COMMERCIALIZATION OF HFAC ELECTRONIC 
NERVE BLOCK TECHNOLOGY TO TREAT CHRONIC 
POST SURGICAL PAIN

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Dedicated to Revathy Narasimhan
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I also wish to thank all those who helped me in this endeavor.
Commercialization of HFAC Electronic Nerve Block Technology to Treat Chronic Post-Surgical Pain

Abstract

by

ANIRUDHAN NARASIMHAN

Previous studies have shown that the application of High Frequency Alternating Current to nerve fibers results in a reversible quick acting conduction block. The commercialization pathway for the application of HFAC technology to treat chronic postsurgical pain in patients has been explored. The technical portion of the thesis provides a general overview of the nervous system, mechanism of pain, neuromodulation and its therapeutic application as well as a detailed explanation of the HFAC technology. The business portion of the thesis explores the commercial feasibility of the technology against market, competitive landscape, FDA regulatory pathway, reimbursement, intellectual property, financing required and potential exit strategies
Introduction

Introduction to STEP

The Science and Technology Entrepreneurship Program at Case Western Reserve University is a two year program that focuses on commercialization of technologies. There are three streams in the STEP program - Physics, Chemistry and Biotechnology.

The Biotechnology stream also called Entrepreneurial Biotechnology focuses specifically on commercialization of biotech/biomedical technologies; taking it from the lab to the marketplace. There are four core courses, two that focus on biotechnology innovation, one feasibility and technology analysis course and technology venture creation course. All these courses lay the foundation for entrepreneurs in the biotechnology field. Once these core requirements are met, students are allowed to take additional courses from any department/school if approved by the respective course instructor. For example additional courses taken by me were patent law from the law school, enterprise development and Models of healthcare systems from the business school and Regulatory affairs for Biosciences from Biomedical engineering department.

During the course of the program, all students must do an internship with a startup company in their area of interest and specialization, which exposes the students to real world technical and business problems. The students provide support to the early stage company by writing grants, business plans as well as assisting in other work a startup company may be involved with. My internship with BioEnterprise as a Business Development Associate, gave me the opportunity to interact with and assist various
startup companies in the Northeast Ohio region. A detailed description of BioEnterprise and my role is discussed below.

**Internship at BioEnterprise**

BioEnterprise is a Cleveland based nonprofit company that helps accelerate the growth of bioscience companies in the region. BioEnterprise is partnered with the Cleveland Clinic, Summa Health systems, University Hospitals, Case Western Reserve University and the Bioinnovation Institute in Akron, all of which help and support BioEnterprise’s mission.

Since its inception in July 2002, BioEnterprise has recruited and accelerated around 97 bioscience companies that have together attract over $925 million in funding to the region. The company has assisted the technology transfer offices of its partner institutions gain revenues of $135 million.

BioEnterprise evaluates around 130 new business opportunities and 275 invention disclosures every year, out of these only 10% of the companies become portfolio companies. Becoming a BioEnterprise portfolio company means, the company does not have to pay BioEnterprise for their services – which include:

- Access to the Venture Capital community and help in SBIR and DOD grant writing
- Privileged introductions with partner institutions
- Experienced management guidance
- Business development support and help in finding strategic partnerships.
Starting off as a Business Development Associate, I was involved with initial evaluation of opportunities, grant writing, patent analysis, patent searches, and secondary market research. Later in the year, I authored due diligence reports for investors, conducted primary market research and assisted the medical device team in recruiting medical device companies to Cleveland.

Over the past year and a half, I have worked on more than 25 projects for various biotech and medical device companies; this exposed me to various business models, strategies and technologies.

During my employment at BioEnterprise, I have worked on a project for Neuros Medical, a startup company that was commercializing a nerve block therapy to address and alleviate chronic pain. My interests in the field of neurostimulation motivated me to do my thesis on a newly targeted application of the company’s technology.

**Neuros Medical Overview**

Neuros Medical is a Cleveland based medical device company formed in 2008 by Mr. Jon Snyder to commercialize an electronic Nerve Block technology developed at Case Western Reserve by Dr. Kevin Kilgore and Dr. Niloy Bhadra. The company’s mission is to become the worldwide leader in the development, manufacturing and marketing of neurostimulation therapies for patients to alleviate chronic pain. The company’s objectives are to:

- Increase the value of the Company.
- Establish Neuros Medical products and services as the Standard of Practice for chronic pain and neuromuscular therapy patient care.
➢ Ensure customer satisfaction by providing the highest levels of quality and performance.

➢ Develop at least one significant new product line or application each year.

➢ Provide a safe, stimulating, challenging, and cooperative work environment with growth opportunities for all employees.

➢ Establish a market oriented multi-national business presence to address the worldwide needs and opportunities for our systems, products, services, and technologies.

The company initially started off by commercializing the technology to treat chronic residual limb pain in amputee patients. As time progressed, Neuros Medical has increased its employee size to two members by adding a Chief Technology Officer (CTO) and now is exploring the option of entering new markets to solve unmet needs and increase revenue potential. One such opportunity is the chronic post-surgical pain market. This thesis explores the application of the HFAC electronic nerve block technology to treat chronic post-surgical pain experienced after certain surgical procedures. The targeted procedures are Hernia repair, mastectomy, hip arthroplasty and thoracotomy because of the high incidence of chronic pain reported by the patients.

