrafascicular contacts required a selectivity definition which is more discriminative than previous definitions. Previous modeling simulations quantified selectivity using a method which compares the Recruitment Cost and the Recruitment Benefit as shown in Equation 1 (Schiefer, Triolo, and Tyler 2008).

\[ S = RB - RC, \text{ where } RC = \frac{A_i}{N_i} \]

This method calculates selectivity by subtracting the Recruiting Cost from the Recruitment Benefit. The “Recruitment Benefit” is defined as the number of activated axons within the target fascicle as a fraction of the total axons within the target fascicle. “Recruitment Cost” was likewise defined as the number of activated axons outside of the target fascicle as a fraction of the total number of axons outside of the target fascicle. This definition minimizes the impact of axons activated outside of the target fascicle if the nerve has a large number of non-target axons. Additionally, this definition does not take into account the percentage of each fascicle that is activated. Fully activating one target and one non-target fascicle should be reported as less selective than activating one target fascicle and a tenth of ten non-target fascicles because of the
functional differences between the two levels of activation. To gain a more detailed
view of the selectivity achieved with interfascicular stimulation, a different
selectivity definition was developed. The new definition calculates the recruitment
cost as the number axons within each non-target fascicle multiplied with a proportionality factor which weights the non-target fascicles based on the percentage activated. This value is calculated for each non-target fascicle and then summed to give a total Recruitment Cost. Each fascicle, whether target or non-target, can report a maximum recruitment benefit or cost of 100. Since typical nerves contain more non-target fascicles than target fascicles, this definition can lead to counterintuitive negative values of selectivity. With this definition, a negative value of selectivity simply means that the sum of the recruitment cost for each non-target fascicle is greater than the recruitment benefit from the target axon. For example, in a nerve with 12 fascicles the selectivity definition has an upper bound of 100 corresponding to full selectivity and a lower bound of -1100 corresponding to the activation of the entire nerve. A probabilistic mapping of the same nerve and stimulation parameters when both the old and new selectivity definitions report 80% selectivity can be used to visualize the selectivity measures (Figure 3.2). In the old definition there is activation in 5 non-target fascicles with one of the activated non-target fascicles being 100% activated. In the new selectivity definition, there is primarily one activated non-target fascicle with about 50% of its axons activated. The new definition reports 80% selectivity with many less activated axons than the previous definition because of the small non-target fascicle which has a high percentage of activated axons. The new definition
takes into account the percentage of the non-target fascicular activation in addition to the number of axons activated for a more detailed representation of selectivity in realistic simulations.

**Electrode Design**

A directed interfascicular contact was developed for use in these simulations. The contact consisted of two nested cubes which shared one face. The outer cube was constructed of highly resistive silicone and the inner cube was platinum. The nested cube design enabled a border of insulating silicone around the platinum contact. This design creates an asymmetric field which can be directed toward the target fascicle.

The simulations investigated several design parameters which influence the performance of the directed interfascicular contact. The specific design of the directed interfascicular contact has not been previously investigated. The contact was designed to represent many of the parameters which will be present in a physical design. It is envisioned that the directed interfascicular contact will be
constructed by removing a square section of insulation from an insulated wire. Therefore, the size of both the contact and the insulation was constrained by the diameters and insulation thicknesses of currently available wires. Due to FEM meshing constraints, the contact was modeled as a cube instead of a cylinder so that it could lay adjacent to the perineurium surface. The contact was carefully designed to create an asymmetric voltage field by exposing one face of the contact. The asymmetric field allows the current to be directed to a particular fascicle of interest and increases the selectivity of the electrode.

