Electrode Array for Transcutaneous Electrical Stimulation after Spinal Cord Injury

Final Design Report

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ABSTRACT

Spinal cord injuries affect hundreds of thousands of people worldwide. Other vertebrate species, such as rats, can be used in order to model the effects of various treatments on severed or contused spinal cords. Currently, methods involving epidural and transcutaneous stimulation via electrode arrays are available, although few effective, non-invasive devices exist currently for pain management. Our client, Mr. Daniel Hellenbrand, has tasked our team with taking the first steps towards developing a spinal cord electrode array that fulfills these criteria for rats, while keeping in mind that the research and design will be transferred to human models in the future. The methodologies behind such techniques have not been highly researched. Within the scope of this project, three main design elements were tested for efficacy prior to formulating an electrode array: frequency mode of stimulation, number of electrodes within the array, and the location at which the array will be placed on the spine. Through extensive literary research, the lumbar plexus was identified as the location of the spinal cord most relevant to this project, with which the team moved forward. For frequency modes, there was no significant variation in percentage of retained voltage from varying between tonic and high burst frequency modes. However, an increase in retained voltage was recorded when the number of electrode pairs was increased. In the future, the project may focus on ways to increase focality of stimulation to reduce superficial stimulation and increase retained voltage.

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I. INTRODUCTION

A. Motivation

Spinal cord injury (SCI) has been a major point of interest in the medical community for many years. To date, there exists no comprehensive solution or standard routine for patient recovery. Once a nerve pathway is severed or contused, a patient must turn to costly, personalized meetings with medical professionals to remedy their specific points of injury [1]. In addition, the number of people with spinal cord injuries is growing every year. Currently, just under half a million people worldwide develop a SCI each year [2]. Unfortunately, prevention for this type of injury cannot be targeted by lifestyle change as much as some other conditions. For example, leading causes of SCI within the affected populations are motor vehicle accidents in young adults and slips and falls in elderly individuals. The results in either case are drastic; for youth, it can potentially lead to permanent lifestyle disruption, hundreds of thousands of dollars in medical bills over a lifetime, and an involuntary burden on the healthcare system. For the elderly, SCI can be a crucial pivot point in the individual's health and life expectancy. There is a

deficit of knowledge of the best way to both prevent these life-changing injuries and of how to prevent them from worsening, from the time of the first response emergency care to weeks later.

Though there is no universal cure for SCI currently, there are several methods on the market aimed at addressing the needs that these injuries cause. The first of these is the epidural spinal cord stimulation (SCS) system. This consists of a small pulse generator that is surgically implanted in the epidural space of the spine and wired to specific nerve pathways by a medical professional. Epidurals offer the advantage of extremely personalized nerve stimulation, as they are made specifically for the region of the spine needing stimulation. However, such procedures have notable drawbacks. For instance, any modifications for discomfort or function would need to be done in a hospital by an expert, which would delay the timeline of recovery and possibly involve a lengthy waiting period for an appointment. Having an epidural would also raise the number of total hospital visits and therefore raise the total medical expenses of an already costly condition. Additionally, the internal lead wires may cause infections or adverse reactions within the body.

Along with epidural SCS, a very popular method of pain therapy is the TENS (Transcutaneous Electrical Nerve Stimulator) unit. This device is a method of transcutaneous electrical stimulation that focuses primarily on pain relief in the areas underneath the electrode pads placed on the surface of the skin. Key benefits of this device are the ease and mobility with which it enables the addition of physical therapy, as well as the manipulability of the frequency used. These devices are able to be adhered and removed with no clinical assistance and allow an almost complete range of motion while in use, which can be very beneficial for patient comfort. However, a key disadvantage of this device is the lack of specificity concerning the nerve branches affected [3]. Because of this lack of specificity, the electrodes are not made to stimulate with as high of a frequency as is necessary to effectively stimulate locomotion in other parts of the body. Thus, this device would need many modifications in order to be applied to regaining motor functions post-spinal cord injury.

Due to the fact that all of these current, more commercial methods of spinal cord rehabilitation have flaws that can affect the recovery in an individual patient, the team took the first steps towards developing a more modern, less-tested method: an electrode array for Transcutaneous Spinal Cord Stimulation (tSCS). Ultimately, the electrode array will be designed to create a combination of the above current methods by minimizing the negative effects while achieving effective stimulation. tSCS combines the benefits found in epidural SCS and the TENS units, allowing it to be used in tandem with physical therapy. It also takes into account the individual specificity of the patients' physiologies and injuries with relation to the spinal cord and accompanying nerves, as seen in the epidural SCS systems currently on the market. Furthermore, it adds the non-invasive and mobility-enabling features found in the TENS units. Potentially, tSCS could allow for increased mobility so as to work in tandem with physical therapy. Overall, the above factors make tSCS a more complete, cost effective, and functional form of current spinal cord rehabilitation after SCI.

B. Existing Devices

Spinal cord stimulation devices are currently developed by many healthcare companies including Medtronic and Boston Scientific, such as the Medtronic Intellis Implantable Neurostimulator (Figure 1). These devices have been used by hospitals, surgeons, and are available to the public. Most existing devices are epidural spinal stimulators that require surgical placement and are left in place after implantation. In application, these devices are mainly used for chronic pain management or neurological mapping. Transcutaneous stimulation of the spine is a field of growing research in which many different techniques and devices have been used to achieve different goals [4]. Although transcutaneous spinal cord stimulation devices do exist, their frequency modes are not yet optimized for targeting specific neural regions to induce and improve motor function in those with spinal cord injuries [5][6][7]. The development and design of this new electrode array for spinal cord stimulation will have a greater versatility in frequency types and modes of stimulation to improve motor function in conjunction with physical therapy.

Figure 1: Medtronic Intellis Implantable Neurostimulator (left) [8] is a fully implantable neurostimulator that is used through wireless programming. This device is used in conjunction with the wireless external neurostimulator (right) which simplifies testing during trial and implant of the implantable stimulator.

C. Problem Statement

Effectively targeting and stimulating corticospinal nerves *transcutaneously* to aid in recovery after SCI is currently a relatively novel rehabilitation technique. There are presently many effective methods of stimulating these nerves and aiding in motor rehabilitation in the field of *epidural* spinal cord stimulation (eSCS). However, these prototypes rarely make it to the clinical stages of testing, and many patients suffering from SCI recover after having undergone invasive surgery. Because of this, our client has asked the team to take first steps towards creating a transcutaneous electrode array that is effective in regaining motor locomotion for those affected by SCI. In the scope of this semester, the features optimized by the teams should be compatible with an adaptable electrode array for various body morphologies, as all

individuals contain unique neurological pathways. None of the features should impede the array from being wearable, reusable, and comfortable for the individual to use. The product should have the capability of being used in tandem with physical therapy, as literature points to the effects of paired stimulation and physical therapy solution to SCI [9]. For the purpose of the semester, only features that can be provided with grounded transferability from rats to humans should be considered.

II. BACKGROUND

A. Spinal Cord Physiology

Spinal Cord Injuries occur in a wide variety of vertebrate and physiological trends can be translated from model organisms to humans. Model species such as rats, cats, and pigs are used frequently to conduct relevant research on varying SCI's and different methods of repair. Because of this, it is imperative to be aware of the similarities and differences in the physiologies of rat and human spinal cords and neurological pathways in order to conduct research on transferrable methods of spinal cord stimulation for functional locomotive rehabilitation. Rats and humans have a similar construct of their respective spinal cords, and, despite the variation in size and shape of the spinal segments, they both progress from the brain to the pelvis, as cervical, thoracic, lumbar, and sacral segments [10]. Additionally, rats and humans have two major neurological pathways that control much of their locomotive functions, namely the Corticospinal Tract (CST) and the Rubrospinal Tract (RuST) [11]. These neurological tracts travel longitudinally down the spinal cord and communicate with synaptic contacts in both humans and rats alike. In the event that either the CST or the RuST is severed or impaired as a result of SCI, the other one is still capable of extending living axons to connect and continue neurological synapses within the impaired tract [11]. Rats can be useful as models both with and without injuries inflicted to the spinal cord; the action potentials of the intact spinal cords can be measured and contrasted with that of completely or incompletely severed spinal cords, and detailed feedback can be gained through stimulation at specific regions [12]. As literature suggests, this has some correlation with how the injured or severed human spinal cord would respond. However, although the general physiology of both species is relatively the same, there are several notable differences worth considering. Possibly the most predominant difference between rats and humans is the size and orientation of the spinal cord and accompanying nerves within it, as seen in Figure 2.

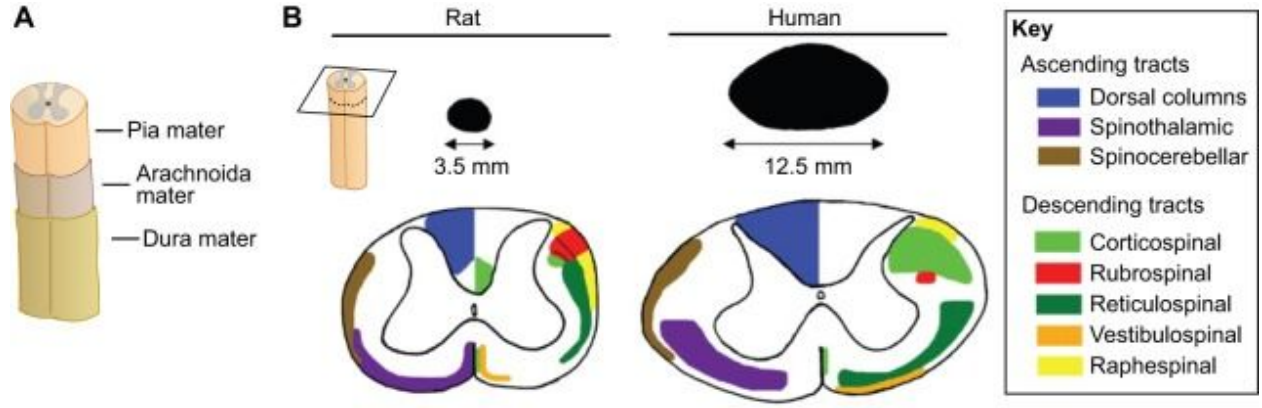

Figure 2: Size comparison and orientation of spinal cord and descending tracts in rats and humans, namely Corticospinal and Rubrospinal tracts [10].