**Biological Science**

**Nervous system Basics**

**Nerve tissue**

**Neuron**
A neural cell also called neuron has four different parts, cell body, axon, axon terminals and dendrites. The cell body like all cells has all the usual components including the genetic material, ribosomes and so on, but the cell body has long root like structures called dendrites that play an important role in receiving input signals from other neurons. A cell can have as many as 400,000 branches of dendrites thus increasing the cell’s capability to receive signals. The cell body is attached to an axon that extends from the cell body or soma up to the axon terminal; axons vary greatly by size depending on the position of the cell. It can be as small as a micrometer and up to a meter. The axons are usually covered with myelin, a substance that is made up of 20 to 200 layers of modified plasma membrane. The myelin is formed by cells called oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). Oligodendrocytes can branch out to form myelin sheaths on around 40 axons while the Schwann cells form only one myelin sheath. The exposed part of the axon between two myelin sheaths is called the node of Ranvier. The axon terminal is responsible for
releasing output to other neurons surrounding the cell; this is carried out by releasing neurotransmitters. The movement of substances from the soma to the axon terminal through microtubules is known as axon transport.

**Types of Neurons**

Neurons are classified into three types based on the direction of flow of information.

*Afferent Neurons*

These neurons carry information from organs and other sensory receptors in the peripheral nervous system to the central nervous system. Afferent neurons have sensory receptors at their peripheral ends, which propagate electrical signals through the axons when they detect changes in the environment to the CNS. The structure of afferent neurons in the body is very unusual in the sense that the axon comes out of the cell body and divides into two branches, one reaches out to the receptors and is called the peripheral process and the other reaches out to the CNS and form junctions with other neurons there, this is called the central process. The cell body and a major part of the cell lies in the peripheral nervous system. These neurons do not have dendrites and hence do not interact with other neuron to receive their input.

*Efferent Neurons*

These neurons transmit information from the CNS to the peripheral nervous system to muscles and other gland cells. Efferent neurons have dendrites unlike afferent neurons. The soma, dendrites and a small portion of their axon lie in the CNS while the other
larger part of the axon lies in the peripheral nervous system attached to axon terminals that transmit signals to effector cells.

*Interneuron*

These neurons primarily connect neurons within the CNS. They constitute the highest ratio of neurons in the body accounting for 99 percent of neurons. They mainly combine groups of efferent and afferent neurons into reflex circuits. The presence of interneurons between afferent or efferent neurons varies depending on the complexity of the function; for example the nerve pathway for knee-jerk reflex does not include interneurons. For a function where memory is involved, it may involve many interneurons.

The junction between two neurons is called a synapse. The neuron that transmits information to the next neuron is called a presynaptic neuron and the neuron that receives it is called a post synaptic neuron. The presynaptic terminals of chemical synapses are filled with neurotransmitters that transmit signals from one cell to another by binding with specific protein receptors on the postsynaptic target cell (Widmaier, Raff and Strang 2004).

*Membrane potentials*

**Basics of electric potential**

When opposite electric charges are separated from each other they tend to re-connect with each other. This force of recombining is called electric potential and it is measured by the difference in charge between the two sides and hence also called as potential difference. In biological systems, this potential is measured in milliVolts since the charges are very small.
Resting Membrane potential

Generally extracellular fluid in the human body contains primarily sodium and chloride ions while the intracellular fluid contains more potassium ions along with macromolecules like proteins that are negatively charged and are nondiffusible. The plasma membrane containing very few charged groups separates the intracellular fluid from the extracellular fluid. The plasma membrane is highly resistant to electricity, hence plays a major role in regulating the flow of ions through them.

In resting conditions, the internal part of the cell is negatively charged when compared to the outside because it contains many negatively charged molecules and few potassium molecules; whereas the cell’s external surrounding is filled with Na and Cl ions. By convention, the outside of the cell is considered to be zero volts. For neurons, the resting membrane potential typically lies between -40 to -90 mV. This magnitude is determined based on two factors:

1) Permeability of the membrane to different ions

2) The difference in the ionic charge inside and outside the cell.

In a nerve cell, the plasma membrane contains 50 to 75 times more open potassium channels as compared to sodium channels and the potassium equilibrium potential and sodium equilibrium potential is -90mV and +60mV respectively. At this point the resting membrane potential is -70mV and neither potassium nor sodium is in its equilibrium potential; however the resting membrane potential is close to potassium’s. This is because

1) The membrane has more potassium channels than sodium channels
2) A few sodium ions constantly move into the cell and cancel out an equivalent number of potassium ions that go outside the cell.

3) Na/K pumps pump in two potassium ions for every three sodium ions they move out.

**Graded potentials**

These are small changes in the membrane potential that occur in certain areas of the plasma membrane. Their magnitude can vary and that is why they are called graded potentials. Graded potentials can only travel short distances and the signals strength decreases with distance. Graded potentials are used by some neurons and play a major role in initiation and integration of long distance signals.

When a graded potential is initiated, the charge flows from the place where it started along the membrane, the signal weakens along the way and finally fades off. At the place of origin, the membrane is depolarized causing the positive ions to flow into the cell towards the resting regions of the membrane inside the cell. As this happens, the positive ions residing outside the cell shift closer from more positive areas to the area where depolarization occurred. This way, the signal traverses across the membrane. As the charge moves away from the cell, the charge is lost within a few millimeters because the membrane contains open channels that are permeable to ions.

**Action potentials**
During an action potential, the membrane potential always rises from -70mV to +30 mV and then repolarizes to -70mV. The membrane potential drops below -70mV to -90mV and slowly reaches back its resting potential. Unlike graded potentials, action potentials travel very long distances and do not lose their signal strength over the distance covered. This process is better explained below.