**Electrode Placement**

In addition to the design of the contact, the simulations provide insight into where to place the contact. Veltink established that as contact-axon distance decrease, selectivity increases in a macroscopic sense (Veltink et al. 1989). For example, he concluded that one of the reasons higher levels of selectivity are achieved with intrafascicular electrodes than extraneuronal electrodes is because intrafascicular contacts are placed closer to the target axon. There have been no studies, however, which have investigated the effect of distance on interfascicular electrodes. Additionally, the effect of neighboring fascicle size has not been investigated in the literature. While the fascicular geometry of a nerve cannot be altered, by investigating the effects of fascicular geometry can lead to more informed placement of contacts within a nerve.
Contact-Fascicle Distance

While several studies have shown that the distance between the stimulating contact and target axon plays a large role in the selectivity achieved by contacts both within and outside of the nerve, there is a lack of specific information on the effect of contact-axon distance for interfascicular electrodes (Cavanaugh, Lin, and Durand 1996). To investigate the effects of contact-axon distance on selectivity, a simplified nerve was developed within a 3D simulation space. This nerve consisted of two axons, a target and non-target axon. The non-target axon was 60% of the size of the target axon and was positioned along a grid to approximate all of the potential locations of a non-target fascicle. The directed interfascicular contact was then placed at various distances from the perineurial surface of the target axon. These simulations have shown that even within the interfascicular electrode space, the selectivity of an electrode is highly dependent on the distance between the electrode and the perineurial surface. To understand the effect that contact-fascicle distance has on selectivity, we performed a sensitivity analysis. The sensitivity curve for contact-fascicle distance has two regions. The sensitivity curve for the relative diameter of the non-target fascicle was linear over the entire analysis region. When the contact is within 50 µm of the fascicle surface, the sensitivity of the selectivity is more influenced by the contact distance. When the contact is beyond 50 µm, the sensitivity of the selectivity is dominated by the relative non-target fascicle diameter. This data suggests that to achieve the highest levels of selectivity, contacts should be placed as close to the surface of the perineurium as possible,
however, the most sensitivity is seen within 50 µm of the fascicle surface.

Additionally, if the contact can be placed directly on the surface of the perineurium, interfascicular contacts can achieve levels of selectivity equal to that of intrafascicular electrodes without penetrating the perineurium. While attaching a contact directly to the perineurium will likely be very difficult given the small size of the contacts and added complexity of the motion of peripheral nerves, these results provide strong motivation. If attaching a contact directly to the perineurium is technically infeasible, placing the contact as close to perineurium surface as possible will result in the highest levels of selectivity.

**Fascicular Geometry**

In addition to the contact-axon distance, the fascicular geometry has a significant impact on the selectivity that an interfascicular contact can achieve. The most resistive tissue within the nerve is the perineurium. It has been shown that the thickness of the perineurium is dependent on the diameter of the nerve that it surrounds. This dependency leads to a large discrepancy in the amount of current required to activate axons within large and small fascicles. In terms of selectivity, it is very difficult to selectively activate a large fascicle when there is a much smaller fascicle nearby. In these situations, the simulations show that the intrafascicular electrodes perform very well. The intrafascicle electrodes are located within the fascicle itself and therefore are much less influenced by neighboring non-target fascicles.
Extrafascicular contacts, including both extraneural and interfascicular contacts, are influenced by the fascicular geometry of a nerve. The effects of fascicular geometry on the selectivity of the directed interfascicular contact were analyzed using a similar simplified nerve model as was used for the contact-fascicle distance analysis. The model consisted of a target fascicle and a non-target fascicle. Both the size and the location of the target fascicle were varied along a grid. The results of the simulation show that the size of a neighboring non-target fascicle does have an effect on the selectivity. When the non-target fascicle is only 10% of the diameter of the target fascicle, the non-target fascicle must be 815 µm away from target fascicle to achieve full selectivity. If the non-target fascicle diameter is an equal to the target fascicle, a diameter of 400 µm, than the non-target fascicle only has to be 425 µm away from the target fascicle to achieve full selectivity. When the diameter of the non-target fascicle is in between those extremes, the distance required for full activation is also between 850 and 425 µm. All of these results assume the worst case scenario that the target fascicle will be larger than the non-target fascicle. In the best case scenario, where the target fascicle was much smaller than the non-target fascicle, than the minimum distance of the non-target fascicle for full selectivity will be much lower.

