A MAPPING OF APPLIED DC ELECTRIC FIELDS IN THE SPINAL CORD VIA FINITE ELEMENT ANALYSIS

by

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ABBREVIATIONS

Alternating Current (AC)
Central Nervous System (CNS)
Cerebrospinal Fluid (CSF)
Cutaneous Trunci Muscle (CTM)
Direct Current (DC)
Electromagnetic Low-Frequency (EM LF)
Finite Element Method (FEM)
Functional Electrical Stimulation (FES)
Oscillating Field Stimulator (OFS)
Polyethylene Glycol (PEG)
Somatosensory Evoked Potentials (SSEP)
Spinal Cord Injury (SCI)
ABSTRACT

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Approximately 17,000 new cases of spinal cord injuries (SCI) occur every year in the United States, resulting in temporary or permanent paralysis in patients. Presently, there are no known FDA approved treatments that restore functional loss after SCI. Previous in vitro studies have shown that axonal outgrowth and pathfinding can be enhanced through the application of weak DC electric fields. For the past several decades, our laboratory has exploited this phenomenon of electric field-induced axon regeneration by developing an implantable device that delivers weak DC current across the spinal lesion. Although the device has shown positive improvements in functional and behavioral recovery in previous animal studies and in FDA Phase 1 trials, few studies have been done to map these electric fields in vivo. Thus, the aim of this research is to characterize and optimize applied DC electric fields in the spinal cord. To achieve this, a finite element analysis model of the human spinal cord and its surrounding tissues was first constructed using human MRI data. Then, electrodes from the device were defined in the model and the resulting electric fields emitted by the device were characterized. Parameters such as electrode to cord distance and electrode shape were varied to optimize the electrode placement for optimum therapeutic effect. Characterization of the electric fields showed that the fields were lower than the fields measured in guinea pig trials. However, optimization of the electrodes and their placements resulted in electric fields reaching the threshold necessary to induce axonal growth, but clearly below the threshold necessary to induce damage. This computational modeling suggests important technical refinements to maximize functional recovery in future clinical trials.
CHAPTER 1. INTRODUCTION

Spinal cord injuries (SCI) commonly result in lifelong symptoms that affect the mental and physical well-being of the patient. In the United States alone, approximately 17,500 new cases of SCI occur, with the most common causes being vehicular crashes, falls, violence, and sports/recreational activities [1]. In addition, there are heavy financial burdens associated with SCI due to the lack of effective treatments available in the market, with lifetime costs ranging from $1.1 million to $4.7 million. The symptoms of SCI vary based on the severity and the location of injury on the spinal cord. These symptoms are generally a loss of sensory and motor function, with the most severe cases affecting body systems that control the bladder, bowel, breathing, and heart [2].

1.1 Biology of Spinal Cord Injuries

The loss of function in SCI is due to a disconnection of axons, in the ascending somatosensory tracts and descending motor tracts, which stops the conduction of electrical impulses that are necessary for the transmission of information [3, 4]. The types of SCI can be broken down into complete and incomplete injuries. Complete injuries involve a transection or crush through the spinal cord that results in a complete loss of sensory and motor function below the level of injury. Incomplete injuries involve a lesion to the spinal cord, but residual sensory and motor functions can exist below the level of injury. The severity of injury often depends on the level of injury. Cervical injuries in C1-C4 commonly result in tetraplegia, with the most severe injuries affecting breathing and requiring ventilator assistance. Thoracic injuries and below result in paraplegia, which result in complete or incomplete paralysis of the legs [2, 5, 6]. The current most frequent forms of SCI are incomplete tetraplegia and paraplegia, followed by complete paraplegia and tetraplegia [1]. The complexity of SCIs requires a deeper understanding of the pathophysiology of acute and chronic stages of SCI.

The pathophysiology of SCI involves two different stages of injury, acute and chronic. Acute SCI is generally characterized as the first few weeks of SCI, while chronic SCI refers to months after initial injury [4]. In the acute stages, primary injury is the initial impact to the spinal cord,
which is characterized by mechanical damage and lesions to the spinal cord. This damages the nerves, vertebrae, and blood vessels in the spinal cord region of impact, leading to edema, inflammation, and hemorrhage[2, 7]. Inadequate blood supply to the cord triggers the secondary injury, where inflammatory cells, such as neutrophils and macrophages, arrive at the site of injury [8]. Cytokine secretion from neutrophils, free radicals from lipid peroxidation, and ionic concentration gradient disruption all lead to the retraction of axons and excitotoxicity, further exacerbating initial damage to the spinal cord and leading to severe loss of function [4, 8, 9].

1.2 Current Therapeutic Techniques and Issues that Arise

From a clinical perspective, complete functional recovery has not yet been possible in SCI. However, current therapeutic techniques are available to minimize the severity of injury. Methods of approach to treating SCI can be distinguished into neuroprotection, neurorehabilitation, and neuroregeneration.