There are 4 steps in an action potential:

*Depolarization*

An action potential is initiated when the membrane is acted upon by a chemical or physical stimulus. At this point voltage-gated sodium channels are opened which causes Na\(^+\) ions to enter the cell making the cell depolarized, this continues until a threshold potential is reached. The threshold potential is the point at which a complete action potential is triggered. This point is very important in an action potential because, if the
stimulus is not strong enough to cause sodium channels to open up until they reach the threshold potential and an action potential will not be triggered. Similarly a relatively stronger stimulus above the threshold will not cause a stronger action potential. The stimuli that depolarize the membrane to this level (-55mV) are called threshold stimuli. This threshold potential is caused by voltage sensors that are present inside these voltage-gated sodium channels that react to positive ions by changing the conformation of the channel protein, opening up some of the sodium channels. After this point the membrane events are no longer dependent upon the stimuli and are caused entirely due to actions of these channels; this is called positive feedback. Once threshold potential is reached, there is a hundredfold increase in sodium permeability as more and more sodium channels open up until the membrane potential becomes positive with a magnitude of 30mV. The region between 0 mV and 30mV is called the overshoot.

Repolarization

Once the membrane potential reaches +30mV, voltage-gated potassium channels begin to open up rapidly and the sodium permeability decreases abruptly allowing the cell to get repolarized, bringing the membrane potential back to -70mV. The sodium channels in reality get inactivated by a part of the channel protein, which blocks the intracellular part of the channel. This small portion of the channel protein is called an inactivation gate. It should be noted that the potassium channels are opened because of the same voltage sensors that opened the sodium channels, but the potassium channels take longer to open up and close causing these steps in an action potential.

Hyperpolarization
As mentioned before, in nerve cells, the voltage-gated potassium do not immediately close once resting potential is reached. This causes a drop in membrane potential lower than the resting level, which is called hyperpolarization.

**Resting membrane potential**

Once the voltage-gated potassium channels close, the membrane potential reaches its resting state. At this stage, the $\text{Na}^+/\text{K}^+ - \text{ATPase}$ pumps restore the sodium and potassium ion concentration in the cell, thus bringing it back to its resting membrane potential concentration.

The most important characteristic of action potential is that they either produce a maximum strength signal or no signal. This is known as the all-or-none law. An action potential has an absolute refractory period when it will not respond to a second stimulus. This period lasts from when the sodium channels are open to the point where the inactivation gates of the channel are removed. This is followed by a relative refractory period, a period of time during the afterhyperpolarization (occurs around 2ms). If a stimuli is applied during this period that is strong enough to overcome the hyperpolarization and reach the threshold limit, another action potential will be initiated.

**Characteristics of action potentials:**

- Travel from one end to the other
- Thicker the nerve fiber, higher the velocity at which the signals travel
- Propagation via myelinated fibers is faster than nonmyelinated fibers
- Nerve conduction occurs at velocities ranging from 0.5m/s to 100m/s
Action potentials in afferent neurons are always caused by receptor potential (graded potential produced by sensory receptors)
Action potentials in other neurons can be due to synaptic potential or pacemaker potential (smooth muscle and cardiac muscle cells, various ion channels in the membrane cause graded potentials)

**Neurotransmitters and neuromodulators**

Neurotransmitters are chemical messengers that travel from the end of one neuron (presynaptic neuron) via the synaptic cleft to another neuron (post synaptic) or effector cells such that it produces some effect on the target cell.

Neuromodulators are chemical messengers that modulate or alter the signals of neurotransmitters through secondary mechanisms. They may amplify or dampen the synaptic activity in the postsynaptic cell or have an effect on the release, metabolism or reuptake of a neurotransmitter of a presynaptic neuron. The activity of neuromodulators is very slow as compared to neurotransmitters and may take either minutes or hours.

**Major classification of Neurotransmitters and Neuromodulators in the body**

- Acetylcholine (Ach)
- Amino Acids
  - Excitatory amino acids
  - Inhibitory amino acids
- Biogenic Amines
  - Dopamine
- Epinephrine
- Norepinephrin
- Catecholamines
- Histamine
- Serotonin
  - Neuropeptides
  - Others
    - Gases
    - Purines

**Structure of the nervous system**

The nervous system is divided into the Central Nervous System (CNS) and Peripheral Nervous System (PNS). The central nervous system consists of the Brain and spinal cord.

**Central Nervous System**

The brain is further subdivided into four regions: Cerebrum, brainstem, diencephalon and cerebellum. The cerebrum has been divided into the two hemispheres and these two hemispheres are connected together by the corpus callosum, a big bundle of nerve fibers. The cerebral hemispheres are made up of an outer layer of grey matter called the cerebral cortex, a middle layer called white matter that is composed of myelinated fiber tracts and an innermost grey layer called the subcortical nuclei. The cerebral cortex is further divided into four lobes: Frontal, parietal, occipital and temporal. The cerebral cortex has the maximum integration of afferent neurons and is responsible for the control and governance of the skeletal muscles and hence cortical excitability is very important and
correlates to the individual’s ability to respond to stimuli. The sub cortical nuclei are responsible for movement, posture and behavior because they mostly contain basal ganglia.

Figure 3 Diagram of the human brain. Source: (Fedak n.d.)

The diencephalon consists of the thalamus and hypothalamus. The thalamus acts like an integration center and synaptic relay station for signals moving to the cerebral cortex and plays an important role in focused attention. The hypothalamus accounts for less than 1% of the brain and resides below the thalamus and above the pituitary gland; it acts as the central command for neural and endocrine coordination. The hypothalamus is also responsible for activities like eating and drinking that sustains an individual as well as sexual reproduction. Apart from the above mentioned there is one more functional system called the limbic system that consists of both grey and white matter. The limbic system is connected to the thalamus, hypothalamus, parts of the frontal lobe cortex, and the temporal lobe. This system is responsible for behavior, emotional experience and learning.
The cerebellum consists of an outer layer of cells and an inner layer of cluster of cells. The major role of cerebellum is to coordinate movement and it therefore receives signals from muscles, joints, eyes, nose skin etc. Its function is mainly motor related but it may also have some role in learning.