Another key difference between the neurological pathways of rats and humans is that, in rats, nerve axons do not laterally cross from either CST, and are therefore less able to distribute the neurological signals more functionally across the spine and body in the event of an injury, unlike humans whose axons more readily intertwine between the separate CST hemispheres [10]. The physiological factors listed above must be focused upon when attempting to rehabilitate neurological signals through tSCS in order to reinvigorate locomotive functions when paired with physical therapy.

B. Spinal Cord Injury

Universally, spinal cord injuries pose a high threat to quality of life, leaving more of a long-lasting, drastic effect than other more common injuries. Around 337,000 people in the United States are currently affected by a spinal cord injury (SCI) [13]; however, patients may not report their condition as a spinal cord injury if they are only experiencing pain and did not have a serious accident, and there are more undocumented patients from countries worldwide. Young adults between the ages of 16 to 30 are the most common subset who experience spinal cord injuries, with the top cause being motor accidents [14]. There is also a sizeable portion of the elderly with spinal cord injuries caused by falling. Spinal cord injuries range from complete to incomplete in severity, and the severity of paralysis tends to directly correlate with the level of the spine that was affected (Figure 3). Victims of spinal cord injuries are faced with lifelong effects and lifestyle changes and often have little to no hope for full recovery. In addition, those with SCIs are faced with extremely high medical and lifestyle expenses following the incident, which can be as much as $1.08 million in the first year and averaging six figures in subsequent years [15]. Currently, novel treatments involving stem cell injection therapies and spinal cord nerve stimulation are offering the most hope for recovery. Unfortunately, stem cell therapies are

expensive, albeit personalized, procedures and epidural spinal cord stimulation requires an equivalently costly surgical operation. Of the two, spinal cord stimulation treatments are more suited to be adjusted for at-home or non-clinical settings. Therefore, a less invasive or non-invasive device for spinal cord stimulation would be the best method for reducing costs of insertion and operation, risk of infection or post-operative injury, and ease of adjustability and maintenance. As most injuries to the spinal cord are contusions, rather than transections, nervous tracts are frequently intact, but simply less functional. There is a need to stimulate patients' existing nervous pathways to the reach the action potential thresholds which they can no longer reach post-injury.

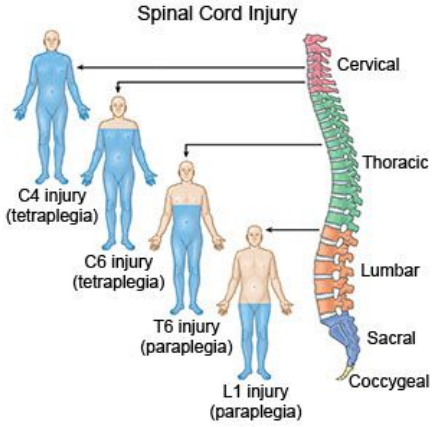

Figure 3. The image depicts the correlation of the region of the spine injured and the resulting injury's affected area

C. Spinal Cord Stimulation

The core purpose of spinal cord stimulation (SCS) is to deliver electrical impulses to the spinal cord, and in doing so, activate desired nerve pathways. These nerve pathways are activated in order to either mask a pain signal coming from a specific nerve plexus or to achieve a motor function, such as activating motion in the legs for walking. As mentioned, there are two main types of devices on the market for achieving these functions. The first, an epidural spinal cord stimulator, is a small medical device that is surgically implanted in the epidural space of the spine and is hooked up to specific nerve pathways and plexuses by medical professionals. The device is a pulse generator and requires a lead wire for connecting and directing the current to the desired nerve fibers. Due to the invasive nature of this method, infections are likely and pain or discomfort might be difficult to resolve without surgical modifications. Epidural stimulators also pair well with intrathecal drug injections that aid in the function of treating pain. The other main type of device is called a transcutaneous spinal cord stimulator. These are commonly pads of material that adhere to the skin, and they can be made with or without wires leading to a pulse generator, which doubles as a user-interaction device. Devices often involve use of a conductive

gel under the electrode pad, and they can short if the gel spreads and stop functioning if the gel dries. They are primarily tailored for at-home use and can be used without clinical professional guidance. Transcutaneous devices have traditionally been used for treating pain, such as with TENS units, as it is more difficult to penetrate to deeper nerves with a standard, high definition transcutaneous electrode array. Therefore, transcutaneous units made for regaining motor functions has remained an area that is relatively unexplored. Interestingly, studies have found that both transcutaneous and epidural SCS used for recovery of motor functions have shown most promising results when physical therapy was used in tandem with the stimulation. For example, patients in harnesses that removed all or some of the weight-bearing load on their lower extremities, with the assistance of epidural or transcutaneous stimulators, were able to move their legs, and they showed increased ability to do it (while bearing an increased amount of the weight) over time. A crucial component of testing this semester, and of how spinal cord stimulation works in general, is Ohm's Law, which has direct application to circuitry set-up. This formula states the relationship between voltage, current, and resistance, and allows precise knowledge about the impedance of differing regions being stimulated. All circuits created during stimulation will be subject to this law.

D. Client Information

Mr. Daniel Hellenbrand is an Assistant Researcher in Dr. Amgad Hanna's Spinal Cord and Nerve Lab. He earned his Masters of Biomedical Engineering from the University of Wisconsin in 2010. After sustaining a C5-C6 spinal cord injury in 2003, he has been primarily interested in finding solutions to improve functional recovery after such injuries to the central nervous system.

E. Design Specifications

The wearable spinal cord stimulation device must consist of an electrode array that is non-invasive and applies stimulation transcutaneously. This would avoid the costs of surgery and any complications that come after. A rat model should be utilized for testing, but application to humans should be kept in mind for the future in this design. The size and function should correspond to that of a 250 gram standard male rat. The system should be adjustable to allow for some variation between subject size. The wearable device should not hinder any movement of the rat, including walking, turning, and other general movements, as it should eventually have the ability to be used in tandem with physical therapy. The current applied through the electrodes must penetrate deeply into the body to reach spinal nerves, and the system should also have a versatility in its function, including the ability to stimulate with various waveforms, and flexibility in the placement of electrodes. Due to electrode placement on bare skin, the device must take precaution to not harm the patient in the form of shocking, burning, excessive pain, or pressure sores. The system should also minimize the stimulation of incorrect nerves so as to avoid spasms and other unintended reactions. Accuracy of stimulation is an important consideration, and spinal physiology between subjects will vary, including the location of

different neural plexuses. Therefore, any deviation between regions stimulated, electrode frequency, and results of the treatment will decrease the significance of research and introduce confounding variables. The end goal of the stimulation is focused on locomotion and increased bodily function. Overall, the device must greatly consider comfort and simplicity in design for ease of future commercialization. Within the timeframe and scope of the semester, the team accomplished as much as possible of the design specifications by testing to eliminate key variables such as number of electrodes used and mode of stimulation applied, which can be applied in the future to a physical prototype.

III. PRELIMINARY DESIGNS

Based on the clients specifications, and the challenges of transcutaneous spinal cord stimulation, the team decided to look into design variables more thoroughly. Prior to formulating an electrode array for transcutaneous stimulation, there were real problems revealed in literature that need to be addressed and tested to understand the abilities of transcutaneous electrical activation. There are conflicting results in articles, describing techniques such as interferential stimulation with seemingly different results. In studies within the past two years, Grossman has suggested that transcranial interferential techniques used on rats showed impressively successful effects, while Huang and Parra suggest that interferential is not any more focal or potent than conventional or other forms of stimulation [16][17]. This discrepancy in success of stimulation suggests that variability is common between test results, and these deviations make it hard to discern which method of stimulation is best for spinal cord stimulation. Therefore, experimentally testing variables of stimulation can give insight into which strategies are worth pursuing in an electrode array. First, the type of frequency has a major effect on the viability of stimulation. Current from stimulation is typically in the form of square waves, pulsed at varying frequencies. These frequencies interact with cells differently. Secondly, the number of electrodes used for stimulating can have an impact on the versatility and adaptability of the system. Typically, two electrode pairs are used to send current form an anode to a cathode, and stimulate regions of nerves in between. This is nice for simple stimulating, but current research suggests it is not the ideal method for ensuring patient comfort, effective and accurate stimulation. Finally, placement of electrodes at specific location along the spinal cord is vital to ensuring the current is localized to the region of nerves specified for the given application. This is paired with physiology, and the understanding of the limitations when using a model system such as a rat.

A. Design Element 1: Frequency Modes

Many studies show 20-50Hz as a sufficient frequency to reach stimulation of nerves [18] [19]. However, this type of stimulation will also inadvertently stimulate superficial nerves in the

process of stimulating deeper nerves. The other frequency modes the team has found as viable are interferential, high definition, inter-sectional, and high burst.

