COMPUTATIONAL MODELING TO EVALUATE HELICAL
ELECTRODE DESIGNS FOR USE IN VAGUS NERVE STIMULATION

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Anthony Cowley

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Committee Membership

Title:	Computational modeling to evaluate helical electrode designs for use in vagus nerve stimulation
Author:	Anthony Cowley
Date Submitted:	August 2010
Committee Chair:	Dr. Robert Szlavik, Associate Professor Biomedical & General Engineering Department California Polytechnic State University, San Luis Obispo
Committee Member	Dr. Scott Hazelwood, Associate Professor Biomedical & General Engineering Department California Polytechnic State University, San Luis Obispo
Committee Member	Dr. David Clague, Associate Professor Biomedical & General Engineering Department California Polytechnic State University, San Luis Obispo

Abstract

COMPUTATIONAL MODELLING TO EVALUATE HELICAL ELECTRODE DESIGNS FOR USE IN VAGUS NERVE STIMULATION

Anthony Cowley

An estimated 0.5% of world's population has been diagnosed with epilepsy. Of these patients 20-30% will be unable to achieve seizure control with anti-epileptic drugs. Vagus nerve stimulation (VNS) may be an appropriate treatment option for some patients with pharmaceutically refractory, partial-onset seizures.

VNS therapy uses a helical electrode to interface between the implantable pulse generator and the vagus nerve. While there have been several studies related to the mechanical and electrical safety of such electrodes, little work has been done toward understanding the effectiveness of the helical electrode in nerve stimulation. A better understanding of the voltage field and nerve fiber activation patterns produced by a helical electrode is necessary in order to evaluate its effectiveness and suggest design improvements.

This thesis is primarily focused on investigating the effect on nerve fiber activation of changing the circumferential coverage of the platinum conductor. Finite Element Analysis and a nerve fiber model were used to evaluate several electrode designs.

The circumferential coverage caused significant changes to nerve fiber activation. Coverage greater than 330°-360° was found to be inversely related to fiber activation. It was also noted that neurons located near the electrode ends, or near where the ends cross when coverage is greater than 360° were more difficult to activate. The phenomenon is discussed at length and several electrode design improvements were suggested based on these findings.

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Chapter 1: Introduction

Vagus Nerve Stimulation is used as a treatment for intractable epilepsy. In virtually all human studies and clinical practice this is achieved by stimulating the left cervical vagus nerve using the NeuroCybernetic Prosthesis (NCP) (Cyberonics, Inc. Houston, TX). VNS has been available for clinical treatment of epilepsy in the US since 1997.³ The therapy is delivered through an implantable pulse generator that produces a bipolar, pseudo-biphasic pulse. The implant procedure is very similar to the implantation of a pacemaker. The generator is implanted subcutaneously in the upper left chest wall. The lead is connected from the generator to the left vagus nerve in the carotid sheath using a subcutaneous tunneling tool.

The current VNS electrode was originally designed by Huntington Medical Research Institute (HMRI) and is made from platinum embedded in silicon. The electrodes are helical in shape, and consist of an anode, a cathode and a tether helical (Figure 1.1). Helical electrodes were developed as an alternative to the traditional nerve cuff, a cylinder with an open side which is placed on the nerve and sutured closed. The helical design gives the electrode a “self-sizing” feature, allowing it to expand and contract to account for post-implant inflammation and fibrotic tissue ingrowth without increased pressure on the nerve. Before implantation, the silicon portion of the helical consists of 2.5 turns ($\theta = 900^\circ$), and the platinum conductor consists of slightly less than one turn ($\theta = 330^\circ$). Unpublished autopsy studies from HMRI show that the ingrowth of connective tissue between the electrode and the nerve causes an increase in the diameter of the helix. This increase in diameter results in the platinum conductor going around three-fourths the circumference of the vagus ($\theta = 270^\circ$).⁴

There have been several studies related to the safety of helical electrodes. These studies attempt to predict or measure nerve damage due to mechanical pressure of the electrode and injury caused during implantation.⁵ Other studies investigated damage caused by electrical stimulation using helical electrodes.^{5,6} There has been little work done, however, to investigate the electric field within the nerve created by helical electrodes. A better understanding of the field and its effect on nerve stimulation is required to evaluate the effectiveness of the electrodes and suggest design improvements.

Finite element analysis (FEA) has been extensively used in the design of electrodes for nerve stimulation. For most functional electrical stimulation applications, that is, electrical stimulation aimed at restoring autonomic or somatic motor control, selective stimulation of a specific group of nerve fibers is necessary. Many published FEA studies have been directed toward this goal. While closed-form solutions to the field equations are available for non-selective stimulation, they are greatly simplified, and would not be applicable to the more complex geometry of a helical electrode. In 1995, Goodall, et al., made use of a 2-D FEA model and non-linear nerve fiber model to study propagation delays in neurons, and investigate proper stimulation techniques for neural blocking.⁷ Deurloo, et al. used a 2D FEA method to investigate fascicular selectivity in a nerve cuff with several electrodes surrounding the nerve. She applied several combinations of stimulus to the electrodes in order to investigate strategies to stimulate only a single fascicle.⁸ Another notable study used a 3D FEA model to aid in the design of a selective multi-contact electrode. In this study, Choi, et al. modeled two different

geometries, a round nerve cuff and a flat cuff, each with several distinct electrode configurations.⁹

The purpose of this study is to investigate the electric field created by VNS electrodes and suggest improvements in the current VNS lead in order to improve the efficacy of treatment and conserve generator battery power. The current objective of VNS therapy is to elicit maximal stimulation of the afferent A and B fibers in the vagus nerve in order to achieve a therapeutic effect. There are several reasons why maximal stimulation of these fibers is required for the treatment. First, because the causes of epilepsy are varied and not well understood, selective stimulation of a group of fibers to affect only a certain portion of the brain would likely not be effective. Also, unlike stimulation of motor neurons, there is no easily measured response to stimulation, making it difficult to determine which fibers are being stimulated during implantation of the device. Lastly, the low incidence of side effects associated with VNS suggests that maximal stimulation of the A and B afferents is well tolerated.¹⁰ The initial goal of the modeling study was to investigate lengthening of the platinum electrode and determine an optimal θ value to enhance nerve fiber recruitment. However, it was found that nerve fiber activation was inversely related to the length of the electrode. Adding length to the electrode increases its surface area and lowers the surface charge density on the platinum electrode. Further modeling was done to investigate changing the length while holding the surface area of the conductor constant.

Figure 1.1: VNS helical electrodes. Two of the helices deliver the stimulation, and the third is a tether to improve stability.

Chapter 2: Vagus Nerve Stimulation

VNS was approved by the FDA in 1998 as an adjunctive therapy for medically intractable epilepsy with partial onset seizures. Of people diagnosed with epilepsy, 20-30% will have medically intractable epilepsy,¹¹ meaning their seizures cannot be controlled by antiepileptic drugs. VNS is used in combination with anti-epileptic drugs bring relief to some of these patients.