All signals between the forebrain, cerebellum and spinal cord have to pass through the brainstem. The most important aspect of the brainstem is the reticular formation, freely arranged bundles of neuron cell bodies that are interconnected with bundles of axons. It receives and process input from all sources and has a massive influence on the rest of the central nervous system. It is responsible for mechanisms that regulate sleep and consciousness, motor functions and respiratory and cardiovascular functions. The nuclei of the 12 pairs of cranial nerves reside in the brainstem and extend to other parts of the brain and head, innervating muscles sensors and receptors.

The spinal cord is secured inside a hollow bone structure and extends from the head till the base of the spinal vertebrae. The innermost grey matter area consists of cell bodies and dendrites of efferent and afferent neurons, entering neurons of afferent cells and glial cells. Adjacent and around the grey matter is white matter consisting primarily of myelinated axon fibers that run longitudinally carrying information to and from the brain as well as pathways in various locations to transmit information into the peripheral system. Afferent neurons enter the spinal cord through the dorsal side via dorsal roots, whereas the efferent neurons leave the spinal cord from the ventral side via ventral roots. Both afferent and efferent roots combine together within a short distance from the cord to form a spinal nerve.
Peripheral nervous system

The peripheral nervous system transmits information between the spinal cord and sensors or receptors. The system consists of 43 pairs of nerves, 12 pairs of which are cranial nerves and 31 pairs are spinal nerves. Table 1 lists all cranial nerves and Table 2 lists all the spinal nerves.

Table 1 Cranial nerves

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Name</th>
<th>Direction of fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Accessory</td>
<td>Efferent</td>
</tr>
<tr>
<td>2</td>
<td>Abducens</td>
<td>Both</td>
</tr>
<tr>
<td>3</td>
<td>Facial</td>
<td>Both</td>
</tr>
<tr>
<td>4</td>
<td>Glossopharyngeal</td>
<td>Both</td>
</tr>
<tr>
<td>5</td>
<td>Hypoglossal</td>
<td>Efferent</td>
</tr>
<tr>
<td>6</td>
<td>Oculomotor</td>
<td>Efferent</td>
</tr>
<tr>
<td>7</td>
<td>Olfactory</td>
<td>Afferent</td>
</tr>
<tr>
<td>8</td>
<td>Optic</td>
<td>Afferent</td>
</tr>
<tr>
<td>9</td>
<td>Trigeminal</td>
<td>Both</td>
</tr>
<tr>
<td>10</td>
<td>Trochlear</td>
<td>Both</td>
</tr>
<tr>
<td>11</td>
<td>Vagus</td>
<td>Both</td>
</tr>
<tr>
<td>12</td>
<td>Vestibulocochlear</td>
<td>Afferent</td>
</tr>
</tbody>
</table>

Table 2 Spinal nerves

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Vertebral level</th>
<th>No. of nerves</th>
<th>Function</th>
</tr>
</thead>
</table>

17
In the peripheral nervous system a nerve may carry either afferent or efferent or both type of fibers. In this case the nerve fibers may be referred to as the afferent or efferent division of the PNS. All spinal nerves contain both types of fibers except for a few cranial nerves (optic nerve) that are only afferent.

The efferent neurons in the peripheral nervous system are further subdivided into somatic and autonomic nervous systems. The somatic nervous system innervates skeletal muscles whereas the autonomic nervous system innervates cardiac and smooth muscle, glands and other neurons in the GI tract. The somatic nerves consist of a single neuron that extend from the central nervous system to the skeletal muscle and can only produce excitation of muscles. The autonomic nerves on the other hand are comprised of two neuron chains that connect the central nervous system and the other effector organs mentioned above. Autonomic nerves are capable of both an inhibitory as well as excitatory response.

The somatic nerves have their cell bodies located in groups within the brainstem or spinal cord. Their nerves are usually large in diameter, do not have synapses and have acetylcholine as their neurotransmitter. Somatic neurons are also called motor neurons.
Motor neurons only get excited which causes muscle contraction but not relaxation (Widmaier, Raff and Strang 2004).

**Pain Mechanism**

**Sensory receptors**

The sensory system encompasses those components and that focuses on stimuli received from external and internal environments. The usual process in simple terms is the production of graded potential in sensory receptors in response to a stimulus that further initiates an action potential that reaches the CNS for processing. If an individual realizes this stimulus, it’s called sensation and understanding this sensation is called perception. The signal or form of energy that activates a sensory receptor is called a stimulus and the conversion of this energy into electrical response is known as stimulus transduction.

Sensory receptors are specialized endings present on the terminal ends of afferent neurons or can be separate cells that produce chemical signals that alter the ion channels of the afferent neuron terminals. There are various types of receptors in the body. They are classified based on the type of stimulus (form of energy) they respond to, also known as stimulus modality. For example, mechanoreceptors respond to mechanical stimuli, whereas thermoreceptors to temperature changes. Although sensory receptors in some cases might respond to other stimuli, one type of receptor will always produce the same sensation.

There are ion channels located in specialized receptor membranes at the tip of the terminal axon that open and close according to the stimulus and change the ion flux. This change in ion flux causes an alteration in the membrane potential (graded potential) also
known as a receptor potential. The graded potential then travels a short distance until it reaches voltage gated channels and initiates an action potential if it reaches the threshold. If the receptor membrane is part of a different cell, then that cell would release neurotransmitters that would trigger a membrane potential in the second nerve cell.

In the case of afferent neurons, action potentials are fired as long as the graded potential is above the threshold frequency. An increase in graded potential causes an increase in the frequency of action potentials up to a limit, which is set by the refractory period of the neuron. Sensory potentials have a unique property called adaptation: the receptor sensitivity decreases over a period of time even though the stimulus strength remains stable.