Interferential, as the name suggests, involves interfering signals (figure 4). The theory states that when two signals of similar high frequency interfere, a waveform similar to a much lower frequency is formed. For example, when 3kHz and 3.01kHz interfere, a 10Hz signal is seen. Despite some contradicting literature, initial studies suggest it is not any more focal than conventional methods [16], but the theory behind the technique suggests that it can penetrate deeper, and with more accuracy. Cells may even be modelled as low pass filters [20], and therefore a high enough frequency could pass through nerves that are not meant to be targeted.

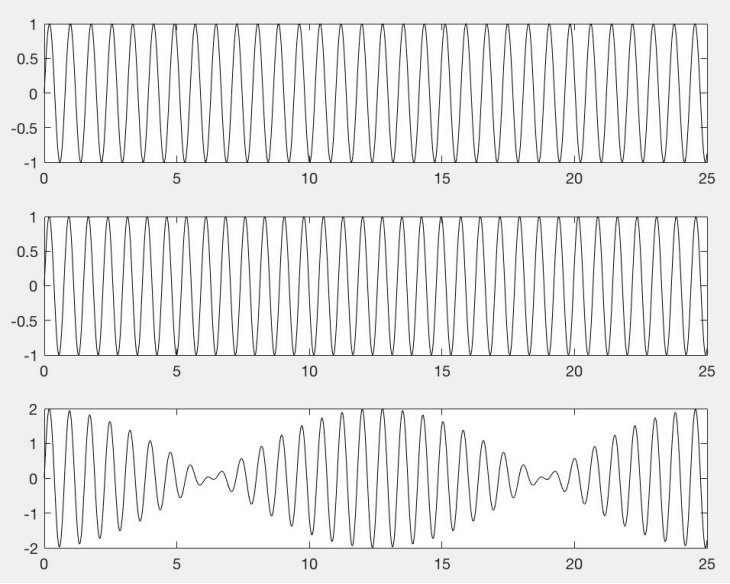

Figure 4: This MATLAB screenshot shows how two interfering frequencies interact and cause the third waveform. The third waveform is the addition of the first two, where the interference is either constructive, deconstructive, or in between.

Inter-sectional stimulation refers to the use of four or more electrode pairs, and iterating through each at a high frequency. The benefit of this is the ability to use a higher current than normal, because the current is spread over multiple electrodes, and therefore does not harm the patient as it would in conventional stimulation. Inter-sectional can be used in a manner that pulses fast enough so as to not polarize unintended neurons.

High definition stimulation is the use of one main cathode electrode, and four anode electrodes, typically referred to as 4x1 stimulation. This has been shown to develop much less skin irritation, and be very confined stimulation.

High burst stimulation (figure 5) is a form of stimulation that is increasing in popularity. A review article from 2018 states that it's novel waveform simulates the natural firings of action potentials in the nervous system, and therefore is better at stimulating nerves precisely High

burst is essentially closely packed high frequency pulses followed by a quiescent period. Studies of the nervous system have shown that nervous signals can be transferred tonically or as rhythmic bursts, and vary in function based on which type of signalling is utilized. However, high burst stimulation has mostly been utilized for pain relief, such as the BurstDR system [21]. In a study using burst and tonic stimulation with 96 patients, 70.8% prefered high burst over tonic stimulation [22]. These novel waveforms and frequency modes all show promise for creating more effective, more accurate stimulation that stimulates only the nerve plexus targeted by design.

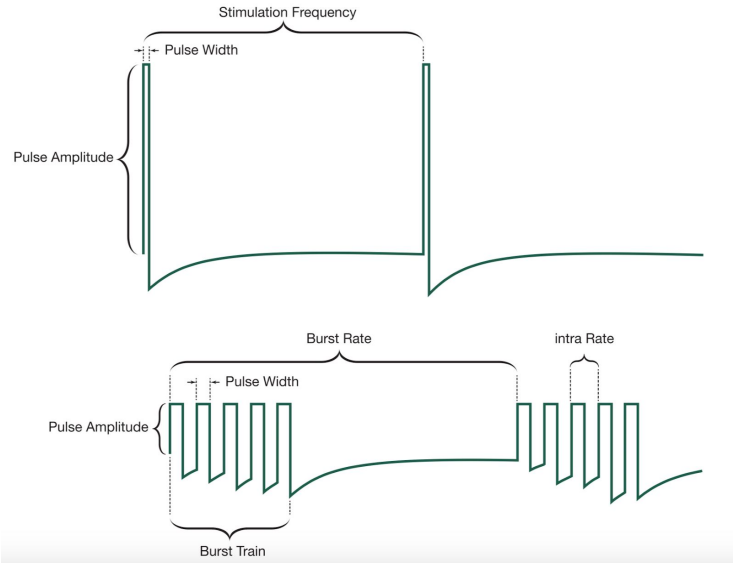

Figure 5: High Burst frequency waveform is shown in comparison to conventional stimulation. Shorter pulses are sufficient to boost an action potential.

B. Design Element 2: Number of Electrodes

The second design element that was considered in developing the final overall design was the number of electrodes that would be incorporated in the electrode array itself. The number of electrodes within an array can greatly impact the magnitude of the electric field generated, as well as that of the current applied to the subject. Without a large enough current, stimulation of the targeted nerves will not occur. Action potential thresholds must be reached in order to propagate current throughout the rest of the nervous pathway.

Considered first in this design element is a smaller number of electrode pairs (1-3 pairs). With fewer electrodes in the array, current is maintained at lower magnitudes, stimulating a smaller and more specific region of the spine. Such a design is easily implemented and cost effective, though it is not always terribly effective. Depending on the region of the spine on which the array is situated, current may not be able to penetrate many of the physiological

barriers (such as tissue, cerebrospinal fluid, etc.) between the outer layer of the skin and the spinal cord itself.

Another alternative is using a greater number of electrode pairs (10-30 pairs). This method enables greater and deeper stimulation as a result of a greater magnitude of electric field and current produced [23]. Such a design can also implement a wider variety of frequency modes, such as high definition and inter-sectional stimulation frequencies; these forms of stimulation are commonly more accurate as a result of the larger electrode array. Apart from these advantages, one must be sure not to overstimulate the subject. Overstimulation can result in the activation of nerves in regions that were not targeted and can even cause excessive pain in some cases. A more moderate number of electrode pairs may mitigate these issues while still providing an effective level of stimulation.

C. Design Element 3: Location of Electrodes

The placement of the array on the spine was the final design element taken into consideration. Each portion of the spinal cord is subject to various physiological phenomena, such as cerebrospinal fluid levels, different nerve clusters (or plexuses), and changing layers of epithelial tissue. Certain organs/areas of the body also react to stimulation in particular regions along the spine.

The possibilities considered were the four main regions of the spine that contain major nerve plexuses (Figure 3). The first area is the cervical region of spine; the nerves specific to this portion are located generally between regions C1-C4 of the spinal cord. These nerves are commonly very superficial in relation to other portions of the spine and are much more easily stimulated as a result. Due to the higher level of this plexus on the body itself, a greater number of areas on the body can be affected by stimulation of cervical nerves.

The second alternative is the thoracic (or brachial) plexus of the spine, usually situated near the vertebrae from C5 through T4. This region of the spinal cord is not easily stimulated by external impulses as a result of greater levels of cerebrospinal fluid and thicker layers of tissue surrounding the spine. The dura mater, a thick outer membrane, is an example of the dense tissue through which current must travel in order to reach the spine; it extends down the spinal cord from the brain.

The third option for this design element is the lumbar plexus of the spine. This region of the rat spinal cord is unique in that it is fairly compatible to that of the human spinal cord. The nerve plexus in this region rests roughly within the region comprised of vertebrae T12-L4, extending from the lower thoracic region down through most of the lumbar. In both rats and humans, the nerves within this area have been used to stimulate the lower extremities of the body, such as the hind legs in rodents and the bladder and legs in humans. This plexus is also surrounded by cerebrospinal fluid thick tissue, though to a lesser degree than that of the brachial region above it.

The fourth and final spinal plexus considered is that within the sacral region. This portion of the spine rests below all others. In rats, fewer nerves are located within this area because of how small this region of the spinal cord is; the nerves also stimulate fewer areas of the body due to their location downstream of the rest of the spinal cord. As a result the size of the sacral region, the nerves here are more concentrated. Cerebrospinal fluid is present in much smaller amounts, as well. The combination of the greater concentration of nerves and the decreased CSF presence enables easier stimulation of the sacral plexus.

IV. DESIGN EVALUATION

Design matrix/matrices

The three design elements were evaluated independently of each other and given its own set of constraints, although consideration of each will be taken into account for the testing of the transcutaneous stimulation. There is some overlap of variables in the scope of some techniques. For example, inter-sectional stimulation involves a specific waveform and an unusual number of electrode pairs, and therefore has an effect on two of the three variables. This technique should therefore be evaluated carefully in each design matrix to take into account the interdependence of the variables.

The first design matrix (Table 1) shows the evaluation of the frequency modes. Depth of stimulation was evaluated with heavy weight because the primary problem with transcutaneous stimulation is reaching the nerves necessary for inducing electrical effects. Interferential has the highest rating for depth and precision because in theory it should reach the deepest into tissue. Localization and precision are important because while depth of stimulation is necessary, stimulating the correct plexus of nerves is necessary for achieving the desired stimulation. Accuracy was best achieved by intersectional and high definition because they have been shown to be focal in current propagation. Interferential and high definition were the most feasible because of the numerous literature sources that allow us to repeat methods. High definition and high burst use the least current, and therefore are the most safe.