The NCP contains two main components, the pulse generator and the lead which provides the interface between the pulse generator and the vagus nerve. The pulse generator is multi-programmable and allows the physician to control several parameters. The programmable parameters are signal amplitude (0-3.5 mA), frequency (1-30 Hz), pulse width (130-1000 μ s), signal ON time (7-60 sec), and signal OFF time (0.2-180 min). The pulses are then delivered at the specified amplitude and frequency over the course of the ON time, and then during the OFF time, no stimulation takes place. The device does not stimulate continuously because the antiepileptic effect lasts much longer than the actual time of stimulation. A typical setting might be 2 mA, 15 Hz frequency, 250 μ s pulse width, 30 sec ON time, and 5 min OFF time. The variability in parameters allows for the physician to adjust for greater efficacy or less severe side effects, depending on the patient.¹

The VNS electrodes are made in 2 mm and 3 mm diameters to accommodate for patient variability in the diameter of the vagus. The lead has two helical electrodes aligned axially and a third helical which acts as a tether to provide additional mechanical support for the electrodes (Figure 1.1). These three helices are wrapped around the mid-

cervical portion of the vagus nerve, inferior to the cardiac branches of the left vagus (Figure 5.1). The left vagus is implicated for VNS, because vagal innervation of the heart is asymmetric. The right vagus heavily innervates the atria, while the left primarily innervates the ventricles, making it more resistant to the cardiac fibrillation during stimulation which has been noted in some animal studies.¹⁰

Chapter 3: Epilepsy

In order to better understand the complexity involved in treating epilepsy either pharmaceutically or with VNS, and understand the possible mechanisms of action of the treatment, a basic discussion of the disorder is required. Epilepsy is a chronic disorder that is caused by an increased tendency toward an uncontrolled firing of a large number of neurons simultaneously. The International League Against Epilepsy (ILAE) defines it as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurological, cognitive, psychological and social consequences of this condition.”¹² A seizure occurs when an abnormal number of neurons fire in synchronicity. This is also called a paroxysmal discharge or an ictal event. Abnormal neural activity, is regularly observed in persons with epilepsy even when a seizure is not occurring.¹³ This is termed interictal activity. A single, observed seizure does not always constitute a diagnosis of epilepsy, as many other medical and physical factors may cause a seizure or seizure-like symptoms. In some cases, the ictal event may only occur once in a person's life, and would then be considered non-epileptic in nature.¹⁴

The ILAE defined several different classes of epileptic seizures in 1981, and a wide array of very specific types of epilepsy and epileptic seizures. Each type of epilepsy has a characteristic electroencephalogram (EEG) pattern which is helpful in diagnosis; although it is sometimes difficult to distinguish between different types of epilepsy due to their similarities or events that occur deep in the brain that don't register on the EEG. The most commonly used classifications come in the form of two broad groups, partial onset and generalized onset seizures, which are characterized by the areas of the brain

involved in initiating the seizure. Partial onset or focal seizures begin in a specific area of the cerebral cortex, while generalized onset seizures do not start at a specific point within the brain, and activity is seen throughout the cortex, in both hemispheres, at seizure initialization. The sub-classifications of partial onset seizures include simple partial seizures, complex partial seizures, and secondarily generalized tonic-clonic seizures. A simple partial seizure is a small localized seizure that does not result in loss or alteration of consciousness. These seizures are also called auras and can occur as sensory, motor, autonomic, and psychic types. A simple partial seizure can escalate to a complex partial seizure in which consciousness is impaired. The complex partial seizure will generally start with an aura and is followed by behavioral and movement changes and loss of consciousness. A patient may remember the aura, but not be aware of what followed. A complex partial seizure may further develop to a secondarily generalized seizure. These seizures usually begin with an aura, then a complex partial seizure, followed by a generalized tonic-clonic seizure; although, they may evolve to a generalized seizure directly from an aura, with no noticeable complex partial seizure.¹⁵

There are six major types of generalized seizures, including absence, tonic, clonic, myoclonic, primary generalized tonic-clonic, and atonic seizures. Absence seizures are incidents where consciousness is impaired. They are not preceded by an aura, are rarely remembered postictally and occur with very few visible external signs. Tonic seizures refer to a sudden extension or flexion of the neck, torso, and extremities, which is sustained for several seconds. While clonic seizures are rhythmic or jerking movements which may or may not be combined with impaired consciousness and often lasting several seconds. Another similar type is myoclonic seizures which are very short events

lasting less than a second. Myoclonic seizures are not always epileptic; many people experience myoclonic seizures shortly after falling asleep. These seizures, when epileptic in origin, can occur repeatedly and evolve into a clonic seizure. Primarily generalized tonic-clonic seizures are more commonly known as *gran mal* seizures. The event consists of a tonic extension of all extremities, and then widespread clonic rhythmic movements. *Gran mal* seizures result in consciousness impairment or loss and a large degree of post-seizure confusion. The only difference between primarily and secondarily (i.e., partial-onset) generalized tonic-clonic seizures is that the former lacks an aura. However, the aura, if it occurred, is often forgotten due to postictal amnesia. While most seizures are very brief, if a seizure lasts for longer than 30 minutes without a resumption of normal behavior, it is termed “status epilepticus.” If status epilepticus occurs with a generalized seizure, the mortality rates may be as high as 32%, according to some reports.¹⁶

Epilepsy has a wide variety of causes. *Symptomatic* epilepsies are those that arise through known events such as head injury, infection, or stroke. Epilepsies that occur due to unknown abnormalities within the brain, or that arise with no precipitating external event are called *idiopathic*. It is generally understood that a seizure occurs through the imbalance between the excitatory and inhibitory mechanisms within the brain in order to promote a net excitation of many neurons. In partial seizures, the symptoms displayed are dependent upon the specific area of the brain undergoing the seizure. For example, if a simple partial seizure occurred in the visual cortex, the symptoms associated would be visual in nature. Many factors have been identified that would likely make this net excitation more likely to occur. One of these factors is a defect in the function of sodium,

calcium, and potassium channels, and is supported by experimental observations. Drugs that prolong the length of time sodium ion channels are open, as well as drugs that block the potassium channels are known to cause seizures. Also, in animal studies, potassium-channel-knockout mice usually develop epilepsy, and ion channel mutations are linked to inherited epilepsy in mice and rats.¹⁵ Another factor is abnormality of neurotransmitters and their receptors, particularly inhibitory transport molecules. Evidence for this can be found in animal studies in which seizures are induced through drugs that lessen gamma amino-butyric acid (GABA) production or block inhibitory GABA receptors.¹³ Deficiency in tonic inhibition, an inhibitory response due to ambient GABA in the cortex, may also be a factor in epilepsy. The concentration of this neurotransmitter is regulated by a certain type of GABA receptor that senses ambient GABA concentration.¹⁵

A genetic factor in the formation of epilepsy has been recognized since the time of Hippocrates.¹⁷ However, the genetics of this disease are still not well understood. Forty years ago, Lennox and Lennox, proposed the theory that certain people may be genetically predisposed to epilepsy and that the disorder is triggered more easily in these individuals. More recent discoveries have been made that link certain types of idiopathic epilepsy to specific genes. Most of the identified genes regulate the formation of the ion channels in the nerve.^{13,18,19} Although some genes have been identified, the inheritance does not follow a simple Mendelian pattern. For an individual with idiopathic epilepsy, the chance that a sibling will have epilepsy increases from that of the general population (1.7%) to 3.6%, and the chance that offspring will have the disorder is 10.6%.²⁰ More distant relatives however have no increased risk for the disorder. Further evidence of genetic inheritance comes from twin studies. In monozygotic twins, if one has idiopathic

epilepsy, the probability that the other will have it is 49%. If the twins are dizygotic, the rate is only 16%.