Neuroprotection and neurorestoration methods involve the suppression of events that happen in secondary injury via the administration of pharmacological drugs such as methylprednisolone, polyethylene glycol, and 4-aminopyridine. Methylprednisolone, a glucocorticoid, is thought to suppress the inflammatory events that happen in secondary injury through the inhibition of lipid peroxidation [8, 10]. However, research studying the benefits of methylprednisolone treatments have been inconclusive[11]. Polyethylene glycol (PEG), known for its fusogenic abilities, was shown to help the repair of damaged axons and minimizing axonal death and dieback [12, 13]. 4-aminopyridine, a neurorestoration method, works to minimize the demyelination of axons that have survived at the site of injury through the blockage of voltage-gated potassium channels to improve and restore conduction and function to the spinal cord [14-16]. Though neuroprotective and neurorestorative methods have been shown to minimize secondary injury damage in the area of injury, these strategies work through the preservation of the spinal cord and functional recovery is minimal.

Neurorehabilitation methods mainly look at the preservation of the peripheral nervous system and the functional use of muscles. One method involves functional electrical stimulation
(FES) to minimize muscle atrophy and restore body functions through electrical stimulation of the intact peripheral nerves. However, the commercially available devices for functional electrical stimulation have some limitations; namely, the affordability and availability of the device and the ease of use of the system [4, 17, 18].

The last method of approach in treating SCI involves regenerating axons in the spinal cord and reconnecting the break in the lesion by making the spinal cord environment more responsive to regeneration. Unlike the peripheral nervous system, where regeneration occurs for the repair of damaged nerves, the central nervous system (CNS) microenvironment has inhibitors that prevent the regeneration and growth of axons in the spinal cord [19, 20]. To solve this, some treatments involve the suppression of myelin inhibitors, such as Nogo and oligodendrocyte-myelin glycoprotein [9, 19, 21]. Though the suppression of inhibitory factors might help in facilitating regeneration in the CNS, the presence of numerous inhibitors imposes a problem in the efficacy of suppressing just one inhibitor at a time.

The work presented here focuses on overcoming the inhibitory post-SCI environment by using DC electric fields to promote regeneration. Because there is a lack of effective therapeutic treatments for the regeneration and regrowth of axons in the spinal cord, there is a need for different regenerative strategies that promote axonal guidance and growth.

1.3 Previous Use of Electric Fields in Development

The presence of endogenous electric fields in neural development is well established [22, 23]. These electric fields are known to promote neurite growth and guidance and are necessary in the rostral-caudal development in vertebrate embryos [24]. Due to the importance of electric fields in neural development, studies were performed in cell culture to see the effects of applied exogenous electric fields, with results showing that neurite growth and guidance are possible [25-27].

Studies have also shown that applied weak direct current (DC) electric fields have guided axonal outgrowth both in vitro and in vivo. In in vitro experiments, applied DC electric fields caused the neurite to grow towards the cathode (negative) within the first few minutes of the
experiment and after 30 minutes of time, the neurite began to retract on the anodal (positive) side. The neurites responded strongest to electric fields in a DC field between 70 and 140 mV/mm [26]. Orientation of the fields also affected the neurites in that the neurites reoriented themselves to be parallel to the electric fields [26, 28]. Furthermore, studies showed that reversal of field polarity within an hour helped slow anodal resorption, while increasing the growth towards the new cathode [29]. This result was crucial in establishing the possibility of bi-directional growth of neurites through the reversal of field polarities.

In vivo application of electric fields in animals have also been connected to axonal growth and guidance in response to electric fields. Though the exact reason for axonal regeneration and guidance through the application of DC electric fields is unknown, it has been postulated that the axonal growth is due to the reduction of astrocyte accumulation and inducing oligodendrocyte precursor cell differentiation, which encourages remyelination post-injury [30, 31]. Experiments performed on guinea pigs showed recovery in cutaneous trunci muscle (CTM) reflex [32, 33]. Lateral hemisections in the thoracic section of the spinal cord were followed by an application of DC electric fields. The cathode was placed rostral to the site of injury and the anode was placed caudal to the site of injury. In this electrode placement, the guinea pig trials showed some recovery of CTM reflex response, indicating regrowth of ascending nerve fibers in the spinal cord region towards the rostral cathode [2, 32, 34, 35]. Furthermore, CTM reflex recovery was lost and not recovered in guinea pigs when the anode was placed rostral to the site of injury [32, 33], indicating that the nerve fibers only grew in one direction: towards the cathode. Since optimal recovery should include the regrowth of both ascending (somatosensory) and descending nerve fibers (motor), field polarity reversal was considered following in vitro studies that showed bi-directional growth of neurites [29]. Thus, a new device was formed to test neurite regeneration in canines and humans with SCI, now equipped with technology that switched the polarity of the electric fields.