Frequency Constraints	Interferential		Inter-sectional		High Definition		High Burst	
Depth (25)	5/5	25	4/5	20	4/5	20	3/5	15
Localization/Precision (20)	5/5	20	4/5	16	4/5	16	4/5	16
Accuracy (20)	3/5	12	4/5	16	4/5	16	3/5	12
Feasibility (25)	4/5	20	1/5	5	4/5	20	3/5	15
Safety (10)	3/5	6	1/5	2	4/5	8	4/5	8
Total (100)	83		59		80		66	

Table 1: This is the Frequency Mode Design Matrix, showing the types of frequency modes that are evaluated for their depth, accuracy, and concern for the patient.

The design criteria used within the matrix for the second design element (Table 2) were overall feasibility of implementing the electrodes, versatility of the design, cost, overall efficacy, and the potential depth of the stimulation created by the array. One and two electrode pairs received the highest rating for feasibility due to the ease with which they could be implemented. On a rat, it may be difficult to fit a greater number of electrodes due to the size of the animal. In regard to versatility, though, the team decided that more testing and frequency modes could be incorporated with an increased number of pairs. For instance, high definition and inter-sectional stimulation require multiple pairs of electrodes in order to function properly and be most effective. Naturally, fewer electrodes would be most cost effective, though this criterium was weighted least because it does not heavily impact the overall design. Eighteen and thirty-six electrode pairs would achieve the greatest depth due to the greater electric field generated by the array, potentially overcoming the physiological barriers to stimulation. Six electrode pairs received the highest rating for overall efficacy because it incorporates advantages from both fewer and greater amounts of electrode pairs. Based on the ratings of the design matrix, six electrode pairs showed the most promise, though designs incorporating two and eighteen electrode pairs may also be tested because of their respective advantages.

Electrode Pairs	1		2		6		18		36	
Feasibility (20)	5/5	20	5/5	20	4/5	16	3/5	12	2/5	8
Versatility (20)	2/5	8	2/5	8	3/5	12	4/5	16	4/5	16
Cost (15)	5/5	15	5/5	15	4/5	12	3/5	9	2/5	6
Efficacy (25)	2/5	10	3/5	15	5/5	25	4/5	20	3/5	15
Depth (20)	2/5	8	3/5	12	4/5	16	5/5	20	5/5	20
Total (100)	61		70		81		77		65	

Table 2: Shown above is the design matrix developed for the number of electrode pairs considered for the electrode array.

Electrode location shows the locations on the spine that have been tested in literature. The various regions are evaluated for their applicability for our project. The lumbar region of the spine happens to activate the region of the body that most concerns this project, the hind limbs of the rat. The sacral area of the spine, though, contains fewer and more concentrated nerves, which allows for a more selective stimulation. The physiological transferability from rats to humans makes the evaluation difficult because when stimulating one region of nerves on a rat, the function and location on a human may be very different. However, the lumbar portion of the rat spine is the most physiologically similar to the human equivalent, which is why this location

received the highest rating in this category. The cervical and sacral plexuses are most easily stimulated because the nerves are most superficial and not blocked by many physical barriers. Ultimately, the lumbar plexus seemed most effective due to its ability to stimulate the hind limbs and eventually provide insight into human spinal cord stimulation.

Electrode Location	Cervical Plexus C1-C4		Thoracic/Brachial Plexus C5-T4		Lumbar Plexus T12-L4		Sacral Plexus L5-S4	
Hindlimb Activation (30)	1/5	6	3/5	18	5/5	30	2/5	12
Selective Scope (15)	1/5	3	2/5	6	4/5	9	5/5	15
Transferability (30)	2/5	12	3/5	18	4/5	24	3/5	18
Sensitivity to Stimulation (25)	5/5	25	2/5	10	4/5	20	5/5	25
Total (100)	46		52		83		70	

Table 3: This third design matrix outlines the regions of the spine researched for application of the electrode array.

Proposed Final Design

The final design for the testing set-up used the lumbar plexus evaluated in '*Table 3: Electrode Location'*. The final design set-up involves a "stereotaxic frame" that both holds the stimulating electrode in place and is helpful to lower recording electrodes into the rat. As shown in Figure 6, two of the recording electrodes (G1, G2) are attached to the probe holder with tape and pens. The 'ground' recording electrode is taped to tail of the rat. The recording electrodes were attached to a TI oscilloscope, from which most of the data was recorded. In the final testing set-up, the pairs of electrodes were oriented with anodes and cathodes across from each the on the spinal cord as demonstrated in Figure 6.

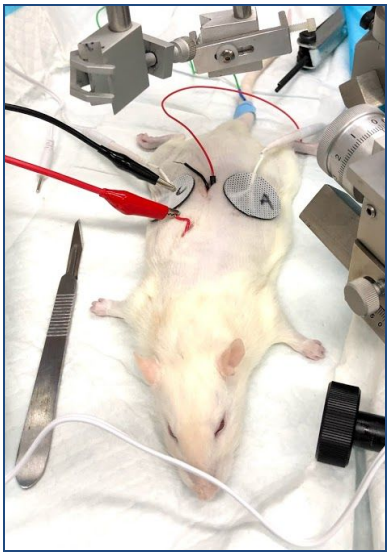

Figure 6. Post-Mortem Rat with Stimulation. A cathode and an anode were placed on either side of the spinal cord while two recording probes were used to measure the voltage generated at the lumbar portion of the spine.

In this configuration, any number of electrode pairs could be added or removed, and all of the frequency could have been potentially been tested. In the scope of this semester, equipment limitations dictated the number of electrode used, as well as the frequency modes tested. Potentially, future semesters could use this set-up as a baseline to limit sources of errors.

V. DEVELOPMENT PROCESS

A. Materials

The testing of stimulation involved the general system of a waveform generator, current supply, stimulating electrodes, gel, recording electrodes, and an oscilloscope. Available instrumentation was utilized to deliver current through the S88K Dual Output Square Pulse Stimulator and an A385 Constant Current Stimulus Isolator. The Pulse Stimulator and Stimulus Isolator were made available to us through the Hanna Lab. The former was used in order to modulate the frequency modes utilized throughout the testing procedure. The variables of frequency, pulse width, and train duration were varied during various portions of the protocol. The Stimulus Isolator was used in order to vary the magnitude of the current supplied to the model (either chicken thigh or a rat model system).

Based off of similar experiments, 1 inch diameter, self-adhesive stimulating electrodes were used to balance comfort and charge density for transcutaneous electrical stimulation [24]. For optimized connection and conduction, Spectra 360 electrode gel was used in order to ensure that electrical contact was consistently present on the subject. An Agilent 54621A Oscilloscope

provided by the BME Department at UW-Madison was utilized to record voltage readings. As well as these materials, 12 gauge wires were applied as recording electrodes.

Chicken thighs were used initially in the testing process, particularly during the first phase of the protocol. For further testing during the second phase of the protocol, euthanized rat specimens were provided by the Hanna Lab and were tested upon within thirty minutes of euthanization. This was done in order to ensure that electrical stimulation was still observable within the model [25].

B. Testing

Testing was conducted in multiple phases to better analyze the effects of multiple variables. The first phase was focused around frequency mode, electrode pairs, and applied stimulation across meat samples (chicken thighs with skin). The second phase of testing applied stimulation to post-mortem rats in configurations of which all of the design elements could be evaluated concurrently.

Shannon Equation: We utilized the Shannon Equation to determine if we would be safely stimulating on live tissue. $log\,(D) = k - log(Q)$ or $10^{k} = Q * D$, where D is the charge density per phase and Q is the charge per phase. D=IT/A and Q=D*A, where I is current, T is duration of biphasic pulse, and A is the surface area of electrode. For k < 1.85, the stimulation levels are considered non-damaging to the tissues [26] [27].

Tonic Stimulation	**High Burst Stimulation**
50 Hz with 4 ms pulse width	5 pulses 500 Hz, repeated at 40 Hz with 1 ms pulse width
Surface Area (A) = 5.067 cm^2	Surface Area (A) = 5.067 cm2
Current (I) = 1 mA	Current (I) = 1 mA
Duration (T) = 4 ms/phase	Duration (T) = 1 ms/phase
D = 1 mA * 4 ms / 5.067 cm^2 =	D = 1 mA * 1 ms / 5.067 cm2 =
0.7894 μCoulombs/(phase•cm^2)	0.1973 μCoulombs/(phase•cm^2)
Q = 0.7894 * 5.067 cm^2 = 4 μCoulombs	Q = 0.1973 * 5.067 cm^2 = 1 μCoulomb
k = log(D) + log(Q) = log(0.7894) + log(4) = .4993 < 1.85	k = log(D) + log(Q) = log(0.1973) + log(1) = -0.7048 < 1.85

Figure 7: The Shannon Equation Determining Stimulation Safety. The results shown indicate that the stimulation induced by the procedure is far below the threshold that would potentially induce harm to the patient.