Estimates of the prevalence of epilepsy are varied, which is most likely the result of differing definitions of epilepsy. The most accurate figures suggest that 0.5% of the population have epilepsy. Of this number, 20% to 30% of individuals will have intractable seizures, seizures that cannot be controlled pharmaceutically. It is estimated that 0.05 to 0.1% of the population will be diagnosed with epilepsy each year.²⁰

On average, people with epilepsy make less money and have an overall lower quality of life than the general public. Most epilepsy sufferers list anxiety, due to the unpredictable nature of the seizures, as one of their biggest concerns. Several studies indicate mental health is often affected in people with epilepsy. This could partially account for the higher rate of suicide and depression in people with epilepsy. One common cause of distress for those with epilepsy is the loss of driving privileges, often resulting in a feeling of loss of independence. Many states revoke a driver's license for a period of time following a seizure.¹¹ For further information about the effects of epilepsy on the life of the patients, refer to Appendix A.

Treating a patient who has had a single seizure or recurring seizures requires first discerning whether the patient has epilepsy or another disease that appears to mimic epilepsy. Examples of diseases that may appear similar to epilepsy are cardiac syncope, anoxic seizures, and breath-holding attacks. Once a diagnosis of epilepsy is reached, the physician must determine the seizure type experienced and/or a particular epilepsy syndrome. The proper determination will decide the treatment regimen and its success.

Chapter 4: Diagnosis and Treatment of Epilepsy

The clinical diagnosis of epilepsy and seizure type is heavily based on patient history, patient accounts, and witness accounts of seizure events. Physical examination and neurological tests are used mainly as support for the diagnosis. The patient medical history is helpful to physicians in determining whether the seizure was an acute event, or if it was a recurrent seizure in a person with chronic epilepsy. The physician should be aware of other seizure events in the past, as well as an occurrence of certain medical problems that would put the patient at a higher risk for epilepsy, such as high fever, meningitis, cerebral malaria, convulsions coinciding with a high fever (febrile seizures), head trauma, or other cerebral injuries. If the patient has, in fact, had other paroxysmal events, detailed history of these seizures should be sought in order to give the physician more information on the severity and progression of the disorder. Other facts the physician should gather in his diagnosis include descriptions of an aura, events during the seizure, specific environmental stimuli prior to the seizure, and any occurrence of status epilepticus.^{12,15}

Physical examination of a patient is also conducted during diagnosis of epilepsy. This can be helpful in ruling out epilepsy as a diagnosis in favor of another disease. It can also help determine whether there are factors within the heart or any systemic disease suggesting whether the seizure was an acute event or a chronic occurrence. Because epilepsy could stem from a structural abnormality in the brain, any injury or disease that may damage the brain would be of special interest. For example, evidence of arrhythmia, valve malfunction, or heart failure could cause an embolism resulting in a brain infarct. A thorough neurological examination may uncover brain lesions or evidence of another

neurological disorder as the cause of the ictal event. Evidence of bruising, lesions in the mouth, and prolonged confusion may indicate the seizure was generalized and epileptic in nature.^{14,15}

The major neurological diagnostic test is the electroencephalogram (EEG). While generally considered secondary to patient history in the initial diagnosis of epilepsy, it is used extensively in the determination of the seizure type. Interictal EEG tests in patients with generalized seizures may show a focal region of electrical abnormality strongly suggesting that the seizure is partial onset instead of primarily generalized. Furthermore, an EEG during an ictal event could show a recognizable pattern associated with a certain type of seizure.^{14,15,20}

Neuroimaging methods such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT) are mostly used by physicians in two situations. First, if a lesion is suspected as the cause of epilepsy in patients exhibiting progressive loss of neural function, neuroimaging is valuable in locating the lesion for possible surgical removal. The other instance is a patient with refractory partial onset seizures being considered for resection surgery. In this case, MRI can be combined with PET and/or SPECT to help find the focus of ictal onset.^{14,20,21}

The treatment of epilepsy is almost always initially pharmaceutical. A detailed discussion of specific drugs, their efficacy on certain types of epilepsy, and their mechanism of action is beyond the scope of this thesis. There is a wide array of anti-epileptic drugs, and each of these has specific types of epilepsy for which it is indicated along with certain situations where the drug is contraindicated. As an example, certain

drugs that were developed for partial seizures have been known to worsen generalized seizures in susceptible patients. Antiepileptic drugs are not always used alone; they can be used in combination with other drugs or another form of treatment for an adjunctive effect. Many of these drugs have a high frequency of cognitive side effects including lowered verbal memory, sedation, and attention problems. Other side effects can include dizziness, nausea, and tremor. These side effects can be severe enough to be debilitating. Unfortunately up to 30% of patients do not exhibit satisfactory seizure control without debilitating side effects.²²

One of the possible treatment options for those with refractory partial onset epilepsy is resection surgery. The procedure includes the use of neuroimaging and EEG data to determine the focus of the seizure onset, and physically removing or destroying the focus. This procedure is generally 30-50% successful in controlling seizures depending upon the size of the focal area and the absence of a nearby functionally crucial cortical area. Another surgical option is the implantation of the VNS system.²⁰

Chapter 5: Anatomy of the Vagus Nerve

The vagus nerve or cranial nerve X is made up of predominately narrow unmyelinated C fibers ($<1\ \mu\text{m}$), but with a significant portion of intermediate diameter B (1-3 μm) and large diameter A fibers (1-22 μm), both of which are myelinated. A large portion of the neurons (80%) are afferent fibers.³ The nerve was given the name vagus (Latin: “wanderer”) due to the complex pathways and many branches that innervate almost all of the organs in the thorax and abdomen. Cranial nerve X exits the skull through the jugular foramen, and travels bilaterally down each side of the neck. Within the neck it lies within the carotid sheath, deep to the sternocleidomastoid muscle and between the carotid artery and the jugular vein. There are several branches from the vagus that arise in the neck, these include the pharyngeal branch, the carotid sinus branch, the superior cardiac branch and the inferior cardiac branch (Figure 5.1). Most of the vagal efferent fibers are parasympathetic and innervate the heart, digestive system, liver, pancreas and kidneys. These fibers originate from two structures within the medulla, the dorsal motor nucleus of the vagus and the nucleus ambiguus. The vagal efferents terminate in the parasympathetic ganglia, which are located near the target organ. Most of the afferent fibers carry sensory information from the visceral organs. The cell bodies for the vagal afferents are located in the superior (jugular) vagal ganglion within the jugular foramen and inferior (nodose) vagal ganglion just exterior to the foramen.¹⁰ After the ganglia, the neurons cross the brainstem within the *tractus solitarius*, and synapse within several structures of the medulla including the nucleus of the tractus solitarius (NTS), the nucleus of the spinal tract of the trigeminal nerve, medial reticular formation of the medulla, area postrema, dorsal motor nucleus of the vagus, and the

nucleus ambiguus. The NTS receives the most afferent fibers of all of the medullary structures.