Afferent neurons have various terminal branches, all of which end with a sensory receptor. The area around which stimuli are sensed is called the receptive field for that neuron. In most instances, the receptive field of one neuron will be mixed with that of another. Stimuli strength is strongest when it lies in the center of the receptive field. Thus when there is a stimulus all neurons around the stimuli will get affected but the stimulus intensity of the neuron that has the stimuli at the center of its receptive field is the strongest. The receptive field also plays a major role in the person’s ability to detect the location of stimulus, e.g. the lips contain many small receptive fields and stimulus can be located easily whereas in certain areas of the dorsal skin it is difficult to locate the stimulus.

Lateral inhibition another phenomenon that occurs in the nerves also helps in the stimuli identification and location process. Information from neurons whose receptors are away
from the stimulus site is inhibited by interneurons in the CNS. The neuron with the strongest stimulus strength inhibits the lateral neuron’s signals with the help of interneurons. This allows for screening only important messages while ignoring the rest. Modalities like pain and temperature use less lateral inhibition as compared to the other modalities.

The stimulus duration greatly depends on the type of receptors. There are two types of receptors, the rapidly adapting receptors and the slowly adapting receptors. Rapidly adapting receptors respond immediately upon stimulus onset and then may fire slowly or not fire at all until the end of the stimulus. Those receptors that fire only once at the onset of stimuli are called on response and those that fire at the beginning and end of the stimuli are called on-off responses. Slowly adapting receptors maintain the same frequency of firing until the full duration of the stimulus.

**Pain receptors**

Pain receptors are called nociceptors and they respond to signals like excessive heat, mechanical deformation and some chemicals like neuropeptide transmitters, histamine, cytokines, bradykinin, prostaglandins. These chemicals may be produced by damage cells or secreted by cells of the immune system. Nociceptors have free nerve endings and are excited by ligand-gated ion channels. The neurotransmitters that are released by pain afferents to the CNS are ‘substance P’ and glutamate.

The mechanism of pain perception differs from other types of modalities. Some nociceptive afferents end on interneurons due to which the pain is not identified at the point of damage; rather it may be experienced at some other site. An example of this is
during a heart attack, the person feels pain in his left arm rather than the heart. This is called referred pain. This occurs because the somatic and visceral afferent usually converge on the same neuron in the spinal cord and since the excitation of the somatic afferent fibers is so common, the mind perceives it to be the source of origin.

Many modifications occur in the pain pathway after the first action potential; the sensitivity to pain may increase (hyperalgesia) or decrease (analgesia). There are many factors that contribute to this phenomenon, anxiety, emotions and past experience are some of them. The pain can be blocked when descending pathways from the reticular formation inhibit signal transduction by producing endogenous opioids that act on the afferent neurons.

**Physiology of pain**

The 1965 gate control theory of pain sparked the whole concept of managing chronic pain. Since then many destructive procedures for pain had been abolished and new therapies have emerged.

There are two types of pain: nociceptive pain and neuropathic pain. Nociceptive pain is experienced when the body responds to noxious stimuli, theoretically caused by cell damage and subsequent leakage of histamine, bradykinin and other chemical mediators. In contrast, neuropathic pain occurs not as a result of noxious stimuli but rather from damaged or dysfunctional neural tissue.

Once there is adequate noxious stimuli at the receptor site, chemical stimuli will bind and generate an action potential. Transmembrane ion current will flow and transmit the signal
along the afferent nerve fibers towards the cell bodies, which are commonly located in the dorsal root ganglia (DRG) of the spinal cord.

A number of different pathways are used to conduct the pain sensation to the sensory cortex of the brain. Fast-onset, “First pain” is experienced typically with a very localized pricking sensation, sent along myelinated Aδ-fibers via the spinothalmic tract. Slow-onset “second pain”, is sent along unmyelinated C-fibers and is more diffuse pain, which begins after injury has occurred and lingers after first pain has dissipated. C-fibers take a more diffuse pathway through the spinoreticulothalamic system. Auxiliary signals pass through the reticular formation and are responsible for the unpleasant, emotional response associated with pain.

Signals from the sensory, afferent nerve fibers are transmitted toward the DRG, synapse occurring in the dorsal horn of the spinal cord. Pain input is concentrated specifically in the substantia gelatinosa, lamina II layer of the posterior grey horn of the spinal cord. The Lamina V region of the posterior grey horn is composed mostly of wide dynamic range cells (WDR). WDR cells respond to noxious and non-noxious stimuli. These cells have large receptive fields; fast conduction velocity and can alter their discharge frequency to respond to different stimuli, all which play a substantial role in chronic neuropathic pain.

Chronic pain encompasses neuropathic pain as well as referred and projected pain. Referred pain is manifested by visceral sensation along a dermatome, which is innervated by the same segment of the spinal cord. Projected pain occurs when pain fibers are stimulated within a pain pathway, resulting in the perception of pain, referred to as phantom limb sensation. Chronic pain occurs when sensation of pain exists long after the
noxious stimuli have been removed. Theorists propose that chronic pain occurs when the pain signals continues to fire within the circuit or is related to denervation super sensitivity.

Antinociception, the physiologic process of suppressing nociceptive pain signals, often achieved by the body via neurotransmitters that include: Gamma-aminobutyric acid (GABA), endogenous opioids, and other neuropeptides. Externally, antinociception has been attempted by stimulating various parts of the brain, many times focusing on the intralaminar nuclei of the thalamus and the insula. Neuropathic pain may not respond or may respond poorly to narcotic therapies, requiring very strong doses of narcotics to dampen symptoms. Sodium channel blocking agents, including Gabapentin, Phenytoin and Carbamezepine are able to bring some symptomatic relief. (Rosenow 2009) (Bullock, Boyle III and Wang 2001) (Costanzo 2010).