Phase 1: Chicken Thigh Skin Impedance Simulation

The purpose of initial testing was to determine trends of different types of stimulation when providing current over a meat sample with the impedance of skin and tissue, as well as develop reliable testing procedures and understanding of the instrumentation. These preliminary tests provided valuable insight into depth and retained voltage measurements as related to frequency modes, frequency, current, and other variables that may be applied to the following phases of testing. Chicken thigh was selected because it was readily accessible and has a composition of skin and tissue somewhat comparable to live rat tissue. Initially, the instrumentation was tested, including the SK88 Stimulator and A385 Stimulus Isolator, to ensure proper function and measure the waveform output and current supply that could be generated by each machine, respectively. Similarly, the variable types of waveforms that could be supplied by the stimulus isolator were explored so that the ideal waveform could clearly be repeated in future experiments. The first phase was also used as an opportunity to explore methods to reduce noise readings from different instrumentation and frequencies within the experimentation room. Through this consideration, a routine protocol and data recording habits were developed to decrease the amount of confounding variables in the data collection. Outlined is a step-by-step protocol for rat testing:

1. Disinfect surgical areas, place chicken thigh on surgical area, and wear gloves
2. Attach recording electrodes to the oscilloscope and connect stimulating electrode pads to the stimulus isolator
3. Strip a very small portion of the recording electrode
    a. Initially, the team stripped about half an inch of the recording electrode; after multiple of rounds of testing, the oscilloscope probes were kept as insulated as possible to limit noise
4. Use gel to place electrodes on the chicken thigh and use caliper to measure placement distance
5. Test various frequencies, frequency pulses, currents, and duration pulses
6. Place reference electrode at point of measurement to determine voltage
7. Record all observations
    a. This step was taken as a measure to keep the data recorded error-free and ensure that all experiments are repeatable

Phase 2: Post-Mortem Rat Stimulation

For the second phase of testing, trends established and confirmed during Phase 1 were used to develop additional testing procedures for the next phase. Rat models were used within thirty minutes of euthanization. This window of time is significant because action potentials and nervous responses can still be seen within that time period in non-living tissue. After about 30 minutes, neuronal axons begin to stiffen [24]. This testing could give insight into rats' responses to spinal cord stimulation while nervous responses are still active, as well as indicate if our results are worth pursuing in live rats.

Furthermore, superficial stimulation was visualized in the rat during these tests. The rats were shaved to allow for better conduction to the skin, and the application of gel was utilized as earlier tests suggested that this is useful. The rats had no lesions on their spinal cords; injuring a dead rat would not form the glial scars associated with spinal cord injury [28] and therefore would not be useful for testing at this point.

Knowledge and understanding of the equipment and average readings through skin impedance was gained from the previous phase in order to determine the efficacy of stimulation in the predetermined regions. During testing, target voltages were determined through background research. Through both visual observations and formulaic assessment (see the "Shannon Equation" below), it is concluded that the dead rats and chicken thighs did not incur any physical damage.

High burst and tonic frequency modes were tested, as interferential and inter-sectional modes were not deemed feasible with the given equipment. This phase also lead to the formation of hypotheses of potential effects on live rats treated with this level of stimulation, such as overheating, overstimulation, etc. High burst stimulation involved a frequency of 500 Hz and a 1 ms pulse width repeated five times at 40 Hz. Tonic stimulation involved a 50 Hz frequency with a 4 ms pulse width, which matched the high burst's total pulse width per second (200 ms). These features were confirmed to be safe from damaging nervous tissue through the Shannon Equation, which is the empirical rule for neural engineering tissue damage evaluation.

The following step-by-step process outlines Phase 2:

1. Disinfect surgical areas and place rat on the surgical area
2. Align the stereotaxic frame
3. Attach recording electrodes to the oscilloscope and connect stimulating electrode pads to the stimulus isolator
4. Adjust stereotaxic frame
5. Strip a very small portion of the recording electrode while keeping most of the wire insulated
6. Apply gel and use caliper to measure electrode placement
7. Make a small incision along the back of the rat with a scalpel

8. Vary frequency settings and apply a 1 mA current
9. Measure voltage across the electrodes, directly beneath the skin, and at the region of the spinal cord
10. Record all observations

The voltage measured at the electrodes is used to create a proportion of how much stimulation is reaching the points below the skin and at the spinal cord. This is to ensure that for each trial the voltage recorded is based upon the impedance of the individual specimen.

VI. RESULTS

Phase 1 - Chicken Thigh with Skin

During the initial phase of testing, multiple different combinations of variables were tested on a piece of meat obtained from chicken thigh. These stimulation tests led to a refined protocol and familiarity with the equipment based on the experimental observations. Many observations were recorded, but the most significant findings concerned the roles played by frequency of pulse, duration of pulse, and current. Varying the duration of the pulse by increments of 10 ms had no significant effect on the retained voltage stimulus measured underneath the skin. A similar pattern was found when the frequency was varied from 5 Hz to 100 Hz with a 5 mA current supplied, and the stimulus recorded stayed close to 250 mV with no significant deviation. The parameter having the greatest effect on the magnitude of voltage measured, though, is the variation of current. As current was increased from 1 to 10 mA, the measured voltage did steadily increase.

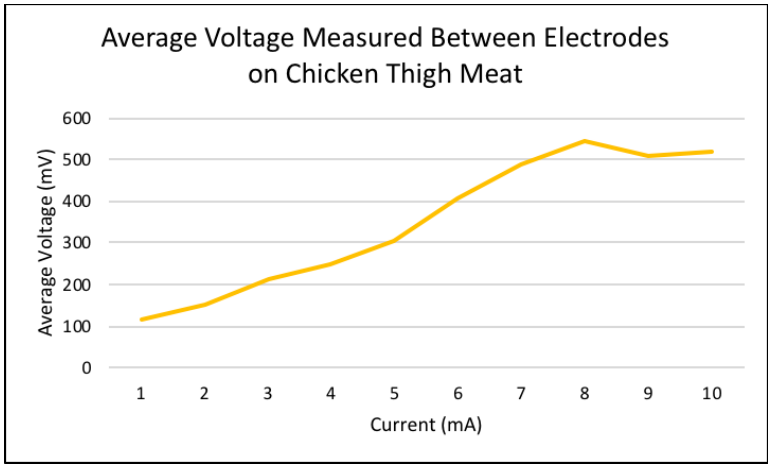

Figure 8. Displayed are the average voltages measured on a chicken thigh at varying magnitudes of current. One inch electrodes were placed 0.5 inches apart, and the voltages were measured directly in between the electrodes at the surface of the skin. Current was applied between a range

of 1 and 10 mA with a high burst frequency of 500 Hz and pulse width of 1 ms. As the current was increased, the level of stimulation also increased at the recording point.

Phase 2 - Euthanized Rats

Refined testing was then completed on post mortem rats. The entirety of the second phase testing was conducted on rats directly after euthanization, within the 30 minute neural activity window. During this phase, the mode of frequency delivered to the specimen was varied between a tonic stimulation of 50 Hz and 4 ms pulse width (Figure 9) and a high burst stimulation of 500 Hz and 1 ms pulse width (Figure 10). (Interferential and intersectional modes of stimulation were not tested because they could not be produced with the equipment available to the team.) The voltages retained at the levels directly beneath the skin of the rat and at the spinal cord were calculated and averaged. These retention values were obtained by dividing the voltage found at either the level of the skin or at the spinal cord by the voltage measured through the entire rat specimen (respectively). These tests were conducted with both one electrode pair and two electrode pairs. A significance level of 0.05 was used for all statistical analyses. Identical tests were also conducted with a high definition electrode array (one central anode and four peripheral cathodes). All data was obtained from a single rat specimen.

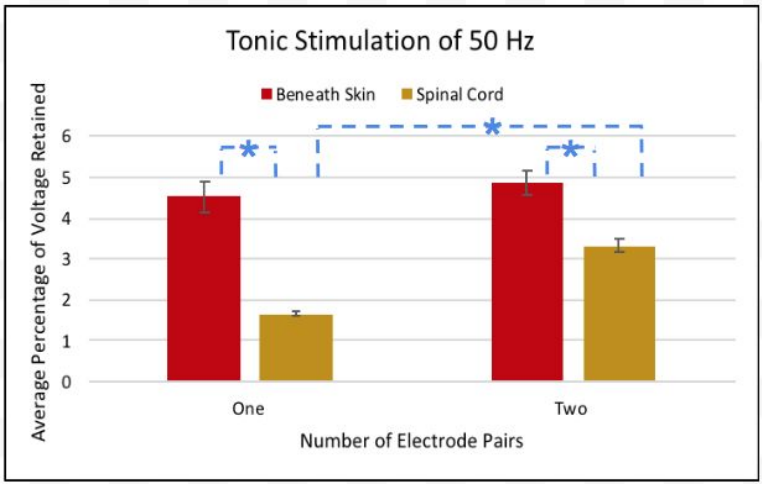

Figure 9. Displayed are the average percentages of the voltage retained at the levels directly beneath the skin and at the spinal cord within a rat specimen when stimulated with a 50 Hz tonic frequency. The averages of both the percentages measured with one electrode pair and with two electrode pairs are shown. When a single electrode pair was used within the electrode array, an average of 4.5% +/- 0.39% of voltage retained was observed beneath the skin, while about 1.7% +/- 0.063% retention was measured at the spinal cord. These data were significantly different from one another when compared with a two-sample t-test of unequal variance (p-value = 0.0020, t-statistic = 7.2). When a second electrode pair was added to the array, 4.9% +/- 0.30% retention was observed beneath the skin, while 3.3% +/- 0.17% retention was measured at the

spinal cord; both of these values were significantly different from one another when compared with a two-sample t-test of unequal variance (p-value = 0.0042, t-statistic = 4.5). The two values measured beneath the skin were not significantly different from one another (compared with a two-sample t-test of equal variance, p-value = 0.52, t-statistic = -0.68). The two values measured at the spinal cord between electrode arrays were significantly different from one another (compared with a two-sample t-test of equal variance, p-value = 1.4e-5, t-statistic = -9.3).