Figure 5.1: *Anatomy of the vagus nerve, its branches, and location of implantation for VNS electrodes¹*

The NTS has been described as a small brain within the larger brain. It receives a large amount of information from skeletal muscle, visceral afferent fibers, and many different regions of the brain. It processes much of this information internally and

produces motor and autonomic outputs. It also relays sensory information to the rest of the brain through three pathways: an autonomic feedback loop, through the reticular formation in the medulla, and ascending projections to the forebrain. The path to the forebrain is facilitated by the parabrachial nucleus and the locus ceruleus, which is one of the main norepinephrine containing areas in the brain. The parabrachial nucleus/locus ceruleus has direct connections to many areas of the forebrain, including the thalamus, hypothalamus, the insula, and the orbitofrontal and prefrontal cortices. Many of these areas are indicated in partial onset seizures and mood disorders. Through the locus ceruleus, the vagal afferent fibers allow access to many areas of the brain.

For many years, researchers have been interested in how the autonomic functions cause changes in the cortex. Bailey and Bremer in 1938 reported that VNS in the cat caused synchronized activity in the orbital cortex. Later in 1949, Maclean and Pribram used VNS combined with EEG recordings to show that VNS caused a slow-wave signal to arise from the lateral frontal cortex in monkeys. It was also found by Dell and Olson, that VNS affected an electrical response in the amygdala in a cat model. Zabara , in 1985, drew from the previous research and knowledge of the anatomy of the vagus and was the first to demonstrate the anticonvulsant action of VNS on a canine model of epilepsy.³ Not only did he find that VNS was able to prevent and in some cases, arrest seizures, he also found that the antiepileptic effect lasted longer than the actual stimulation by a factor of about four. In 1988, the first human was treated for epilepsy with an implantable VNS device.

Chapter 6: History of VNS Therapy

The first widespread clinical trials using an implantable VNS device began in 1994. In two separate double blind studies, a total of 313 subjects with pharmaceutically intractable partial onset epilepsy were treated with VNS for 12 weeks. The average decline in seizure frequency was 25-30%. Out of these subjects 12% saw a decline in seizure frequency greater than 50%. While this number may seem low, it is compared to a “pseudo-placebo” group being stimulated with a lower current, pulse width, frequency, and ON time. It is likely that some of these pseudo-placebo subjects received some therapeutic benefit. The efficacy of VNS compares well with many new antiepileptic drugs targeted toward refractory patients.²³ Long-term, uncontrolled data was collected for subjects in these and other trials which suggest that the seizure control improves over the first 24 months of treatment. In fact, the decline in seizure frequency averaged 40% after 24 months.

During the clinical trials, there were no serious adverse events (AEs) directly related to VNS, as judged by investigators. Many of the AEs were related to the surgery and subsided over time, with the exception of a 1.5% post-surgical infection rate resulting in device removal. There were a wide variety of stimulation related AEs, each reported in very few cases, the most common of these was voice alteration/hoarseness. Other AEs were cough, throat pain, nonspecific pain, dyspnea, paresthesia, dyspepsia and vomiting. Many of these were relieved by lowering the stimulation amplitude. The long term data further suggested that the treatment is well-tolerated chronically. Ninety-five percent (95%) of patients continued treatment after one year, and 82% after two years.^{1,3}

Chapter 7: Mechanism of Action of VNS Therapy

The basic cause of the antiepileptic effect of VNS is unknown. However, several mechanistic studies have given some insight. Early animal studies suggested that stimulation of unmyelinated C fibers was required for seizure control. In later human studies, the effective therapeutic parameters did not seem to be sufficient for C fiber recruitment. Also, there were no reports of autonomic side effects which would be expected if C fibers were being stimulated. In a 2001 study, researchers treated a group of rats with capsaicin to destroy peripheral C fibers. No significant difference in VNS efficacy was found between these rats and control groups, suggesting that the seizure control mechanism is not dependent on activation of C fibers.²⁴

Another theory from animal studies showed desynchronization of the EEG during VNS. It was suggested that this desynchronization interfered with the initiation and maintenance of the hypersynchronous seizure event. EEG data was recorded before, during, and after VNS pulses, following at least 6 months of chronic VNS. Visual and quantitative analysis showed no significant differences during any of the three stimulation conditions for all subjects, suggesting that VNS has little effect on the electrical signals produced by the brain.²⁵ One possible mechanism of action identified is an increase in the inhibitory neurotransmitter GABA levels within the brain through VNS. An overall increase in GABA may assist in greater tonic inhibition. Experimental evidence has shown that after 3 months of VNS in human subjects, GABA concentrations in the cerebrospinal fluid increased significantly. Furthermore, the cerebrospinal fluid concentrations of two excitatory amino acids, glutamate and aspartate, decreased after 9 months. These studies however, showed similar results for treatment responsive subjects

and non-responsive subjects. While these results show that VNS does cause changes in neurotransmitter levels within the brain, it is unclear whether this effect is, in fact, antiepileptic. Another clue to how seizure suppression is achieved through VNS is its actions on the locus coeruleus (LC), one of the main norepinephrine containing areas in the brain with connections to every level of the forebrain. The implication of the LC during VNS was first observed during antinociceptive VNS studies, which found the LC to be a critical component in pain attenuation. Studies in rats have also shown that the LC is related to the anticonvulsant actions of VNS. Researchers found that lesioning of the LC in rats eliminated the ability of VNS to suppress seizures.²⁶

Another popular theory is that VNS acts upon the thalamic regions of the brain which are then actively involved in preventing seizure onset and/or limiting the propagation of a paroxysmal discharge. The thalamus contains thalamocortical relay neurons which project into the cortex and all of the subcortical structures; these neurons are involved in synchronizing cortical rhythms and modulate cortical activities. Aside from the anatomy, this theory is further supported, but not proven, by evidence from neuroimaging studies showing activity changes in the thalami in patients undergoing VNS.²¹

Chapter 8: History of Nerve Stimulation and Modeling

While little is known about the effect of VNS in seizure control within the brain, the principles of electrically stimulating the nervous system have been studied for many years. In fact, observations drawn by Volta, in 1791, on electrophysiological experiments by Galvani, were integral in developing the first battery, the voltaic bimetallic pile.²⁷ This interest in “animal electricity” fueled many other experiments, including the work of Aldini, who was interested in “reanimation” of tissue. Aldini was able to produce skeletal muscle contractions in animals and human cadavers, (Figure 8.1). He was, however, disappointed that he wasn’t able to produce contractions in the heart.² Also, Aldini used Volta’s battery to treat depression, and other mental disorders, through transcranial stimulation, after applying the battery to his own head first. The next major advance in neuromodulation came after Faraday invented the electric generator. This new technology was seized on by Dubois-Reymond, who, in 1848, proved its usefulness in nerve stimulation and developed the first strength-duration curve, relating pulse-width and amplitude. It was also used by Duchenne, the “father of electrotherapy” in treating the facial nerve for palsy, in 1852. This spawned a wave of “electrical machines” used to treat many ailments and stimulate literally every part of the body.²⁷