**Modalities for pain management**

*TENS:* Transcutaneous Electrical Neural Stimulation is a small device that produces biphasic low level electrical current that penetrates two inches below the skin to block pain. It usually takes 30 minutes for the device to start relieving pain (Pain management Technologies 2002).

*Nerve Blocks:* These are local anesthetics that are supplied to the pain site constantly through catheters. These chemicals block the signal transmission between the nerve receptor and the brain hence numbing the area (Davis 2010).
Radiofrequency ablation: A needle is placed near the damaged nerve using CT imaging. The nerve is then heated and destroyed using radio waves. This method has been proven to relieve pain for a period of up to six months in specific cases (Davis 2010).

Pain relief creams: These are topical painkillers like Zostrix and Bengay, used to treat mild pain.

Non opioids and NSAIDS: There are oral medications that are used for mild to moderate pain relief.

Narcotics: Drugs like codeine and morphine are administered for severe chronic pain. These are usually prescribed along with other drugs like extended release antidepressants. There is a risk of addiction with patients with chronic pain.

Neurostimulators: These are spinal cord stimulators that are usually used when most of the other treatments are ineffective. The implanted device produces low level electrical signals that prevent pain signals from reaching the brain. The intensity of the device can be adjusted as well turned on or off using a switch.

Spinal Drug pumps: These are pumps operated by the patient and deliver anesthetics and narcotics directly to the spinal cord with a push of a button. These doses are much lower than oral doses and hence lower risk of side effects (Davis 2010).

Neuromodulation

Neuromodulation can be defined as “a field of science, medicine and bioengineering that encompasses implantable and non-implantable technologies, electrical or chemical for the purpose of improving quality of life and functioning of humans” – The INS (International
Neuromodulation Society). For any therapy to be called a neuromodulation therapy, the following criteria must be met.

1. It must be an ongoing and dynamic intervention

2. It must have an effect on specific neural networks by means of its stimulation process

3. The clinical effect should be controllable continuously by being able to varying at least one stimulation parameter such that the patient’s need is satisfied.

Neuromodulation can be either electrical or chemical in nature. Electrical neuromodulation can be defined as electrical stimulation of peripheral nerves, the spinal cord, plexus of nerves, autonomic system and muscles whereas chemical modulation is the application of chemical agents at neural tissues either through intrathecal or epidural delivery systems. Neuromodulation addresses the needs of various sub specialties of medicine like cardiology, anesthesiology, gastroenterology, neurology, neurosurgery, ophthalmology, pain and physical medicine (Krames, Peckham and Rezai 2009).

**Neurostimulation basics**

Application of electrical current via an electrode causes changes in voltage gated ion channels; this can either initiate an action potential or suppress a propagated action potential (Mortimer and Bhadra 2009).

*An electrode:* It is the interface between the targeted nerve and the neuromodulation device.
**Anode and Cathode:** Negatively charged electrons flow from the cathode (where reduction occurs – electron gain) to the anode (where oxidation occurs – electron removal). The current flows in the opposite direction from the anode to the cathode.

**Voltage and current:** Current is the rate of flow of charge while voltage is the measure of energy carried by charge. Ohms law relates both of them as follows:

\[ V = IR \]

V is the voltage, I is the current and R is the resistance.

**Stimulus Characteristics:** A current pulse is defined by its amplitude (Amps or Volts), duration (pulse width) and pulse shape (triangular, rectangular or sinusoidal). The rate of repetition of these pulses is called pulse rate or stimulus frequency.

**Electrode characteristics:** The size of the nerve tissue-electrode interface has an impact on the charge and current density of the stimulus that is applied. The larger the area, lower the stimulus strength. The current density decreases with increase in distance from electrode.

**Effect on axon diameter:** The larger the axon diameter, more the sensitivity of the neuron to the applied stimulus. There are many factors that contribute to this, larger diameter neurons have a longer separation between the nodes of Ranvier and hence smaller axon diameters require greater stimulus amplitude to produce action potentials. Also a larger axon has a lower axial axonal resistance due to larger cross sectional area, therefore the current induced inside a larger axon in a given extracellular electric field will be higher than that in a smaller axon.
Nerve depolarization: A propagated action potential is initiated when sufficient amount of voltage gated sodium channels transition from a resting-excitable state to an active state, caused by lowering of membrane potential. Applying a cathodic stimulus at or near the site of excitation causes the transmembrane current to flow from the inside to the outside of the cell, which causes this effect.

Nerve hyperpolarization: Application of an anodic stimulus to a site increases the transmembrane potential from a resting state due to which prevents the voltage gated sodium channels from going into an active state. At this point the net transmembrane current flows from outside of the cell to the inside.

History of electrical neurostimulation
The use of electric shock to treat various ailments dates back to 46 A.D. In ancient Egypt, the inhabitants made use of electrogenic species like the electric catfish to treat headaches, gout and other pain conditions (Henderson 2008). The first electrostatic generator was used in 1744 to therapeutically treat paralysis and by 1752 electrical stimulation was embraced by the medical community as cures for various ailments like paralysis etc. Around late 1700s and early 1800s, Aldini, worked on many experiments and was able to induce muscle contractions in the face of oxen and human cadavers using direct brain stimulation. Later in 1855 after the discovery of the first electric generator by Faraday, Dr. G.B Duchenne, a.k.a. the father of electrotherapy stimulated the facial nerve that caused palsy. By 1900s many physicians had an electrical machine that was used to treat many nervous ailments. (DiLorenzo and Bronzino 2008). It wasn’t until 1965, when the Gate control theory was introduced by Melzack and Wall, that there existed a real rationale for the treatments (Henderson 2008).
**First Clinical study**

The first clinical trial involved subjecting eight volunteers suffering from chronic cutaneous pain to electrical nerve stimulation. Any one among the three electrodes, skin surface electrodes, implantable split ring electrodes and percutaneous concentric bipolar electrodes was used in this study. At the end of the study, all of the patients felt tingling paresthesias but had spectacular relief from pain except for two patients who had become tolerant to the stimulation (Henderson 2008).