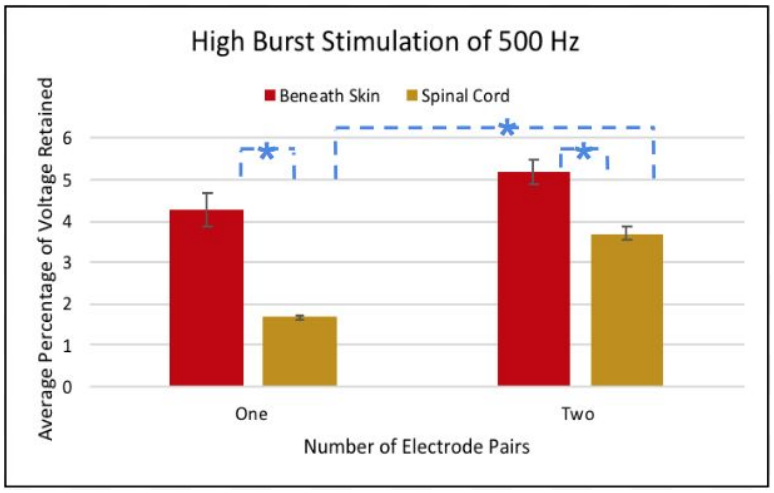

Figure 10. Displayed are the average percentages of the voltage retained at the levels directly beneath the skin and at the spinal cord within a rat specimen when stimulated with a high burst frequency of 500 Hz. The averages of both the percentages measured with one electrode pair and with two electrode pairs are shown. When a single electrode pair was used within the electrode array, an average of 4.3% +/- 0.39% of voltage retained was observed beneath the skin, while about 1.7% +/- 0.064% retention was measured at the spinal cord. These data were significantly different from one another when compared with a two-sample t-test of unequal variance (p-value = 3.5e-4, t-statistic = 8.6). When a second electrode pair was added to the array, 5.2% +/- 0.30% retention was observed beneath the skin, while 3.7% +/- 0.17% retention was measured at the spinal cord; both of these values were significantly different from one another when compared with a two-sample t-test of unequal variance (p-value = 9.0e-4, t-statistic = 7.0). The two values measured beneath the skin were found to be significantly different from one another (compared with a two-sample t-test of equal variance, p-value = 0.029, t-statistic = -2.6). The two values measured at the spinal cord between electrode arrays were significantly different from one another (compared with a two-sample t-test of equal variance, p-value = 1.2e-7, t-statistic = -18).

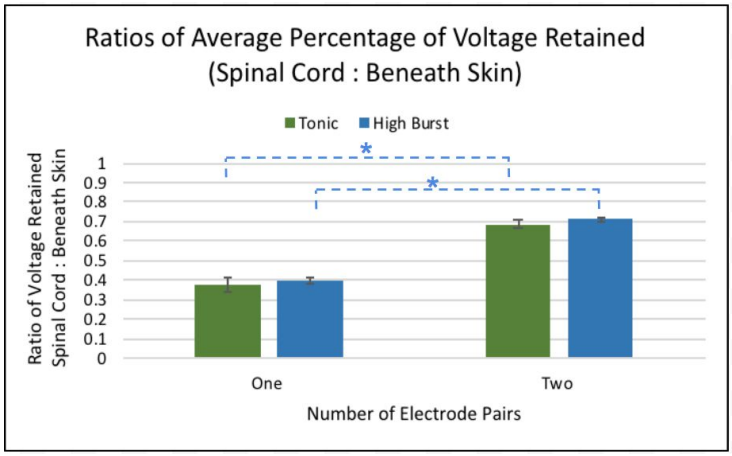

Figure 11. Displayed are the average ratios of the average percentages of voltage retained between the skin and spinal cord of the rat specimen. Data are provided from both electrode arrays (containing one and two electrode pairs, respectively). The ratios for the tonic and high burst frequencies were 0.38 +/- 0.034 and 0.40 +/- 0.016, respectively, when a single electrode pair array was applied. When a second electrode pair was implemented within the electrode array, the average ratios for the tonic and high burst frequencies were 0.68 +/- 0.020 and 0.71 +/- 0.012, respectively. A two-sample t-test of unequal variance was conducted between both tonic groups, resulting in a significant difference between the two ratios (p-value = 1.8e-4, t-statistic = -8.2). The same test was conducted between both electrode arrays stimulated with a high burst frequency, again resulting in a significant difference between the two average ratios (p-value = 1.0e-5, t-statistic = -13).

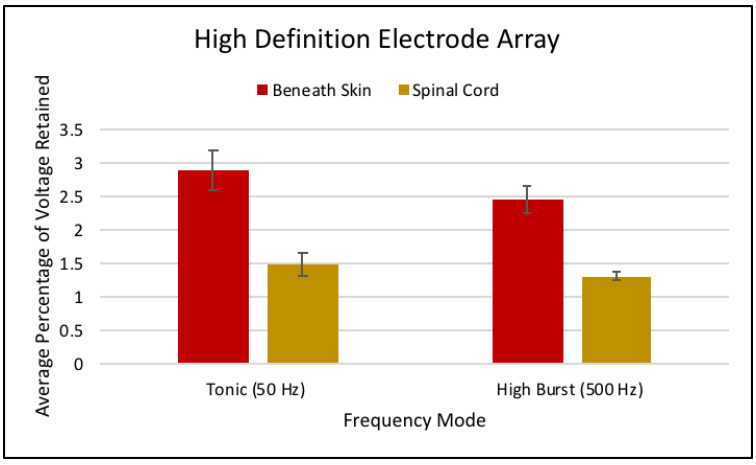

Figure 12. Displayed are the average percentages of voltage retention at both the level directly beneath the skin and that at the spinal cord for a high definition array applied to a rat specimen. The values were calculated when both a tonic frequency of 50 Hz and a high burst frequency of 500 Hz were used by the array. The measurements pertaining to the former frequency mode were found to be 2.9% +/- 0.30% and 1.5% +/- 0.18% for the level beneath the skin and that at the

spinal cord, respectively. With high burst frequency mode of 500 Hz applied, average percentages of retention were found to be 2.5% +/- 0.19% and 1.3% +/- 0.066% at the skin and at the spinal cord, respectively. No statistical analyses were conducted on this set of data because values were obtained outside of the perceived viability window of the neural cells within the rat specimen.

VII. DISCUSSION

A. Implications

Number of Electrodes Used

The results obtained from testing provided conclusive implications with respect to the number of stimulating electrodes used. It was noted from the results that in both the tonic and high burst frequency mode trials, that as the number of stimulating electrodes increased, there was a resulting increase in voltage retained at target deep nerves. The results, within all trials, also provided a consistency in that, as the number of stimulating electrodes increased, there was no corresponding variance in the voltage retained directly underneath the skin. These trends in combination suggest that as the number of electrodes used increase, there is an increase in the efficacy of stimulating deep nerve targets without any adverse effects with respect to nearby superficial nerves. Given that these results were consistent throughout all frequency mode trials, it can also be implied that varying frequency mode does not significantly impact the efficacy of stimulus retained at target nerves as the number of electrodes increases. It should be noted that there were several limitations within the testing sessions that may or may not have had adverse effects on the implications seen above.

Frequency Modes Used

Through our final testing phase, Tonic and High Burst frequency modes were used, and our results depict there was no statistically significant difference measured with respect to the ratio of voltage retained at deep nerve locations. These tests imply that there is no difference in the efficacy of voltage retained at target nerves when comparing Tonic and High Burst frequency modes. However, based on literature, this implication is rather inconclusive. In a study comparing tonic and high burst simulations using over 100 human subjects, it was found that a High Burst stimulation mode was more beneficial to 70% of patients' locomotive recovery in comparison to a Tonic stimulation mode [29]. Another consideration that must be made when determining the verification behind our implication is the effect of specific frequencies within each frequency mode. It was decided, based off of frequencies compiled from literature, that only one frequency within each frequency mode would be used. This is not necessarily conclusive in regards to determining the efficacy of voltages retained at target nerves through the use of various frequency mode. This is a parameter that should be emphasized in future works.

Effects on Superficial Nerves

Through direct observations made during testing, as well as from literature research, it can be definitively concluded that electrical voltage retained is greatly reduced when traveling through impedances such as the skin and superficial muscles [29]. This allows for the implication that both the skin and superficial muscles are being adversely stimulated in the pathways to stimulate target spinal cord nerves. The tests varying Frequency Modes also provides the implication that the adverse effects on superficial nerves and muscles is not affected between Tonic and High Burst modes of stimulation. These implications are key parameters that have been considered and will have to be considered in future experiments with respect to the eventual progression towards commercial application of a determined electrode array.

Limitations

Within the scope of this semester, there were several technical limitations that effectively nullified a large portion of the data that was obtained through phase two tests, along with our final testing session. Specifically, there was a limitation of the amplifier (attached to the Sk88 Stimulus Isolator) maxing out its power source before recording the actual amount of stimulus from the recording electrodes. Because of this, the absolute value of the stimulus retained at the electrodes, under the skin, and at target deep nerves was not accurately measured.