1.4 The Oscillating Field Stimulator

Using previous data on the ability of electric fields to assist neurite regeneration, a device was developed that exploits weak DC electric fields via implantable electrodes. The oscillating field stimulator (OFS) has six total leads, three rostral to the site of injury and three caudal to the site of injury, with the caudal or rostral set delivering a total of 600 µA at a given time point[36].
The electrodes are sutured onto the musculature surrounding dorsal vertebral processes [37]. Each lead delivers 200 μA of current. The 200 μA current output was determined based on the surface area of the electrodes, so as not to exceed the current density threshold that could cause damage to tissues when DC electric fields are applied for extended periods of time [38]. The device applies DC electric fields for 15 minutes and then reversed the polarity of the fields. The reasoning behind switching field polarities was to reduce axonal resorption on the anodal side and possibly induce bi-directional growth of both ascending and descending nerve fibers [29], as opposed to previous studies which suggested unidirectional growth in the absence of field reversal [32]. Reversing the polarities every 15 minutes also minimizes electrochemical and pH changes that happen when DC fields are exposed to tissues for extended periods of time [38].

The OFS employs a battery source that provides constant current, a binary counter set at 15 minutes, an analog switch that changes the polarity of the current every 15 minutes, a current regulator that delivers 200 μA to each lead, and a fail-safe chip programmed to shut down if voltage falls below 2.6 V (Fig. 1)[36, 37]. The electrode leads are made from pacemaker cable and a coiled platinum tip. The device is implanted for 15 weeks in acute SCI patients, due to studies that show the benefits of early rehabilitation and treatment of SCI [2, 39].

This device was then tested in canine trials and human FDA Phase 1 clinical trials. In the canine trials, dogs with acute spinal cord injury and paraplegia were treated with both active and control stimulators followed by behavioral testing. The electric fields estimated in dogs in these trials were around 0.5 – 0.6 V/m. Though ability to walk was not recovered, some functional recovery in deep pain sensation was present and recovery for superficial pain sensation was significant [36]. Following these experiments, human FDA Phase 1 clinical trials were done on ten patients with complete SCI between the C5 to T10 vertebrae (Fig. 2, Fig. 3). The patients showed significant improvements in pinprick sensation, somatosensory evoked potentials (SSEP), and light touch, with one patient showing recovery in sexual sensation [37]. In both canine and human trials, it is important to note that only sensory function showed significant recovery, with no recovery present in motor function. The discrepancy between sensory and motor recovery could be due to the electric field distribution along the dorsoventral plane of the spinal cord. Sensory tracts are primarily on the dorsal side, while motor tracts are primarily on the ventral side of the
spinal cord [5]. Since the electrodes are implanted on the dorsal side of the vertebral processes, this could bias the electric field distributions towards the dorsal side.

![Image of Oscillating Field Stimulator (OFS)](image1)

**Figure 1.** First generation depiction of Oscillating Field Stimulator (OFS) consisting of the main unit and 3 pairs of electrodes. Scale: 2 cm.

![Image of electrode placements](image2)

**Figure 2.** Photograph of electrode placements of the OFS sutured to the T3 spinous and transverse processes (small white arrow) and T5 spinous and transverse processes (long white arrow). Reprinted with permission from [35]. Copyright [2005] by the American Association Neurological Surgeons.
Figure 3. Radiograph of the OFS and its electrode placements. Reprinted with permission from [35]. Copyright [2005] by the American Association of Neurological Surgeons.

Though the OFS showed significant success in sensory recovery in both the human and canine trials, there are some drawbacks with the first-generation device. Since the device is implanted for 13 to 14 weeks, there is no feedback for voltage or current output of the device after the implantation. Due to these reasons, an improved OFS was developed (Fig. 4). This new OFS employs the same circuitry as the first generation, but has an added breadboard that incorporates a Zentri Bluetooth chip for wireless communication with the device. The Bluetooth chip will be connected to an iOS application that can access the real-time performance of the device. In addition, a secondary lithium battery was added due to additional battery drainage from the Bluetooth chip. This is to ensure that the device will be active for the full 14-15 weeks of implantation.
Figure 4. New OFS technology (bottom left) with iOS app (top left) and its relation to the human body (right).

The biggest limitation to the OFS remains, which is the inability to measure and map the field strengths of the device in vivo. Though in vitro studies show that fields of much higher magnitudes produced optimal results in neurite growth, the field strengths used in clinical studies were estimated to be around 0.5-0.6 V/m, making it difficult to correlate in vitro and in vivo data. The inability to characterize electric fields in vivo inhibits future studies from optimizing electrode design and placement.

Finite element models (FEM) have previously been used to study the application of electromagnetic devices and their effects [40-42]. Benefits of using FEM include device optimization and the ability to measure and characterize electric fields in complex body systems, such as the human cervical spinal region. To address the lack of knowledge of electric field strengths once the device is implanted, this work aims to characterize the electric fields using FEM and ultimately utilize the electric field measurements for optimal electrode placements to maximize therapeutic effects of the device.
1.5 Studying Applied Electric Fields via Finite Element Models

Previous simulations have been created for applied electric fields to the spinal cord. However, these models do not compare directly with therapy delivered by the OFS [43, 44]. These limitations include:

- not using exact electrode placement configurations used in the clinical trials.
- inaccurate vertebral column geometries.
- applying current outputs that differed from the device used in clinical trials.
- not using representative electrode shapes that were used in the clinical trials.