Bernstein, in 1868, was the first to theorize that the membranes of nerve cells were normally polarized at rest, with negative ions in the inside and positive ions on the outside, a concept now known as the resting potential. He also believed that the electrical signals measured in nerve cells were caused by a depolarization due to a flow of ions.²⁸ This passive membrane polarization was first described mathematically by Weber in 1873, using Lord Kelvin’s cable theory to create his core conductor model and was

studied extensively into the early 1900's. The core conductor model consisted of a conductive core encased in a thin membrane and submersed in an electrolyte solution.²⁸

The all-or-nothing property of the action potential of a neuron was first detected by Koch in 1902, which led to research in the refractory period of the nerve. The modern understanding of the mechanics of nerve membrane depolarization and refractory period owes much to the later work of Hodgkin and Huxley who developed voltage clamp techniques on a single squid giant axon. Hodgkin and Huxley created a mathematical model describing the nonlinear sodium and potassium conductivity through the cell membrane during an action potential based on experimental measurements. Since then, several similar models have been developed. Frankenhauser and Moore studied the effect of temperature on the action potential of the squid giant axon, and modified the parameters of the Hodgkin-Huxley model to better approximate a physiologic temperature.²⁹ Also, a model was developed by Chiu, et al. several years later using rabbit myelinated axons.³⁰ McNeal combined aspects of the core conductor model with Frankenhauser and Huxley's nonlinear transmembrane ion conductances to develop a model for stimulation of a myelinated neuron in an electric field.³¹

Figure 8.1: *An engraving showing various experiments performed by Aldini on warm blooded animals and the corpses of decapitated criminals.²*

Chapter 9: Methods

Finite Element Model

A simplified solid model of the vagus nerve was created, similar to the geometry used by Choi, et al.⁹ The 8 cm long nerve model had a diameter of 1.8 mm and contained several internal features including six 0.36 mm diameter fascicles with a 0.03 mm layer of perineurium surrounding each (Figure 9.1). The other features were epineurium between the fascicles and a 0.115 mm layer of connective tissue surrounding the nerve. Models of two 2mm VNS electrodes were placed around the nerve.

Figure 9.1: Geometry and structures within the modeled vagus nerve.

The ANSYS Version 11.0 finite element package was used to calculate the voltage field within the modeled vagus nerve, for each of the modeled electrodes. Because the pulse widths investigated were sufficiently long, and the capacitive effect of

biological tissue is very small (less than 10%),³² DC current conduction FEA models were used.³³ A cylindrical domain with a radius of 6 cm was created around the nerve and electrodes to represent the surrounding tissue and fluid. A zero-volt boundary condition was used, a negative electric current load was applied to the face of the cathode, and a positive load to the anode. The tissue conductivities used can be found in Table 9.1 below. The perineurium conductivity was adjusted, as described by Frieswijk³⁴ to account for a thicker layer in the model than in the actual nerve.⁷ The conductivity of the helical was chosen to be a perfect insulator. Due to the thin internal structures within the modeled nerve, it was swept with 2D quadrilateral mesh elements, to form hexahedral elements, while the domain and helices were meshed with tetrahedral elements. Hexahedral to tetrahedral transitional elements were used in the connective tissue region to interface between the two different element geometries. All elements were quadratic. The choices for the length of the nerve, radius of the domain, and element size were based on practical limits on computational time.

Figure 9.2: Meshed vagus nerve model.

Figure 9.3: Meshed VNS helical electrodes

Material	Conductivity (S/m)	Source
Epineurium	0.008	[7]
Perineurium	0.0023	[7, 34]
Fascicle – Longitudinal	0.5	[31]
Fascicle – Transverse	0.08	[31]
Surrounding Tissue	0.2	[7]
Connective Tissue (Chronic Implant)	0.16667	[32]
Helical	$1*10^{-17}$	

Table 9.1: *Conductivities for all materials used in the ANSYS FEA model*

Symbol	Description
D	Fiber diameter
d	Axon diameter
l	Length of Node of Ranvier
R_m	Membrane resistance
R_a	Axoplasm resistance
C_m	Membrane capacitance
L	Internodal length
$V_e(n, t)$	Time dependent extracellular voltage at node n
$V_i(n, t)$	Time dependent intracellular voltage at node n
$V_m(n, t)$	Time dependent transmembrane potential at node n
V_r	Membrane resting potential
$I_i(n, t)$	Equivalent intracellularly injected current at node n

Table 9.2: *Symbols and descriptions*

The transmembrane potential across a nerve fiber is given in equation 9.1. The resting potential in myelinated fibers is around -70 mV and arises from the differences in ion concentrations inside and outside of the cell. In order to stimulate a neuron and cause it to generate an action potential, the cell must be depolarized. This can be achieved by either increasing V_i or by decreasing V_e . An increase V_i can be produced by injecting a positive current into the cell, and a decrease V_e is best thought of as placing the neuron in a negative electric field. When stimulating a bundle of fibers or an entire nerve, the change in V_m is caused mostly by decreasing V_e , so depolarization will take place below the cathode.^{35,36}

$$V_m(n, t) = V_i(n, t) - V_e(n, t) - V_r(n, t) \quad (9.1)$$

A linear cable model was constructed to investigate the locations and fiber diameters being stimulated. The model assumes that the myelin between nodes is a perfect insulator.³¹ Figure 9.4 shows an equivalent circuit model overlaid on a representation of an axial cross-section of nerve fiber.

Figure 9.4: *Equivalent circuit model of a nerve fiber.*

The model was constructed using constant transmembrane conductances. In actuality, the transmembrane conductance is based on the dynamics of the voltage gated ion channels in the membrane and is a function of the transmembrane potential and time. The assumption inherent in the passive model is the membrane conductances are constant until a certain threshold value is reached and excitation occurs. The decision to use a passive, linear model, as opposed to an active, non-linear model, was made in order to make the determination of neuron activation patterns of a large number of fibers less computationally costly.³⁷ The assumption is generally considered valid and is often used

in situations where investigation of many fibers is necessary, due to the long computation time associated with a non-linear model.³⁸

Kirchoff's current law can be written at each of the intracellular nodes in Figure 9.5 below. Note that V_m , the transmembrane potential, V_i , the internal cell potential, V_e , the internal cell potential, and V_r , the resting cellular potential are related by equation 9.1, and also that the cell conductances G_a and G_m are the inverses of the resistances of R_a and R_m , respectively. Writing KCL at node n yields equation 9.2, and by rearranging, equation 9.3.

$$C_m \frac{dV_m(n,t)}{dt} + G_m V_m(n,t) + G_a [V_e(n,t) + V_m(n,t)] - G_a [V_e(n-1,t) + V_m(n-1,t)] + G_a [V_e(n,t) + V_m(n,t)] - G_a [V_e(n+1,t) + V_m(n+1,t)] = 0 \quad (9.2)$$

$$C_m \frac{dV_m(n,t)}{dt} + G_m V_m(n,t) - G_a [V_m(n-1,t) - 2V_m(n,t) + V_m(n+1,t)] = G_a [V_e(n-1,t) - 2V_e(n,t) + V_e(n+1,t)] \quad (9.3)$$