This limitation was not the only technical limitation encountered. During the final testing session, a limitation was found during which the recording oscilloscope was maxing out its readings at 15 V. This limitation may have nullified ⅓ of the data recorded. Although the stimulus measured at the electrodes may have exceeded 15 V in some test sessions, the voltages retained underneath the skin and directly at target nerve locations did not exceed the capacity of the amplifier and did provide optimal data. These limitations were encountered throughout several weeks of testing and are a primary factor that limited the range of data that could be collected with respect to different variables.

Finally, seeing as the limitations of our results were not noted until after each testing session had concluded and testing sessions involved the use of euthanized rats, a limitation stemmed from a limited supply of specimens on which to test. These key limitations encountered throughout the semester that should be considered for both the limited variation in testing results obtained, as well as for further progression into future testing sessions.

B. Sources of Error

There are numerous sources of error that need to be acknowledged to correctly interpret the results of the stimulation testing. A short list of the variables noted as important in stimulation and controlled during testing included: hair removal, amount of gel, size of rat, noise from environment, electrode size, and electrode placement. These variables, while controlled,

were not perfectly regulated and potentially contributed to the effects that were observed during testing. There are many variables within the body that result in varied results such as muscle density, fluids that can shunt current, and bones which all change the impedance of current. In general, current flows very differently through regions of organic matter. The variability of the results was caused directly by variability in the testing design.

While testing on euthanized rats, the data was taken within approximately a 30 minute time period directly following euthanasia, although it was not possible to test exclusively within this time window. Additionally, we were testing with a large amount of current. These two facts in combination with the reality that the rat tissue began to degrade over time lead to later tests having tissue that was farther away from the characteristics of live tissue. This can lead to a number of implications, the first and foremost of which being a small change in the overall impedance, which we found to be 15 kΩ, and stayed relatively constant, while increasing by 0.5 kΩ throughout testing.

One significant source of error was that the voltage was railing when testing directly at the stimulating electrodes, due to a voltage above 15 V recorded on the oscilloscope. This was evident when looking at the voltage across the two electrodes and four electrodes because the voltage should have halved when doubling electrodes. This can be observed with basic circuit analysis, as shown in figure 13. The voltage is half across the resistance as you double the number of electrodes.

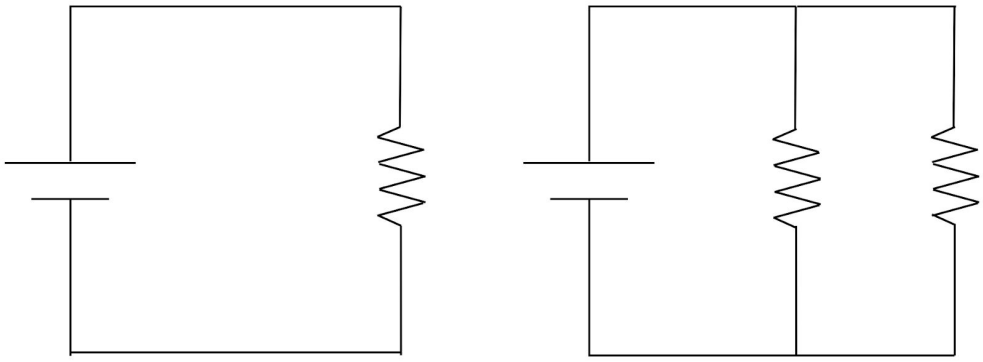

Figure 13: Basic Circuit Models of Rat Stimulation. The left shows two electrodes stimulating across an impedance. The second shows four electrodes stimulating across two impedances, if the resistance was the approximately the same, the voltage will be half across an electrode pair relative to the first setup, as the current flows across both paths equally.

The effect of railing could have been controlled by reducing the current delivered. Although, this would have been a current lower than what is required in most rat spinal cord stimulations. This has some implication on the validity of the results, although it was not a factor in recording at the skin level or spinal cord level, so the implications made still stand as long as the data was not drastically affected by the electrode voltage.

C. Ethical Considerations

A portion of testing was conducted using euthanized rat subjects. These subjects were euthanized by students of the Hanna Lab at the University of Wisconsin-Madison under the protocol specified by the institution. This was done under the supervision of Mr. Daniel Hellenbrand and Dr. Amgad Hanna, the Principle Investigator. It should be noted that ethical considerations were still incorporated throughout testing sessions following euthanization of the rats.

Other ethical considerations that should be taken into account are those with respect to the future use of a distinguished electrode array and of current transcutaneous electrical stimulators currently on the market. Long and short term effects on the physiologies of the patients should be considered, as well. In particular, it has been noted that several current electrical stimulators applied clinically have resulted in inexplicable short-term moments of pain in the day to day lives of the patients, which can ultimately lead to more severe injuries [30]. With respect to adverse long-term ethical considerations, it is important to recognize the retainability of function in neurons being stimulated. Data obtained from literature describe how the long-term retainability of neurological functions of pre- and post-synaptic responses is variant within different types of neurons. Specifically, it was noted that long-term effects of electrical stimulus decreased action potential in interneurons but did not adversely affect motor neurons [31]. With the these consideration in mind, it should be recognized, from an ethical standpoint, that altering the retainability of neurons without considering the amount of current applied to the patient can result in adverse physiological effects. These ethical considerations are especially important when considering the design of a Transcutaneous Spinal Cord Stimulating Electrode Array that could potentially be available on a commercial level.

VIII. CONCLUSION

The initial design request by Mr. Dan Hellenbrand included an electrode array or device to apply transcutaneous stimulation to the spinal cord with the goal of improving motor function after spinal cord injury. As the field of transcutaneous stimulation and neuromodulation within rehabilitation of incomplete spinal cord injuries is relatively new, the goals of this project were focused around taking the first steps towards developing an electrode array. Within the scope of the project, multiple prominent variables affecting the feasibility of transcutaneous spinal cord stimulation were analyzed with the hope of compiling significant data on each. In order to accomplish this, multiple design elements were tested including frequency mode, electrode pairs and electrode location, to evaluate the depth of the applied current, the retained voltage at target sites, as well as superficial effects caused by these different variables in post mortem rats. The data and results were then collected and evaluated for significance and can be read above.

The field of transcutaneous spinal cord stimulation will continue to advance in efficacy and scope, and lead to the development of influential devices through the collaboration

and compilation of research. Therefore, the addition of meaningful and significant data will benefit future research. In reference to the results and implications, the above experiments conducted provide data that further supports the ability of transcutaneous stimulation to reach the spinal cord with a retained voltage. However, a trending concern is the safety of the patient and the possibility of transmitting electrodes to provide discomfort, pain, shocks, and burns over the skin where the stimulation is applied. Although research will continue for the safety of the patient, the results of retained voltage at the spinal cord as compared to voltage applied through the skin from this experiment are hopeful. With both two and four electrodes at the specified frequencies and frequency modes, each had the power of reaching the spinal cord with a specific amount of retained voltage. The significant finding included the ability to stimulate with greater voltage at the spinal cord without increasing the voltage at or underneath the skin with four electrodes as compared to two.

Within the scope of the semester long design project, significant and helpful data and conclusions were made, however, there remains an infinite amount of tests and research left to be completed. The ideas and results of this project and its experimentation will ideally continue into the future for similar design teams to build on. One significant variable to be addressed next would be the difficulty of creating a focal stimulation by finding a way to stimulate the cord in a specific region, at target plexuses, without stimulating all surrounding nerves. During the post mortem rat testing of the studied variables, following the applied stimulation, significant responses of superficial stimulation were seen including muscle spasms and full limb movements. Developing a mechanism to actively target deep nerves would decrease unwanted effects of the stimulation while increasing recovered voltage at the target site. By developing a more focal stimulation, analysis of the true effects of transcutaneous spinal cord stimulation can also advance because any positive or negative effects of the stimulation on spinal cord injuries can be directly attributed to that stimulation. Focality decreases the amount of confounding variables and other factors that may have influenced any specific physical result of the SCS, and prevents a fair amount of false conclusions.

In order to limit the variables that were being controlled and tested in this experiment, solely one inch and a half diameter circular electrodes were used for collecting all data. Ideally, a variation of electrode sizes and shapes can be tested. Although there is a clear advantage of smaller electrodes for increased therapy focality, prominent effects including burning of the skin and tissue, skin irritation and intense muscle pain are also associated with decreasing diameter and maintained current [32]. Finding a size of electrode and effective current that can coexist and provide focal stimulation while also reaching the target location is another test that could be added to the protocol. Similarly, optimization of conductivity through gels can be increased by creating a better connection between the electrode and the skin. Another motivation to increase focality is to better regulate the neurophysiological effects that occur during and after stimulation, such as blood flow, bladder and bowel functions, and other unexpected effects [33]. Overall, finding ways to increase the efficiency of the electrode and its ability to send current

through the impedance of the skin and other tissues while simultaneously remaining focal is a significant focus for any research pursuing transcutaneous electrical stimulation.

The design of a physical electrode array is another future goal that can improve focal stimulation. The implications of the above results and future tests can be bettered through the use of a specified electrode array. Ideally, the electrode array will be designed with the knowledge of different types of frequency modes and their functions within different configurations of electrodes. Although a high definition array was employed under the assumption from relevant literature that it created a more focused stimulation, there remains many more options for electrode placement that may also increase focality. A specified electrode array that can be used with multiple different frequencies and that can be easily worn or applied by the patient themselves would help commercialize the system and allow for greater and easier access to the technology by those wishing to improve their spinal cord injury through neuromodulation.