In this work, to truly understand the effects of the OFS, the above limitations are addressed with an internal validation of the FEM software and the model, accurate electrode placements of the OFS, anatomical geometries of the relevant tissues obtained from MRI scans, and correct current outputs emitted by the electrodes. In addition to this, electrode size and placements are also studied to achieve deeper penetration of electric fields in the spinal cord. Thus, the main goal of this study can be broken down into three aims:

- **Aim 1**: Create and validate an FEM model of the spinal cord using geometrically relevant anatomical tissues and their respective conductivities.
- **Aim 2**: Calculate distribution of electric fields and current densities in the spinal cord after device implantation in the clinical cases.
- **Aim 3**: Optimize the electrode placement and size to achieve deeper penetration of electric fields in hopes of maximizing therapeutic effect of the device.
CHAPTER 2. DEVELOPING AN FEM MODEL

2.1 Electromagnetic Low Frequency Simulation Theory

The FEM software used to create the computational models is Sim4Life, a Multiphysics solver created by ZurichMedTech [45]. The model focuses on the Electromagnetic Low-Frequency (EM LF) solver, which uses Maxwell’s curl equations and constitutive equations in electromagnetism in the frequency domain to solve for electric fields and current densities. The equations are

\[
\nabla \times \mathbf{E} = -j\omega \mathbf{B}, \tag{1}
\]

\[
\nabla \times \mathbf{H} = j\omega \mathbf{D} + \mathbf{J}, \tag{2}
\]

\[
\nabla \cdot \mathbf{D} = \rho, \tag{3}
\]

\[
\nabla \cdot \mathbf{B} = 0, \tag{4}
\]

\[
\mathbf{J} = \sigma \mathbf{E} + j_0, \tag{5}
\]

\[
\mathbf{B} = \mu \mathbf{H}, \tag{6}
\]

with electric field \(\mathbf{E}\), magnetic flux (B-field) \(\mathbf{B}\), magnetic field (H-field) \(\mathbf{H}\), displacement current \(\mathbf{D}\), current density field \(\mathbf{J}\), and source current \(j_0\). \(\mathbf{B}, \mathbf{D}, \mathbf{E}, \mathbf{H}, \mathbf{J}\), and \(j_0\) are all complex valued vectors in the frequency domain. The electric conductivity is denoted as \(\sigma\). The charge continuity equation can be derived by taking the divergence of equation (2), which results in:

\[
\nabla \cdot \mathbf{J} + j\omega \rho = 0. \tag{7}
\]

Using a vector potential \(\mathbf{A}\), where

\[
\nabla \times \mathbf{A} = \mathbf{B}, \tag{8}
\]

the charge continuity equation can be rewritten as:

\[
\nabla \cdot \mathbf{\varepsilon} \nabla \phi = -j\omega \nabla \cdot \mathbf{\varepsilon} \nabla \phi, \tag{9}
\]

where the complex permittivity, \(\mathbf{\varepsilon} := \varepsilon \varepsilon_0 + \frac{\sigma}{j\omega}\). These equations used for the solver and their full derivations can be found elsewhere [46].
2.2 Ohmic Quasi-Static Solver for Stationary Currents

The appropriate solver for this model should be one that accounts for stationary currents, since that holds true for the OFS. For stationary currents, \( j_0 = 0 \). In this case, equation (9) becomes
\[
\nabla \cdot \varepsilon \nabla \phi = 0.
\]
(10)

Current densities were calculated using equation (5). To calculate the electric field, \( \mathbf{E} \), the gradient of the electric potential is used to obtain the equation
\[
\mathbf{E} = \nabla \phi,
\]
(11)
where the electric potential, \( \phi \), is calculated using Laplace’s equation, \( \nabla \cdot \sigma \nabla \phi = 0 \). In this case, the assumption that needs to hold true for all materials used in the model is \( \sigma \gg \omega \varepsilon \). For the OFS, since the currents emitted are DC currents, \( \omega = 0 \), and the best solver to use is the Ohmic Quasi-Static condition in the EM LF solver, specifically for stationary currents and when the condition \( \sigma \gg \omega \varepsilon \) is fulfilled [46].

2.3 Sim4Life Anatomical Model and Simulation Setup

The model created represents an estimation of the human cervical region of the spinal cord and its environment. The model consists of the C3 – C7 vertebrae, intervertebral discs, spinal cord, cerebrospinal fluid (CSF), dura, and the vertebral musculature (Fig. 5). The cervical region of the spinal cord was chosen for this simulation due to the heightened severity of the injury when compared to thoracic and lumbar regions and the fact that incomplete and complete cervical SCI make up 59% of SCI [1]. In addition, five of the patients in the phase 1 FDA trial had cervical and complete acute SCI [37]. Thus, both the frequency of cervical injuries and their clinical relevance in previous studies led to choosing the cervical region as the model. Epidural fat was omitted from the simulation due to the absence of fat in the cervical region [44, 47]. The C3 – C7 vertebrae and the intervertebral discs were obtained from an MRI database that is available with Sim4Life. The rest of the anatomy was then built manually on Sim4Life with the vertebrae as a reference. The vertebral musculature approximately represents the neck section of an adult human, where the C3-C7 vertebrae lie. The spinal cord has a 7 mm diameter and is 9 cm long, approximately the length of the vertebral canal of the C3-C7 vertebrae [43]. The CSF surrounds the spinal cord in the vertebral canal and is covered by the dura, with a thickness of 0.4 mm [48].
Figure 5. a-b) Illustrations of human cervical spinal cord region and its tissues in transverse and perspective views, respectively. Axes: x(red), y(green), z(blue).