These results are intuitive, given the dependence on perineurium thickness on fascicle diameter, however they do provide some insight for design. The fascicular geometry and relative fascicle sizes cannot be known a priori and they cannot be
altered. The asymmetry in the minimum distance required for full selectivity plots can be leveraged however. The data show that the non-target fascicle must much further away when it is on the same side of the target fascicle as the contact. When the non-target fascicle is directly opposed from the contact, it can be much closer without affecting the selectivity. This suggests that the relative location of the contact has a large impact on the effect of the non-target fascicles. While the fascicular geometry cannot be known when the electrode is implanted, placing many contacts around each of the fascicles will yield an increased chance of a successful placement. The effects of the fascicular geometry can be minimized by placing many interfascicular contacts within the nerve in many different locations between the fascicles.

Subfascicular Selectivity

As the selectivity of peripheral nerve interfaces continues to increase, the goal of achieving subfascicular selectivity become more realistic. Achieving high levels of subfascicular selectivity will allow for more proximal implants that require the implantation of fewer electrodes. The level of subfascicular selectivity achieved by the directed interfascicular contact was compared with the level of selectivity achieved by intrafascicular selectivity. A simplified model of only one fascicle was used to investigate the levels of subfascicular selectivity. The two interfascicular electrodes were placed 50 µm off the surface of the perineurium. The intrafascicular electrodes were placed as close to the inside surface of the
perineurium as close to the interfascicular electrodes as possible to minimize the spatial differences between the contact placements. The interfascicular electrodes were able to achieve subfascicular selectivity of 86% while the intrafascicular electrodes were able to achieve subfascicular selectivity of 76%. The level of subfascicular selectivity is a measure of the number of axons within the nerve which are able to be independently activated by one of the contacts. In this measure axons which are activated by both contacts as well as those which are not activated are counted the same. The higher level of subfascicular selectivity which were achieved by interfascicular electrodes is supported by Rutten’s work which found that contacts must be separated by at least 250 µm for maximal subfascicular selectivity (Rutten, van Wier, and Put 1991). The selectivity of the intrafascicular contacts is limited by their more narrow separation. These results suggest that in realistic nerves interfascicular electrodes may be able to achieve subfascicular selectivity even if the electrode is not placed directly on the surface of the perineurium.

Anatomically Realistic Simulations

Simulations of anatomically realistic nerves were performed to compare the selectivity of interfascicular electrode and intrafascicular electrodes. The nerve which was modeled contained 12 fascicles of various diameters ranging from 153 µm to 650 µm. Three fascicles were selected as target fascicles for the simulations. The fascicles were chosen to capture a wide range of diameters and fascicular geometries and had diameters of 153 µm, 450 µm, and 650 µm. When the
interfascicular contact was placed directly on the surface of the perineurium, the
directed interfascicular contact was able to achieve 100% selectivity in all three
fascicles. The intrafascicular contact was placed as close to the interfascicular as
possible while still being inside the endoneurium. In all three fascicles the
intrafascicular contact was also able to achieve 100% selectivity. This simulation
shows that the directed interfascicular electrode can achieve levels of subfascicular
selectivity equal to that of intrafascicular contact without penetrating the
perineurium. The effect of the contact-fascicle distance was also analyzed. The
directed interfascicular contact was moved up to 100 µm away from the surface of
the perineurium. As the contact was moved away from the target fascicle, the level
of selectivity decreased. Even as the contact was moved by 10 µm off the surface of
the perineurium the selectivity dropped to 54%. The selectivity continued to
decrease and when the electrode was 100 µm off the surface of the fascicle, the
selectivity was down to 10%. This drastic drop in selectivity highlights the
importance of the electrode-fascicle distance. The more stringent definition of
selectivity strongly penalizes activation outside of the target fascicle. An 8-contact
extraneural electrode was also simulated for context and in all cases the extraneural
electrode was unable to achieve positive levels of selectivity. These results suggest
that functional selectivity gains over extraneural electrodes are possible with the
directed interfascicular electrode. To achieve the greatest increase in selectivity, the
distance between the directed interfascicular contacts must be minimized. If the
contact is placed directly on the surface of the perineurium, the directed
interfascicular contact can achieve levels of fascicular selectivity equal to the selectivity of intrafascicular electrodes without penetrating the perineurium.