**Types of neurostimulators in the market**

The neurostimulators are classified based on their site of action or the particular nerve they stimulate. They can be either implantable or non-implantable.

- **Spinal Cord Stimulation (SCS)**
  
  Spinal cord stimulators are mostly used to treat pain. Depending on the placement of the electrode, it can be used to treat different symptoms. For example placing electrodes between L2 and L3 vertebrae can decrease bladder plasticity and increase its volume tolerance, similarly placement of the electrodes between C1 and C2 results in bronchodilation.

- **Deep Brain Stimulation (DBS)**
  
  Deep brain stimulation is the process of stimulating the brain with mild electrical impulses. In the United States, the FDA has approved the use of DBS for essential tremor in 1997, Parkinson’s disease in 2002 (Mayo Clinic 2010) and dystonia in 2003 (MDVU 2003). Neurosurgeons with the help of Magnetic resonance Imaging (MRI) and Computed Tomography Imaging (CT) locate the problem
area and insert the electrodes. These electrodes are connected to a programmable generator that is implanted in another location in the body (Mayo Clinic 2010).

- **Peripheral Nerve Stimulation (PNS)**
  - **Vagus nerve stimulators**
    These devices are used to stimulate the left vagus nerve to treat disorders like depression or intractable epilepsy. The implantable programmable generator (IPG) is usually placed in the upper part of the chest under the skin. Switching the device on and off is done using a magnet (WebMD 2009).
  - **Sacral nerve stimulators**
    These are devices that are used to provide electrical stimulus to the sacral nerve, which than controls the urge for uncontrolled urination. This technology is therefore used to treat patients suffering from urinary incontinence or urgency-frequency related disorders (Mayo Clinic n.d.) (Frost & Sullivan 2008).
  - **Gastric electric stimulators**
    This type of stimulator is used to mainly to treat gastroparesis. However, the effectiveness of this type of stimulation is yet to be proven and is used only in patients with severe symptoms. It stimulates the smooth muscles of the lower stomach; this reduces symptoms of nausea and vomiting in some patients (Mayo Clinic 2009).
Description of Neuros Medical technology and Products

HFAC technology

The application High Frequency Alternating Current on nerves of mammals has shown to induce a completely reversible conduction block (Bhadra and Kilgore 2005). The company has licensed this technology from Case Western Reserve University and intends to commercialize it for human use to treat various medical complications.

High frequency has been used by many scientists in the past as early as 1935 to block nerve conduction (Kilgore and Bhadra 2004). Over the past century various waveforms and frequencies have been used by researchers to bring about a conduction in block. Dr Kevin Kilgore and Niloy Bhadra in 2004 studied all the different experiments performed and came up with a recommended waveform, frequency and other parameters that could bring about a complete conduction block in mammals as well as hypothesized the mechanism of action of this technology.

Mechanism of action

When High frequency AC current is applied to the nerve, during the first cycle of the waveform the region directly below the nerve gets depolarized due to which it sends action potentials in both directions. The paranodal regions of the axons proximal to the electrode get biased towards depolarization and as these axons encounter a few more cycles, the paranodal regions get totally depolarized due to which an action potential cannot be propagated through them (Kilgore and Bhadra 2004).

Characteristics of HFAC conduction block
There are three phases of the conduction block:

*Onset Phase:* This is the response that is encountered as soon as the block is turned on. When the nerve block is turned on, all nerve fibers in the nerve trunk directly under the electrode get depolarized, propagating an action potential. The summated effect of this action potentials give rise to an onset response (Kilgore and Bhadra 2004). This can range from a single twitch to a summated twitch depending on the amplitude and frequency used. The peak height of the twitch can vary from being similar to a normal twitch encountered in the preblock period to a peak height that is 8 times higher (Figure 4).

*Asynchronous firing:* This phase follows the onset phase and is characterized by asynchronous firing which slowly decreases and merges into the third phase. The magnitude of asynchronous firing is dependent on the amplitude and frequency and varies inversely with frequency and amplitude, higher the frequency and amplitude lower the magnitude of asynchronous firing (Figure 4). Asynchronous firing can also be tremendously reduced by repositioning the electrodes.

*Block phase:* A complete conduction block is achieved when the nerve is incapable of propagating a action potential. The block can be complete or partial, a partial block is defined as “a muscle twitch force during block that is between zero and maximum force”. This can be achieved by reducing the amplitude below the complete block threshold level (Bhadra and Kilgore 2005).
Figure 4 Onset response and asynchronous firing recorded at 30 kHz sinusoid waveform at different amplitudes. Source (Bhadra and Kilgore 2005).

Figure 5 Complete block achieved when high frequency sinusoid waveform is applied from 10s to 30s. Source: (Bhadra and Kilgore 2005)
Product Design

The company’s therapy package would include a pulse generator unit, implantable electrode and connecting wires.

Pulse generator: The pulse generator is similar in size to a pacemaker and consists of an energy source, AC transformer and a waveform generator. The energy source is Direct current, which the transformer converts into alternating current and sends it to the waveform generator, which applies the required output waveform. This programmable generator is attached to the electrodes via biocompatible wires.