The tissue conductivities were then added to the respective tissues. The vertebral musculature section is assumed to have uniform conductivity and composition similar to that of muscle [44]. The conductivity values for all tissue materials except the spinal cord were taken from the IT IS LF database provided by Sim4Life and are tabulated below (Table 2.1) [49]. The spinal cord conductivity was obtained from [44].

Table 2.1 Electric Conductivity for All Tissue Materials

<table>
<thead>
<tr>
<th>Material Settings</th>
<th>Electric Conductivity (S/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal Fluid</td>
<td>1.78</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>0.600</td>
</tr>
<tr>
<td>Dura</td>
<td>0.368</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.355</td>
</tr>
<tr>
<td>Vertebral discs</td>
<td>0.00350</td>
</tr>
<tr>
<td>Intervertebral Disc</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Along with building the anatomical model, each simulation also requires an input of boundary conditions. The boundary conditions for each simulation includes added output currents from the electrodes. The simplifying assumptions that were made for the model include:
• No contact resistance between the electrodes and the tissues.
• No heating or damage to tissues (The current densities emitted from the electrodes are much lower than the safety standard established in previous studies for direct current stimulation) [50].
• No electrochemical reactions near the electrode areas due to DC current application [38].
• No scar tissue formation or encapsulation around the electrode.

In addition to simplifying the model, these assumptions were also supported by clinical data: limited damage to tissues and scar tissue formation was observed [37]. The next step was to build a grid to calculate mesh size of the entire model. The mesh sizes are finer in the spinal cord and electrode area, while they’re the coarsest on the outside regions of the vertebral musculature. The boundary conditions and mesh sizes are further detailed for each simulation in the upcoming chapters.

2.4 Sim4Life Validation

Before calculating and analyzing simulation results, a validation was done using two different methods. The first method compares exact analytical near field calculations for a simple dipole with a simple dipole model built on Sim4Life. The second method tested whether the addition of complex anatomical geometries would affect the simulation results. In this test, the anatomical layers from section 2.3 were added to the simple dipole setup with uniform conductivity and compared with the simple dipole results.

The first validation model utilizes Coulomb’s Law to calculate the near field around the dipole. The calculated electric potential values were then compared to the values calculated by Sim4Life for discrepancies. To calculate electric potential values for the simple dipole created by small finite, spherical electrodes, the electric potential equations for point charges and the near field calculation of a dipole are utilized [51]. Since Sim4Life does not have singular point charges, small spherical electrodes with a 0.5 mm radius were built 14 mm apart to represent the dipole and its charges (Fig. 6). The electrodes were placed in uniform conductivity and had a voltage output of ± 25V.
The maximum voltage given off by the electrode will be when the distance from the electrode is the same as the radius of the electrode. In the case of a simple point charge, 

\[ V_{\text{max}} = \frac{kq}{u}, \]  

(12)

where \( V_{\text{max}} \) is the electric potential, \( k \) is the Coulomb’s constant, \( q \) is a point charge, and \( u \) is the distance from the point charge, which would be the radius of the electrode in this case. Equation (12) can then be written using two point charges, as is the case in a simple dipole (Fig. 7):

\[ V_p = kq \left( \frac{1}{r_2} - \frac{1}{r_1} \right), \]  

(13)

where \( V_p \) is the electric potential at point \( P \), and \( r_1 \) and \( r_2 \) represent the distances from point \( P \) to the respective point charge of a dipole.

Equations (12) and (13) can be combined to obtain the final equation to calculate the voltage potential of a dipole at a given point:

\[ V_p = V_{\text{max}} * u * \left( \frac{1}{r_2} - \frac{1}{r_1} \right). \]  

(14)
Electric potential values were computed with Sim4Life from points along the positive x-axis and the positive side of x = 0.6 mm, due to the y-axis being the null plane. Using equation 14, electric potential values were calculated for each point along both lines and compared to the Sim4Life values (Fig. 8). The greatest percent difference between computed Sim4Life and calculated values for Figure 8a was 1.143%. For Figure 8b, the greatest percent difference between the two sets was 1.033%.
b)

**Figure 8.** **a)** Calculated and computed Sim4Life electric potential values along the positive x-axis. **b)** Calculated and computed Sim4Life electric potential values along the positive x = 0.6 mm line.