**Modeling Error**

Computer simulations approximate conditions in the natural world and contain inherent assumptions and errors. When representing the complex natural world in a computationally efficient manner, assumptions must be made. These assumptions can have a large impact on the results of the simulation. To minimize these errors, it is essential to thoroughly understand the assumptions which are being made. The models used to investigate interfascicular simulation contain several layers of assumptions. The finite element model is built using a commercially available package, Maxwell Ansoft (Ansys, v12). This program creates a three dimensional mesh of the individual elements. Each element represents a discretized section of the natural world. The structures within the model can be assigned electrical properties to simulate electrical conditions in the real world. In practice, each element of the mesh must belong to one structure and can only contain one set of properties. The mesh of discrete sections is only able to approximately represent the physical structure of the nerve. For example, each element is made up of only straight lines. Therefore, smooth curves such as the edge of a round fascicle are constructed of many straight lines arranged in a circle. The construction of the mesh leads to an error in the physical structure. This error is managed by Ansoft as it iteratively constructs the mesh. Smaller elements are used until the mesh error is
below a predefined limit. In these simulations, the mesh error was always below 5%.

The contact used in these simulations does not perfectly reflect a contact which could be implemented in the natural world. First, the dimensions of the contact and insulation were determined based on commonly available wire diameters, however the contact was designed as a square. This shape was chosen to ease the meshing process and to investigate the effects of a contact placed adjacent to the perineurium. Additionally, wire leads were not modeled on this contact. Wires were not modeled to simplify the physical design of the simulation and to reduce the difficulty of the meshing process. Working within simulation space also allowed the contact to be placed in locations which may not be feasible in the natural world. It has not been shown that a contact can be sealed against the perineurium of a fascicle. This type of simulation allows for a feasibility analysis to determine whether developing an electrode which rests upon the perineurium is worth attempting. This type of error is difficult to quantify, but is leveraged to analyze situations which have not occurred in natural space.

In addition to the physical error which is introduced during the construction of the mesh and the placement of the contact, the electrical properties assigned to each tissue within the nerve introduce error. Electrical property data for the tissues of the nerve has been gathered from frogs. The properties and function of amphibian nerves are very close to that of humans. The close resemblance allows for the
approximation of human nerves with much more readily available frog nerves. Additionally, the electrical properties assigned in the model are averages over many different nerves. The properties of individual nerves can vary greatly and lead to varying electrode performance.

**Activation Approximations**

Activation approximation methods were used to reduce the computational cost of the simulations. Two different approximation methods were used, the single node approximation method and the weighted sum approximation method (Peterson, Izad, and Tyler 2011). Both methods use the second spatial difference of the voltage field to determine activation. An activation threshold is predetermined using the nonlinear MRG model of neural activation. The threshold is a function of the pulse width of the voltage and allows for a linear algebraic computation of the activation many times faster than the nonlinear MRG model (Peterson, Izad, and Tyler 2011). The single node and weighted sum approximation methods were chosen for their invariance to electrode axon spacing. Previous approximation methods exhibited large errors as the contact-axon spacing grew large. As contact distance was an important parameter for these simulations, the error due to contact distance had to be minimized. Both the single node and weighted sum method exhibited less than 5% error at all contact-axon distances (Peterson, Izad, and Tyler 2011).