Wireless recharging and operation: The Neuros product will have a wireless patient control unit (PCU) like other neurostimulators manufactured by Medtronic (Figure below). This will allow the patient to turn the block on and off. To charge the batteries of the implantable pulse generator (IPG), this PCU should be kept closest to the device. The patient will be given a belt, which will fit the PCU while charging. The PCU needs to be charged as well after it has been used to charge the IPG.
**Electrodes:** The electrode will be a nerve cuff electrode that goes around the nerve.

**Power source:** The device will use a rechargeable Li-ion battery which is comparable to spinal cord stimulators like Eon Mini and Restore ULTRA from St. Jude Medical. It is very difficult to use a single use battery with this technology because the high frequency range at which the device operated will drain the battery quickly and hence may require replacement of device.

**Advantages of wireless technology**

1) Reduced risk of infection
2) Improves patient’s appearance
3) Enhances patient’s quality of life
4) Risk of electrode dislocation

Potential future applications of advanced wireless technology

With the advancements in wireless technologies, it would be possible to monitor electrical signals propagated through nerves in the future. In a paper published in the IEEE sensors journal in 2006 by Chiel et al., demonstrated that the neural activity of *Aplysia californica*, a common sea slug could be recorded using low power, low noise, multichannel wireless systems. Coupling such technology along with Neuros medical technology will enable more effective and efficient pain treatment. Another possibility is creating an automated closed loop such that the patient’s own neural activity could trigger the pulse generator to reprogram itself to provide complete nerve block (Chestek, et al. 2006).

Risks associated with the therapy

- A complete block could be achieved on amphibian sciatic nerve at 10-20 KHz whereas a mouse sciatic nerve required stimulus at 30 KHz at 10 V to achieve complete nerve block. The frequency required to block human nerves may be higher than that of mouse.

Electrode implantation

- General risks exist similar to those associated with conventional surgical procedure such as excising a peripheral nerve in a limb for the removal of a neuroma.
Specific risks exist related to the implanted electrode and lead, mainly infection around the implants. This occurs in other implanted devices such as pacemakers but has not happened with the 16 or so nerve electrode in previous human studies at CWRU.

Specific risks exist related to the percutaneous interface at the skin exit site of the lead. This occurred in similar leads connected with other types of electrodes such as the intramuscular electrodes used for motor function restoration at CWRU.

**Electrical nerve block**

- Electrical current applied for nerve block may induce discomfort sensation or pain.

**Electrode explanation**

- General risks exist similar to those associated with conventional surgical procedure such as excising a peripheral nerve in a limb for the removal of a neuroma

**Battery**

- Over discharging the battery often may require replacement of the battery, which means it needs to surgical intervention.
Pages 38 to 50 contain confidential data and have been removed from this thesis. Please contact the company for further information.

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Reimbursement

Overview of the reimbursement process in the US

Reimbursement in the healthcare arena means nothing but the payment for service provided by the healthcare provider, unlike most other countries in the world, the U.S. reimbursement system is pretty complex. In the United States, there is a third party that pays for all healthcare services rendered by the provider (Hospitals, pharmacies, clinics, physicians etc.) There are two types of insurances private and public, see Figure 12 for the percentage of population covered by both types of insurance.

Figure 12 Pie chart showing insurance coverage of the US population in 2005. Data from (Mehta 2008)
Public payers

Major public payer in the US is Centers for Medicare & Medicaid Services (CMS) which has two programs – Medicare and Medicaid. Other forms of public insurance include military and veterans administration.

Medicare

Medicare is the insurance program provided by the federal government and it covers a total of 43.1 million (2006) people who are aged 65 and older, disabled and those who have End-Stage Renal Disease (ESRD). Medicare has various parts – A, B, C & D which have different payment structures with variable deductibles etc. Medicare policies have a major impact on the US healthcare system primarily because of its impact on more than 13.7% of the population and secondarily because most insurance companies use Medicare reimbursement policies has the gold standard (Center for Medicare Advocacy, Inc n.d.) (Mehta 2008).

Medicaid

This is a state managed program which covers people who have an annual income below the poverty line. Although the federal government sets broad national policies, each state has its own guidelines.

Private Insurance

These are private companies that provide coverage to the rest of the population. These companies usually have contracts with employers and subsequently cover all employees of that employer. Private insurance include companies like Blue cross, Aetna, Cigna
Kaiser Permanente (HMO). These insurers provide different plans to their customers with various payment options, of these the most common types are Preferred Provider Organizations (PPOs) and Healthcare Maintenance Organizations (HMOs).

**Flow of payment**

Medical device manufacturers either sell their equipment directly to the hospitals or through wholesale distributors. In either case, it is the responsibility of the manufacturer to market their products. While selling medical devices, the sales team has to sell the product to various stakeholders – hospital purchasing department, insurance providers and physicians/surgeons and pharmacies. The flowchart on Figure 13 adds further clarity to the system of payment flow in the US healthcare system.

Figure 13 Flow chart showing payment flow in the healthcare industry. Source: (Mehta 2008)
Coding

In the healthcare industry, coding refers to the alphanumerical code that is assigned to various medical technologies and procedures performed. The hospitals use the codes to identify the services rendered to a patient and submit these codes to the payers; codes are used because it makes it easy to process paperwork over lengthy names. There are two types of code, one that identifies the diagnosis (ICD-9) and the other that identifies procedures and products (CPT, DRG etc.)

The payment rates differ depending on the type of facility the service is rendered. These payments are grouped depending on the facility for example, inpatient procedures usually fall under a DRG code and hence the hospital gets one payment for the admission and has to cover any cost associated with that patient within the prescribed payment. These amounts of payment are determined by CMS and may change from year to year depending on the advancement of technology (the update on payment occurs much later after a new technology is introduced). The flow chart below (Figure 14) provides detailed information on the type of coding used for each facility.
Figure 14 Reimbursement codes based on facility of service delivered Source: (Mehta 2008)
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Bibliography