To ensure that simply adding complex anatomical geometries to a simulation did not affect the results, a second validation was done via the addition of the anatomical model to the simple dipole simulation. The dipole electrodes were placed in an area similar to the location of the OFS electrodes (Fig. 9). Uniform conductivity was applied to all tissues in the simulation for direct comparison with Coulomb’s Law. The electrodes had a voltage output of ± 25V. The magnitude of the electric potential values from the simple dipole and from the anatomical model with simple dipole were then compared. Values were computed in both models from the x-axis and the y = 0.01 m line (light blue), where the spinal cord lies (Fig. 10).
Figure 9. Sagittal view of anatomical parts added to the dipole model. Axes: x (red), y (green), z (blue).
Figure 10. a) Magnitude of the electric potentials of dipole compared to dipole with added anatomical parts along the x-axis. b) Magnitude of electric potentials of dipole compared to dipole with added anatomical parts along y = 0.01 m.

The greatest percent difference between the two datasets was 0.028% for Figure 10a and 0.105% for Figure 10b, assuring that adding anatomical layers will not change the results of the simulation. Thus, the model built in Figure 5 serves as the base for the following simulations modeling electric fields in the spinal cord.
CHAPTER 3. MAPPING OF CLINICALLY APPLIED ELECTRIC FIELDS

3.1 Electrodes and Simulation Set-Up

Three pairs of electrodes were built in a helical shape with dimensions consistent with that of the clinical device (1.32 mm radius, 0.089 mm wire radius, 24 turns). The injury site is assumed to be the C5 vertebral section. Each pair consists of an active (cathodal) electrode, placed cranial to the site of injury (C4), and an inactive, ground (anodal) electrode, placed caudal to the site of injury (C6). The three pairs are placed on the spinal process and the transverse processes of the vertebrae [36, 37]. Figure 11 depicts the anatomical model with the electrodes implanted near the C4 and C6 vertebrae.

![Figure 11. a-b) Electrode placements of the cranial (cathodal) and caudal (anodal) to the site of injury in posterior and sagittal views, respectively.](image)

Boundary conditions were applied to the surface of the vertebral musculature and the electrodes. The active, cathodal electrodes were set to have an output of 200 μA per electrode [36, 37] with the current density around the electrodes not exceeding greater than 1.5 A/m², the threshold shown to show no tissue damage [44]. The anodal electrodes were set as ground. The mesh size was set to fine in the areas of interest (electrodes, spinal cord) and was coarser for the
rest of the model with a total element size of 5.68 million elements. Electric field and current density plots were subsequently generated along the length of the spinal cord.

3.2 Results

Though the in vitro studies show that the electric fields necessary for neurite growth in cell culture range from 70-140 V/m, the applied electric field strength for functional recovery was estimated to be around 0.5-0.6 V/m for humans and dogs [36, 37]. In rodents, damage to the spinal cord was reported at 15 A/m$^2$ with a safety threshold of no induced damage at 1.5 A/m$^2$ [38, 44]. The lower threshold of 1.5 A/m$^2$ was used as the comparison in this simulation. Thus, two factors were considered when examining the effects of electric fields in the spinal cord: whether the electric fields meet or exceed the values referenced above and if the current density is high enough to induce tissue damage. The baseline for electric field stimulation was set to 0.6 V/m for electric field strength and the safety threshold for no induced tissue damage to 1.5 A/m$^2$ for current density. A color map of the mid-sagittal plane of the spinal cord is illustrated (Fig. 12a). Field strengths and current densities were computed along the midline of the mid-sagittal plane of the spinal cord (Fig. 12a-b) and compared to the electric field baseline and the current density threshold (Fig. 12b). Because the device reverses polarity every 15 minutes, active electrode placements were reversed to be caudal to the site of injury and inactive electrodes were placed cranial to the site of injury (Fig. 12c). Lastly, electric fields were computed along the dorsoventral midline of the C5 transverse plane to see if there were differences in the dorsoventral distribution of the spinal cord (Fig. 12d).

Electric field values in the assumed site of injury (C5) ranged from 0.2 V/m to 0.3 V/m, with the color map showing slightly stronger fields on the dorsal side of the spinal cord (Fig. 12a). Electric fields and current densities along the midline of the spinal cord were then compared to the electric field baseline and current density threshold (Fig. 12b). The electric fields computed were around 0.3 V/m in the site of injury, half that of the baseline. Current density values were below 0.2 A/m$^2$. When the field polarities were reversed, electric fields ranged from 0.10 V/m to 0.15 V/m in the C5 section, and current densities were below 0.1 A/m$^2$ (Fig. 12c). This could be due to the increased distance of the reversed electrodes from the spinal cord, since the electrodes are further away from the spinal cord when placed on the C7 vertebrae. Cathodal electrodes placed
caudal to the site of injury are for motor neuron stimulation and since the fields were lower in the caudal side, it could explain the reasoning behind greater sensory recovery. Further analysis in the C5 transverse plane of the spinal cord showed a 0.04 V/m decrease in the dorsoventral direction (Fig. 12d). Though the penetration of electric fields was deeper on the dorsal side of the spinal cord, the change in electric fields is comparatively small. However, the discrepancy between the electric fields on the dorsal and ventral side of the spinal cord could also be an additional reason to why mostly sensory recovery was seen in clinical trials.
Because the electric field values are about half of the electric field baseline of 0.6 V/m that was established, the next step was to increase field distributions by determining if adjusting the electrode placements and dimensions had an effect.
CHAPTER 4. OPTIMIZING THE ELECTRODES