The approximations and simplifications which must be made to make simulations tractable introduce error. Simulation results must, therefore, be viewed in context.
Simulations are especially useful for investigating general trends. The stimulation amplitudes and activation on the axon level will not translate to experimental models. Experiments performed in the natural world must be performed to validate these results. However, the results are useful in examining a very large search space and have the ability to precisely control the simulation environment.

The simulation results must be validated in actual experimental trials. Directed interfascicular electrodes need to be built out of conducting wire and implanted into real nerves. There are many things to be learned during the first few trials. First, the general concept of directed interfascicular selectivity needs to be validated. The presence of an asymmetric field can be detected by looking for significantly different recruitment patterns from the same contact in different orientations. Once the asymmetric field has been validated, the levels of fascicular selectivity need to be examined. The effects and practical consequences placing the contacts as close to the perineurium as possible need to be explored.

The results presented in this thesis have described several of the key design parameters for interfascicular electrodes. The design parameters presented each have a significant impact on the potential selectivity of the directed interfascicular contact design. The directed interfascicular electrode used to investigate these parameters was designed to be simple to help generalize the results. Each of the key design parameters, and the methods used for analyzing the selectivity of interfascicular electrodes, can be applied to new electrode designs. There are
several key results which should be stressed within the context of the interfascicular electrode design. The single most important parameter which affects the selectivity of the electrode is the distance of the contacts from the perineurium of the target fascicle. When the contact is placed directly on the perineurium of the fascicle, the directed interfascicular electrode was able to achieve levels of fascicular selectivity equal to intrafascicular electrodes without penetrating the perineurium. If the contact is placed farther away from the perineurium of the target fascicle, the level of fascicular selectivity drops significantly. Even when the contact was placed over 250 µm away from the surface of the target perineurium, the level of fascicular selectivity was greater than that of extraneural electrodes. These results suggest that even if placing and keeping an interfascicular contact on the surface of the perineurium proves infeasible, interfascicular electrodes could yield improved functional selectivity over extraneural electrodes. Additionally, the results from these simulations have shown that the fascicular geometry plays a significant role in the level of selectivity that a fascicular electrode can achieve. While this is an intuitive result, it highlights the advantage that interfascicular electrodes have over their extraneural counterparts. By placing the directed interfascicular contacts within 50 µm of the target fascicle, the effects of fascicle geometry can be minimized. This result also suggests that since the fascicular geometry of a nerve cannot be determined *a priori*, an array of implanted contacts may achieve the most success. When the two results are combined, the basics of a new interfascicular electrode design become apparent. An electrode with many directed contacts which can reach many different depths but all reach very close or touching the perineurium of the
fascicles of the nerve will be able to achieve high levels of fascicular and possibly even significant subfascicular selectivity.

**Future Applications**

One future application for this new type interfascicular contact is in junction with existing extraneural electrodes. It is not uncommon for most of the fascicles of the nerve to be close the surface of the nerve and easily accessible with extraneural electrodes. As extraneural electrode design gets better and the extraneural contacts get smaller, the benefits of interfascicular electrodes for activating fascicles close the surface may be small. However, extraneural electrodes will always have difficulty selectivity activating fascicles which lie deep within a nerve and are surrounded by non-target fascicles. In these situations, pairing high density surface contacts with directed interfascicular contacts which can penetrate the epineurium of the nerve and lie near the perineurium of fascicles which lie deeper within the nerve may prove beneficial. Adding internal contacts to the beam steering and algorithmic optimization techniques which are being developed for extraneural electrodes will also allow for higher levels of selectivity. Directed interfascicular electrodes may also be leveraged for subfascicular selectivity. These simulation results show that directed interfascicular contacts, even when they are removed from the surface of the perineurium, can achieve higher levels of subfascicular selectivity than intrafascicular selectivity.
Chapter 4: References