In order to simplify the analysis, it can readily be shown that the extracellular potentials, $V_e(n,t)$ can be replaced by intracellular current sources (Figure 9.5). These current sources must be equivalent to the current on the right hand side of equation 9.4. This is sometimes called the activating function, as it determines the amount of current flowing into the neuron. It can be seen from equation 9.5 that the intracellular current sources are dependent on the second spatial difference of the extracellular potential between adjacent nodes. For this reason, the most effective way to stimulate a neuron is a highly localized change in extracellular voltage. If the extracellular voltage change is not localized, current will flow across a large portion of the membrane, resulting in a

change in both the extracellular and intracellular potentials, but very little change in the transmembrane potential.³⁶

$$C_m \frac{dV_m(n,t)}{dt} + G_m V_m(n,t) - G_a [V_m(n-1,t) - 2V_m(n,t) + V_m(n+1,t)] = I_i(n,t) \quad (9.4)$$

$$I_i(n,t) = G_a [V_e(n-1,t) - 2V_e(n,t) + V_e(n+1,t)] \quad (9.5)$$

Figure 9.5: Equivalent circuit diagram showing intracellular injected current source, determined from extracellular potentials.

Two centimeter sections of neuron were simulated at various locations within the nerve, with diameters ranging from 20 μm to 1 μm . Because nodal and internodal length is dependent upon diameter, the number of nodes varied from 31, in the largest fibers, to 149 in the smallest. The cell parameters G_m , G_a , and C_m are also dependent on the cell dimensions and can be readily calculated from equations 9.6-9.8 and published data listed. The FEA voltage field data contains coordinates and a scalar potential value at discrete points within the volume. The extracellular potential is found by averaging the

potential at the nearest points around each node of Ranvier. This is then translated to an intracellularly injected current by equation 9.6. For smaller diameter fibers, the nodes are much closer together (Table 9.3). Because the intracellularly injected current is dependent on the second difference between adjacent nodes, the second difference becomes very small for these short internodal length fibers, making it easily influenced by numerical noise from the FEA results. In the smallest fibers, this numerical noise affected not only the magnitude of the injected current, but also the direction, greatly changing the results. In order to remedy this problem, the voltage field along the nerve was fitted with a 20 segment spline in order to smooth the line and prevent interference from the numerical noise. The injected current is applied to the fiber for a time equal to the specified pulse width, 250 μ s.

The result is a system of time-varying, linear differential equations of the form of equation 9.5. This system of equations was then solved using the ode45 solver in MATLAB. The ode45 function is an explicit 4th order Runge-Kutta differential equation solver and is appropriate for use in this numerically stable (non-stiff) system of differential equations.

In all of the modeled electrodes, 66 nerve locations were examined, 11 per fascicle. It is assumed that the fibers are horizontally aligned with the nerve. Several fiber diameters (1-20 μ m) were tested at each location in order to determine the smallest fiber activated at each location. A threshold value of 25 mV was used to determine excitation.^{38,39} That is, if the transmembrane potential rose 25 mV above the resting potential at any node during the course of the pulse, the program recorded that this fiber had depolarized sufficiently to generate an action potential.

Symbol	Value	Description	Source
ρ_a	54.7 $\Omega\text{-cm}$	Axoplasm Resistivity	[39]
c_m	2 $\mu F / cm^2$	Membrane Capacitance/Unit Area	[40]
g_m	30.4 S / cm^2	Membrane Conductance/Unit Area	[40]
l	2.5 μm	Node gap width	[41]
L / D	100	Ratio of internodal length to fiber diameter	[41]
d/D	0.7	Ratio of axon diameter to fiber diameter	[42]

Table 9.3: *Cell parameters used for the linear nerve fiber model.*

Cell Parameter Equations:

$$G_a = \frac{\pi d^2}{4\rho_a L} \quad (9.6)$$

$$G_m = \pi l d g_m \quad (9.7)$$

$$C_m = \pi l d c_m \quad (9.8)$$

Chapter 10: Results and Discussion

Changing Electrode Length

In order to investigate the effect of the circumferential electrode coverage on nerve stimulation, models were created with different electrode lengths, from $\theta = 270^\circ$ to $\theta = 720^\circ$. In all, 31 models were created with an incremental increase in coverage of $\Delta\theta = 15^\circ$. Although it can be seen from the activating function (equation 9.5) that depolarization could be increased by further concentrating the change in the voltage field, the purpose of overlapping the electrode was to try create, small, but very localized changes in the voltage field between overlapping portions in an attempt to depolarize the smaller diameter fibers. All other dimensions of the nerve and helical were held constant. For all of the FEA models, a 2.5 mA current was applied to one electrode, and -2.5 mA to the other, which are fairly typical VNS settings in a chronic patient. The pulse width used in the nerve fiber model was 250 μs . Figures 10.2-10.5 show a selection of results from the modeling. Table 10.2 shows the average minimum diameter fiber stimulated for all of the modeled θ values. It also shows the results of a t-test of the average minimum fiber diameter for each electrode length against the original length of $\theta = 270^\circ$. Figure 10.6 shows the average of the smallest diameter fibers for all θ values.

Figure 10.1: Colors for current and voltage path graphs. Lines on the graphs correspond to a path down the center of the similarly colored fascicle.

Legend for Fiber Stimulation Graphs

Symbol	Fibers greater than:
1 μm
1.5 μm
2 μm
3 μm
4 μm

Table 10.1: Legend for fiber stimulation graphs. The color of the dot denotes the smallest fiber activated at each location; all fibers larger than this smallest fiber are also activated.

Figure 10.2: *Top Left*, ANSYS representation of 270° electrode.
Top Right, the smallest fiber stimulated at each of the 66 tested locations.
Bottom Left, the potential along a longitudinal path through the center of each fascicle.
Bottom Right, the intracellularly injected currents in the neuron at the center of each fascicle.

Figure 10.3: Top Left, ANSYS representation of 360° electrode.
Top Right, the smallest fiber stimulated at each of the 66 tested locations.
Bottom Left, the potential along a longitudinal path through the center of each fascicle.
Bottom Right, the intracellularly injected currents in the neuron at the center of each fascicle.

Figure 10.4: *Top Left*, ANSYS representation of 540° electrode.
Top Right, the smallest fiber stimulated at each of the 66 tested locations.
Bottom Left, the potential along a longitudinal path through the center of each fascicle.
Bottom Right, the intracellularly injected currents in the neuron at the center of each fascicle.

Figure 10.5: *Top Left*, ANSYS representation of 720° electrode.
Top Right, the smallest fiber stimulated at each of the 66 tested locations.
Bottom Left, the potential along a longitudinal path through the center of each fascicle.
Bottom Right, the intracellularly injected currents in the neuron at the center of each fascicle.

Θ	Mean Smallest Fiber (μm)	t-test p-value
270	1.6591	N/A
285	1.6591	1
300	1.6591	1
315	1.6515	0.791231
330	1.6288	0.267952
345	1.5985	0.016681
360	1.5833	0.001682
375	1.6667	0.882417
390	1.7197	0.325649
405	1.7803	0.084712
420	1.7803	0.084712

Table 10.2: Table showing the mean of the smallest fibers stimulated for each electrode configuration and the p-value from a two sample t-test against the 270° configuration.