4.1 Placing the Electrodes in the Epidural Space

The distance from the electrodes to the spinal cord may hinder the penetration of the electric fields within the spinal cord because the electrodes are placed on the vertebral processes [44]. To see if electrodes at a closer distance would affect the electric field penetration in the spinal cord, the electrodes were placed in the epidural area (Fig. 13). Four electrodes (two caudal and two cranial to the site of injury) were placed on the dorsal side of the spinal cord and two electrodes (one caudal and one cranial to the site of injury) were placed on the ventral side of the spinal cord.

Figure 13. Sagittal view: Electrodes are placed closer to the spinal cord in the epidural region cranial and caudal to the site of injury (C5).

The same boundary conditions were set for this simulation as before, with a 200 μA current output for each cathodal electrode and the anodal electrodes set as ground. The current densities at the electrode level did not surpass the current density threshold. The model had a fine mesh...
around the spinal cord and electrode regions and a coarse mesh for the rest of the tissues. The total number of elements in this model was 4.95 million.

A color map of the electric fields in the mid-sagittal plane of the spinal cord was computed (Fig. 14a). Field strengths were again computed along the midline of the mid-sagittal plane of the spinal cord (Fig. 14a-b) and compared to the baseline electric field and current density threshold (Fig. 14b). Electrode placements were reversed and compared to the original epidural electrode placements (Fig. 14c). The electric fields along the dorsoventral midline of the C5 transverse plane of the epidural electrodes were compared to the clinical placements of the electrodes (Fig. 14d).

Electric field values with the epidural electrode placements were higher by 1.0 V/m when compared to the clinical electrode placements, with the C5 section of the spinal cord peaking at 1.3 V/m (Fig. 14a). A color map of the electric fields in the mid-sagittal plane of the spinal cord showed deeper penetration of electric fields when using epidural placements vs. clinical (Fig. 14a). Electric field strengths surpassed the electric field baseline of 0.6 V/m. Current densities were higher when compared to the clinical electrode placements, but did not pass the threshold of 1.5 A/m² (Fig. 14b). Reversing the active and inactive electrodes in the epidural area did not cause a significant change in field distribution (Fig. 14c). Since all electrodes are placed in the epidural space, distance from the cord is not greatly varied when the fields are reversed to be applied from the caudal side of injury, explaining the similar distributions of fields. Due to the proximity of the ventral electrode to the dura and spinal cord, the electric fields were higher on the ventral side of the spinal cord than the dorsal side by 0.4 V/m (Fig. 14d).
Longitudinal Electric Field Along the Mid-Sagittal Plane of Spinal Cord

a)

Longitudinal Electric Field Along the Mid-Sagittal Plane of Spinal Cord

b)
Figure 14. a) Clinical placements (blue) vs. epidural placements (yellow): Color maps of the mid-sagittal plane of the spinal cord and the longitudinal electric field along the midline of the spinal cord. b) Clinical placements (blue) vs. epidural placements (yellow): longitudinal field strengths and current densities compared to electric field baseline (green) and current density threshold (red). c) Field strength and current density comparison of reversed electrodes (yellow) vs. original epidural electrode placements (blue). d) Clinical placements (blue) vs. epidural placements (yellow): Transverse plane of the model and the dorsoventral electric field in the midline of the spinal cord in the C5 transverse plane.
With the electrodes in the epidural area, the electric field strengths surpassed the assumed electric field baseline with the highest field strength being 1.4 V/m near the ventral side of the site of injury (C5). The current densities stayed below the threshold of 1.5 A/m². The increase in electric field strengths can be attributed to the electrodes being closer in distance to the spinal cord.

4.2 Increasing the Current and Surface Area of the Electrodes

Increasing the current output of the electrodes might increase the current density to damaging thresholds. Thus, the surface areas of the electrodes were increased to compensate for an increased current output. With an increased surface area, the current density from the electrode should be below the damage threshold, but the overall current output will be greater, which could potentially result in larger electric field values and deeper electric field penetration of the spinal cord. The surface areas of the electrodes were about doubled (1.32 mm radius, 0.089 mm wire radius, 50 turns) and the current output was increased from 200 μA per electrode to 400 μA (Fig. 15).
Electrodes with increased surface area. a) Electrode placements on the vertebral segments (C4 and C6). b) Dimensions of electrodes with increased surface area and comparison to original clinical electrodes.