Eventually, developing a live rat testing protocol would also be significant to analyze how the stimulation affects physiological responses in a living system. Analyzing live rats with the treatment would allow researchers to better understand how body functions react to the stimulation. Similarly, testing the configuration on rats with spinal cord contusions would allow a better analysis of recovery after a spinal cord injury and the feasibility of someone regaining motor function through this treatment paired with physical therapy.

The opportunity to advance the treatment of spinal cord injuries through transcutaneous stimulation has motivated an extensive amount of studies and research to move toward a safe and reliable mechanism of SCS. Generating improved care for endless amounts of people by creating a stimulation medium used in tandem with physical therapy to improve the overall motor function and quality of life of those affected by spinal cord injuries pushes the field forward. By further pursuing the possibility of transcutaneous spinal cord stimulation as an accessible treatment for spinal cord injuries, healthcare continues to adapt and transform. Therefore, this project and all others have an important relevancy to continue into the future.

Acknowledgements

The team would like to thank Mr, Daniel Hellenbrand, Dr. Kip Ludwig, Dr. Stephen Johnson, Brian Miller, John Puccinelli, BME program, and Dr. Amgad Hanna's Spinal Cord and Nerve Lab

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X. APPENDIX

A. Final Expense Report

Item	Description	Manufacturer	Part Number	Date	QTY	Cost Each	Total	Link
Tens Lead Wires - 2.5mm mini-plug to Two 2mm Pin Connectors (2)	2.5mm wires, mini plug to Two 2mm Pin Connectors	Discount Tens Products	B01DZB7VJS	11/16/2018	2	7.95	$15.90	https://www.amazon.com/gp/product/B01DZB7VJS/ref=ox_sc_act_title_3?smid=A49X7SPG2WVN&psc=1
Acuzone Premium TENS Unit 40 Electrodes 2"x4" rectangular Electrode for TENS Massage EMS	2x4 rectangular electrode pads with 2mm Pin connections	AcuZone	B01KJ0BA4A	11/2/2018	1	22.99	$22.99	https://www.amazon.com/gp/product/B01KJ0BA4A/ref=ox_sc_act_title_2?smid=A30K32DCAGNHEB&psc=1
Syrtenty TENS Unit Electrodes Pads 1" Round 40 Pcs Replacement Pads Electrode Patches For Electrotherapy	1" round electrode pads for TENS unit, 2mm pin connectors	Syrtenty	TSYR1000-40	10/25/2018	1	19.99	$19.99	https://www.amazon.com/gp/product/B00K504ED4/ref=ox_sc_act_title_1?smid=A3M0C2WPZVB2TH&psc=1
						TOTAL:	$58.88	

Table 1. Finalized Expense Report

The costs of all of the materials purchased through this semester came from three things; TENS Unit Wires, TENS Unit 2”x4” square electrode pads, and TENS Unit 1” circular electrode pads. The sum of these purchases was $55.88 (APP Table 1), which was well within our allotted budget of $3000. It should be noted that several of the materials used (Spectra-360 Electrode Gel, scalpels, Sk88 Stimulus Isolator) came at no cost and are not reported in the expenses table, as they were provided through the UW Hanna lab as a part of their own separate tests.

B. Preliminary Design Specifications (PDS):

Function:

An electrode array for transcutaneous stimulation would facilitate rehabilitation for spinal cord patients in a novel way. It presents a completely non-invasive option that averts the need for surgeries and the complications that may follow them. Due to its general safety and ease-of-use, it would be accessible outside of clinical settings for daily therapeutic functions. It would also present an option for people who may not have been able to afford surgical implant solutions, as there are neither specialists nor follow-up appointments required.

Client Requirements:

- Must involve transcutaneous electrodes that are noninvasive and do not require surgery to place
- Model system of rat should be utilized before human testing
- Cannot cause excessive discomfort to patient
- Must enhance quality of life through stimulation, whether short term or long term

- Budget of $3000

Design Requirements:

1. Physical and Operational Characteristics

a. Performance Requirements: The device should be able to perform under the varied location of electrodes and frequency of pulses. Current must penetrate as deeply into the body as possible to reach spinal nerves. The goal of researching potentially new settings for stimulators means that our device may have capabilities outside of the realm of existing devices. The stimulator should have the the ability to change frequency of pulse without difficulty, as well as be flexible in the placement of electrodes. Since we will be using the model system of the rat, the stimulator should be able to function on a rat for the initial testing, with the knowledge that stimulation will ultimately be scaled for human use.

b. Safety: When conducting with electrodes against the skin, the device must not cause harm to the patient, including shocking, burning, or excessive pain. The current must be low enough so that no damage is done to tissue around the electrodes. The device must also protect against pressure sores, which may become worse if the patient is suspended in a harness. The system must minimize stimulation of incorrect nerves to avoid causing spasms and other unintended reactions.

c. Accuracy and Reliability: The location of specific spinal cord and neural regions differ between people. Any deviation between regions stimulated and results of treatment will decrease the significance of research. Therefore, the device needs to be transferable between different rats, which may require specialization between patients such as defining specific T levels at which electrodes need to be connected, as well as the angles of connection. The device must differentiate between superficial nerve stimulation and deep motor nerve stimulation, and the target stimulation region of the electrodes. Each time this device is used, the electrodes should produce consistent frequency, and the device should target the same neurons and spinal regions in order to deliver consistent treatment. Any large deviations in these specifications could result in painful sensations for the individuals tested, unseen adverse effects related to muscle movement/stimulation, and introduce confounding variables into the results of treatment.

d. Life in Service: The spinal cord stimulator will be used at multiple intervals for testing during the span of our design, which could be extended for a couple of years. The design must be able to withstand repeated use, as well as a variety of levels of current and

voltage.

e. Shelf Life: This product will most likely be used intermittently for short periods of time throughout a given day. It should be able to withstand a wide range of electrical frequencies, as well as maintain shape and function after repeated use and removal. Any gel used should be removable for storage purposes.

f. Operating Environment: The device will need to operate at room temperature in a range from 15℃ - 25℃. The device will also be in contact with the surface of the skin of rats, which will be shaved and have gel applied topically to the electrode sites. Although the device will initially be used in a standard laboratory environment, it will eventually be used in a clinical setting.

g. Ergonomics: The device needs to be worn by a live rat, considering its weight and size. It should withstand basic maneuvering and should not inhibit or restrict normal functions such as walking, running, eating, bending, and turning.

h. Size: The wearable device will need to fit a 250 gram male rat, with slight deviation in size. The electrode system must fit tightly along its spine, yet the design should allow for simple adjustments due to variations in subject size and neuron/spinal regions.

i. Power Source: Several conventional batteries have been used: lithium-ion batteries, nuclear cells, biocells. Rechargeable batteries are excellent choices given the reusability and ease of patient maintenance. These have been used in Implantable Medical Devices [1][2]. In the future, kinetic energy from the body would be ideal since the device would be worn on the patient for potentially extended periods of time. However, due to the constraints of the project we will utilize a more conventional means of power source [3]. Additionally, biodegradable power generators are available, which could be another very biocompatible option for the future [4]. Within the scope of this device however, an external power source of wires connecting to the device will be sufficient for testing and research needs. However, the wires should not impede any motion of the rat.

j. Weight: Most animals can conveniently carry about 10-20% of their body weight. It is clear, though, that increased strain on rat tibias results in an increase in the need for further bone formation [5]. Depending on the type and average size of the rats being used for our project, this value may vary. In general, the device should way around 30 grams to be supported by the 250 gram rat subjects.

k. Materials: Most commonly, ceramics, metals, and polymers with high

biocompatibility ratings are used in biomedical devices, especially when implanted. Common metals include commercial pure titanium and titanium alloys. Metals are typically used for load-bearing devices. Polymers involved include polyurethane (usually for flexibility and its ability to conduct as an insulator). Electrodes are often made from copper, graphite, titanium, brass, silver, and platinum [6]. Many implantable spinal stimulation devices, in particular, are comprised of a wide variety of materials, including biomedical-grade silicone, various epoxies, as well as parylene C, an insulating polymer [7].

l. Aesthetics, Appearance, and Finish: The device should be insulated where necessary and have clear notation of the cathodes and anodes. Any potential triggers or current supplying components should be clearly labelled.

2. Product Characteristics:

a. Quantity: We predict that only one product will be required, as we are working on a unique electrode array for our client.

b. Target Product Cost: We were given a budget of $3,000 to complete this product. We do not anticipate surpassing this budget this semester.

3. Miscellaneous:

a. Patient-Related Concerns:

Our client has repeatedly alluded to the importance of comfort and simplicity of the design in the hopes of being able to make this product simple for consumers to use commercially. Other concerns relevant to the electrode array are the depth of the electric stimulations and how stimulating spinal nerves may also stimulate a plethora of unrelated nerves huddled within the same nerve bunch (the extent of which is currently unpredictable). The end goal of locomotion or increased bodily function may be worth some temporary discomfort to the patient if it brings long term growth, though mitigation of any discomfort is still highly prioritized.

b. Competition:

This design has many competing products from many healthcare companies across the US, including companies located within the Midwest, such as Medtronic and Boston Scientific. These companies have professionalized spinal cord stimulation (SCS) devices that can be used by Hospitals and surgeons across the country [2][8]. However, these companies focus on SCS through epidural stimulation and work on functions related to neurological mapping similar to MRIs, whereas our product will be primarily focused on

SCS through transcutaneous stimulation and will have no neurological mapping capabilities. There are devices similar to our intended product that deal with transcutaneous muscle and nerve stimulation but these devices have been specialized for pain treatment or are not as versatile as we intend our product to be [9][10][11].

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