Figure 10.6: Graph of the mean smallest diameter fiber stimulated for each value of θ .

The results from the models showed no significant decline in the mean values of the smallest fiber stimulated beyond $\theta = 360^\circ$. It can be seen from the graphs in Appendix B that the overlapping electrode did not result in any increase in stimulation of smaller diameter fibers. In fact, the overlap greatly decreased stimulation. The increase in the length of the electrode has spread the electric field across a larger length of the nerve. It can be seen from the voltage vs. length graphs (Figures 10.2-10.5, bottom left) that the peak voltage is smaller and the change in voltage is more gradual, resulting in a lower current injected into the cell (Figures 10.2-10.5, bottom right).

Changing Electrode Dimensions with Constant Charge Density

A second set of models was created to hold the surface area of the electrode constant, while increasing the length. This was accomplished by narrowing the electrode by a factor equal to that of the increase in length. For example, an increase in θ from 270° to 360° , is a 25% increase in the length. In order to keep the surface area of the electrode constant, the width of the electrode strip was narrowed by 25%. The narrowing of the electrode also had the secondary purpose of increasing the distance between the overlapping sections, which was again an attempt to create some small localized fluctuations in the field and stimulate the smaller neurons. The applied current was again 2.5 mA and -2.5 mA, and the pulse width for the nerve fiber model was 250 μ s.

Figure 10.7: *Top Left*, ANSYS representation of 360° narrowed electrode.
Top Right, the smallest fiber stimulated at each of the 66 tested locations.
Bottom Left, the potential along a longitudinal path through the center of each fascicle.
Bottom Right, the intracellularly injected currents in the neuron at the center of each fascicle.

Figure 10.8: *Top Left*, ANSYS representation of 540° narrowed electrode.
Top Right, the smallest fiber stimulated at each of the 66 tested locations.
Bottom Left, the potential along a longitudinal path through the center of each fascicle.
Bottom Right, the intracellularly injected currents in the neuron at the center of each fascicle.

Figure 10.9: *Top Left*, ANSYS representation of 720° narrowed electrode.
Top right, the smallest fiber stimulated at each of the 66 tested locations.
Bottom Left, the potential along a longitudinal path through the center of each fascicle.
Bottom Right, the intracellularly injected currents in the neuron at the center of each fascicle.

θ	Mean Smallest Fiber (μm)	t-test p-value
270	1.6591	N/A
285	1.5833	0.008033
300	1.5682	0.000927
315	1.5758	0.001263
330	1.5909	0.038189
345	1.6212	0.384523
360	1.6742	0.78192
375	1.7197	0.34706
390	1.7197	0.34706
405	1.7424	0.198104
420	1.7803	0.084712

Table 10.3: Table showing the mean of the smallest fibers stimulated for each narrowed electrode configuration and the p-value from a two sample t-test against the 270° normal width configuration.

Figure 10.10: Graph of the mean smallest diameter fiber stimulated for each value of θ .

The results showed a significant decrease in the mean minimum diameter fiber stimulated for electrodes that encircled the nerve up to $\theta = 330^\circ$. The results for the longer electrodes were fairly similar to those without the narrowed electrode in that the overlapping resulted in a decrease in stimulation. The overlapping areas still caused a decrease in peak voltage, made the change in voltage field more gradual, and failed to create localized fluctuations and stimulate the smaller fibers.

Chapter 11: Summary and Conclusions

Strictly from the results of the presented modeling, there are two possible improvements that could be made to the VNS electrode. First, an electrode encircling the nerve 360° with the width the same as the current design (0.8 mm). This has the advantage of being easier to manufacture as the only major change made is the length of platinum ribbon being cut. The current design of the 2mm diameter electrode has $\theta = 330^\circ$ before implantation and tissue ingrowth, but the final radial coverage is approximately 270° , a decrease of about 22%. In order to achieve a final θ of 360° degrees, the initial radial coverage should be approximately 440° . The second option for improvement would be a $\theta = 330^\circ$ electrode with a narrower width. For the situation modeled, the electrode would need to be about 22% more narrow than the current 0.8 mm wide electrode. The initial θ required is about 400° . The disadvantage of this improvement is the change in width of the electrode would require different platinum ribbon stock. This improvement does however require significantly less platinum per electrode than the previous change.

Additionally, the vagus nerve does not have the same diameter in all patients. The results from both sets of models suggest that small variations in nerve size, which would change the circumferential coverage of the electrode, could significantly impact stimulation within this region. With the current design, proper electrode sizing should then be deemed very important. It may be advantageous to create several different lead sizes, other than 2mm and 3mm diameters, and make them available to surgeons.

Examination the figures in Appendix B shows that the neurons nearest the point where the electrode comes together and starts to overlap are the most sensitive to an increase in electrode length. The model of the current VNS electrode shows that stimulation is less effective near the electrode ends. Therefore, rotational orientation of the helical electrode may be an important factor in effectively controlling seizures with minimal side effects. Because there is no way to determine if the proper neurons to produce the antiepileptic effect are being excited when the electrode is implanted, design changes to the electrode should be aimed not only at the stimulation of more fibers but also more uniform stimulation of the nerve. Strictly increasing the length of the electrode might not be sufficient to uniformly activate the neurons.

In order to understand the decrease in stimulation near this “area of overlap,” a closer look at the activating function and the helical geometry of the electrode is needed. Substituting equation 9.6 for the axoplasm conductance in the activating function, equation 9.5, gives equation 11.1, which is the second spatial difference in voltage along the longitudinal axis of the nerve. When $L \rightarrow 0$, equation 11.1 becomes the second spatial derivative of voltage with respect to the longitudinal axis of the nerve, and is related to how abruptly the voltage changes in the longitudinal direction. Therefore, in order to maximize stimulation, the longitudinal change in voltage must be highly concentrated.

$$I(n,t) = \frac{\pi d^2 [V_e(n-1,t) - 2V_e(n,t) + V_e(n+1,t)]}{4\rho_a L} \quad (11.1)$$

In the cases where $\theta < 360^\circ$, most of the field in the areas of the nerve far from the overlap area, is caused by current flowing out of the nearest portions of the electrode, and the change in the field is fairly concentrated along the longitudinal axis of the nerve. However, near the area of overlap, each electrode end creates a distinct field. These two fields overlap somewhat, and because of the pitch of the electrode, they are longitudinally offset from each other along the axis of the nerve. The overlapping fields and the offset of the electrode ends, cause the longitudinal change in voltage to become less concentrated near the area of overlap. This phenomenon is illustrated in Figure 11.1. Further evidence of the decreased concentration of the change in voltage can be seen from the figures in Appendix B. As the electrode continues to overlap radially ($\theta > 360^\circ$), the two fields created by these overlapping sections combine, resulting in less stimulation of the neurons near those areas.

Figure 11.1: An ANSYS calculated voltage on the outer surface of the nerve created by a 330° helical electrode. **Left**, the overlapping voltage near the electrode ends. **Right**, the voltage in the middle of the electrode.

Chapter 12: Further Modeling and Research

While only two dimensions of the electrode were studied, the results suggest some further improvements can be made to the present electrode design. First, there are several parameters that could be modified, including helix pitch, conductor position within the insulating helix, and the spacing between anode and cathode. Each of these parameters could have a large effect on stimulation. An optimization routine could be written with ANSYS Parametric Design Language (APDL) to optimize these parameters as well as the width and radial degree of coverage. This optimization routine would be aimed at maximizing the second spatial difference of the field within the nerve. Implementing such an optimization may be problematic, because ANSYS has difficulty reliably creating a mesh for helical geometries. In all of the models presented, the area to which the current was applied changed in each model, but the overall geometry of the helical volumes was unchanged. Very few meshing problems were encountered because volumes remained the same. Although not impossible, creating an APDL script robust enough to mesh the helices in all the possible geometries used in the described optimization would be difficult and time consuming.

Based on conclusions drawn from the modeling, one aspect important in improving the design of the helical electrode is concentrating the change in voltage along the longitudinal axis near the area of overlap. Several possible improvements could readily be made to accomplish this. A possible solution might be decreasing just the electrode ribbon pitch so that the ends lie at the edge of the insulation (Figure 12.1). This would reduce the axial offset between the ends of the electrode. Tapering the ends of the electrodes might also be effective in preventing a decrease in stimulation at the area of overlap. By tapering each of the electrode ends toward the longitudinal center of the helix, on an electrode that extends close to 360° , the axial distance between the extreme longitudinal edges of the electrode ends is reduced (Figures 12.2 and 12.3). The taper will reduce the axial length of the field created by each of the smaller electrode ends. The two fields will still overlap, but the longitudinal extent of the field should be reduced, leading to a more concentrated change in voltage. Because high current concentrations tend to form near sharp angles, the ends of the tapered electrodes may need to be rounded or flattened. Additionally, tapering the ends of the electrode away

from the longitudinal center of the helix may prevent the fields from overlapping and create two distinct, concentrated, fields at each electrode end.

Figure 12.1: *Electrode design with a smaller pitch conductor to reduce the radial distance between the electrode ends.*

Figure 12.2: *Drawing of a helical electrode conductor with tapered ends.*

Figure 12.3: *Solid model of a tapered-end electrode embedded in insulation.*

Another area for further research is the difference in excitation between the 2mm and 3mm diameter electrodes. Increasing the nerve diameter from 2mm to 3mm would likely create a different excitation pattern. A study into the effects of nerve diameter on stimulation might lead to recommending the use of a higher output current with the 3mm lead. Additionally, a conference paper was published and presented at the 2011 IEEE – Engineering in Medicine and Biology Conference based on this work.⁴³

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Appendix A: The Personal and Social Costs of Epilepsy

Epilepsy has a large impact on the lives of people diagnosed with the disorder. The standardized mortality ratio among people with all types of epilepsy relative to the general population is 2.3.¹¹ Respondents to a survey by Fisher and coworkers listed uncertainty and fear of having a seizure as the worst aspect of epilepsy, with lifestyle changes as a close second. In surveys conducted by the CDC, 45.9% of people with epilepsy reported poor health-related quality of life (HRQOL) compared with 18.5% of people without epilepsy. The surveys also found that people with epilepsy had a higher number of mentally unhealthy days, and another study demonstrated there was a 12% lifetime chance to commit suicide, compared to 1.1-1.2% in the general population. There is also a high incidence of psychiatric comorbidity among epilepsy patients, including significantly higher rates of mood disorders.¹²

The other top concerns for people with epilepsy in Fisher's study were school, driving and employment limitations.¹¹ The effect of epilepsy in cognitive development has been widely studied and the results from these studies have been varied. It has been shown that adult IQ increases linearly with age of onset, suggesting that childhood epilepsy has an effect on the cognitive development and educational achievements in children. The IQ scores ranged from 83 for adults with seizures that began in infancy to 103 for those with adult onset.²⁰ Other studies have found no cognitive impairment over time. Some possible reasons for the variation in results stems from study design, the specific type of epilepsy studied, and factors out of the control of researchers, such as changing anti-epileptic medication and seizure frequency.⁴⁴ Driving laws for epilepsy patients vary in each state. In some states, the doctor is required to notify the licensing bureau, and a mandatory seizure-free time is required before a driver's license will be

reinstated. For example, California health and safety codes require that a person who has experienced a loss of consciousness or marked episodes of confusion be immediately reported by the physician to the Department of Motor Vehicles. Upon this notification, the individual's license may be revoked until a seizure-free period of 6 months has been reached. The DMV may also review the medical evidence, testimony from the physician and patient, and decide not to revoke the driver's license or instead place the patient on medical probation, allowing the individual to drive, but requiring frequent medical reporting.^{20,45} Employment and financial statistics show a marked difference between people with epilepsy and the general population. A telephone survey conducted by INFO Research, Inc. found that people with epilepsy had an average annual income of \$18,750 while the general public made, on average, \$32,000. There were also a significantly larger percentage of people with epilepsy earning a household income of less than \$12,500 annually (33% for people with epilepsy, 15% for the general public). The unemployment rate for people with epilepsy was 33% contrasted by the unemployment rate for the general public at 13%.¹¹

Appendix B: Full Simulation Results

270° Constant Width Electrode

5° Constant Width Electrode

300° Constant Width Electrode

315° Constant Width Electrode

330° Constant Width Electrode

345° Constant Width Electrode

360° Constant Width Electrode

375° Constant Width Electrode

390° Constant Width Electrode

405° Constant Width Electrode

420° Constant Width Electrode

435° Constant Width Electrode

450° Constant Width Electrode

465° Constant Width Electrode

480° Constant Width Electrode

495° Constant Width Electrode

510° Constant Width Electrode

525° Constant Width Electrode

540° Constant Width Electrode

555° Constant Width Electrode

570° Constant Width Electrode

585° Constant Width Electrode

600° Constant Width Electrode

615° Constant Width Electrode

630° Constant Width Electrode

645° Constant Width Electrode

660° Constant Width Electrode

675° Constant Width Electrode

690° Constant Width Electrode

705° Constant Width Electrode

720° Constant Width Electrode

285° Narrowed Electrode

300° Narrowed Electrode

315° Narrowed Electrode

330° Narrowed Electrode

345° Narrowed Electrode

360° Narrowed Electrode

375° Narrowed Electrode

390° Narrowed Electrode

405° Narrowed Electrode

420° Narrowed Electrode

435° Narrowed Electrode

450° Narrowed Electrode

465° Narrowed Electrode

480° Narrowed Electrode

495° Narrowed Electrode

510° Narrowed Electrode

525° Narrowed Electrode

540° Narrowed Electrode

555° Narrowed Electrode

570° Narrowed Electrode

585° Narrowed Electrode

600° Narrowed Electrode

615° Narrowed Electrode

630° Narrowed Electrode

645° Narrowed Electrode

660° Narrowed Electrode

675° Narrowed Electrode

690° Narrowed Electrode

705° Narrowed Electrode

720° Narrowed Electrode