Current density output at the electrode level showed that the electrodes did not breach the damage threshold of 1.5 A/m². The increased surface area electrode placements matched that of the clinical placements, with the cathodal electrodes on the C4 vertebral processes and the anodal electrodes on the C6 vertebral processes. They were not placed in the epidural area because the unfolded length of the new electrodes did not fit in the intervertebral spaces. A color map of the electric fields in the mid-sagittal plane of the spinal cord for the increased surface area electrodes was compared to the original clinical electrodes (Fig. 16a). Their electric field and current density values were compared to the original clinical electrodes and to the electric field baseline and current density threshold (Fig. 16b). The field polarities of the increased surface area electrodes were also reversed to observe the changes in electric field distributions (Fig. 16c). Electric fields were lastly computed along the dorsoventral midline of the C5 transverse plane (Fig. 16d).

A color map of the mid-sagittal plane of the spinal cord showed deeper penetration of electric fields when using increased surface area electrodes vs. the original clinical electrodes (Fig. 16a). The electric fields at the midline of the mid-sagittal plane of the spinal cord ranged from 1.0 to 1.2 V/m, showing an increase from the original clinical electrodes (Fig. 16a). Field strengths of the electrodes with increased surface area surpassed the electric field baseline of 0.6 V/m, while current densities in the spinal cord stayed below the threshold (Fig. 16b). When the current outputs were reversed, the field strengths were lower with a peak value of 0.7 V/m in the C5 region, but still higher than the electric field baseline (Fig. 16c). When comparing the electric fields
dorsoventrally in the C5 transverse plane, electric fields were higher on the dorsal side (1.35 V/m) than the ventral side (1.2 V/m) (Fig. 16d).

Longitudinal Electric Field Along the Mid-Sagittal Plane of Spinal Cord

Longitudinal Electric Field Along the Mid-Sagittal Plane of Spinal Cord

Current Density Along the Mid-Sagittal Plane of Spinal Cord

a)
b)
Figure 16. a) Original clinical electrodes (blue) vs. electrodes with increased surface area (yellow): Color map of the mid-sagittal plane of the spinal cord and longitudinal electric fields along the midline of the spinal cord. b) Original clinical electrodes (blue) vs. electrodes with increased surface area (yellow): Longitudinal electric fields and current densities compared to electric field baseline and current density threshold. c) Electric field and current density comparison of increased surface area electrodes (blue) and reversed polarity electrodes with increased surface area (yellow). d) Transverse view of the model and the dorsoventral electric field in the midline of the spinal cord in the C5 transverse plane.
Though the original electrodes with clinical placements did not reach electric field baselines, the adjustments to the OFS made in sections 4.1 and 4.2 optimize the device to deliver higher electric field values to the spinal cord. Both increasing the electrode surface area and placing the electrode closer to the spinal cord increased electric field values above the baseline that was established and had electric field strengths that were higher than that of the original device. Assuming that increased electric field values will enhance axonal growth and guidance in the spinal cord [26], these adjustments can be made to the electrodes to optimize the therapeutic effect.
CHAPTER 5. DISCUSSION

5.1 Electrode Adjustments Improve the Electric Field Strengths and Distribution

Characterization of electric fields and current densities was possible through the development of a finite element model of the human spinal cord region and the electrodes used in the OFS. Adjustments made to the electrodes showed stronger electric fields delivered to the spinal cord via optimized electrodes and their placements. Placing the electrodes closer to the spinal cord and increasing the surface area of the electrodes increased the electric field strengths in the spinal cord while keeping current densities below the established current density threshold. Due to the increased field strengths, it can be hypothesized that these adjustments will help improve the functional recovery seen in patients that are treated with the OFS.

It is important to note that the electric fields computed were in the longitudinal direction of the spinal cord and are assumed to be parallel to the spinal cord to align and induce axonal growth in the proper direction [27, 37]. A 3D vector image of the electric field lines was created to confirm that the electric fields are parallel to the spinal cord and oriented towards the active electrodes. Computing the electric fields after the reversal of the polarity of electrodes showed a decrease in the electric field strengths in the clinical and the increased surface area electrode configurations, but not the epidural placement configuration. This is due to the increased distance between the electrodes and the spinal cord after field reversal in the clinical and increased surface area configurations. Cathodes on the cranial side of the injury encourage regeneration for the somatosensory (ascending) axons and cathodes on the caudal side of the injury encourage regeneration for the motor (descending) axons. The caudal, cathodal electrodes showed lower electric fields, which could possibly explain the significant sensory recovery and limited motor recovery in human clinical trials [37].

The distribution of electric fields in the spinal cord changed dorsoventrally, with the dorsal side having stronger electric field strengths in the clinical and increased surface area electrode configurations. The epidural electrode placement configuration showed higher values of electric fields in the ventral side, due to the ventral electrodes being closer to the spinal cord than the two
dorsal electrode sets. Both adjustments to the electrodes improve the field distribution within the cord, but additional optimization can still be done to achieve a more uniform distribution of electric fields in the spinal cord.

Combining the adjustments to one model was considered to further optimize the device. However, due to the limited space and availability in the intervertebral regions of the epidural space, the adjustments had to be made separately. The feasibility of placing the electrodes in the epidural space and the ventral side of the spinal cord was also questioned. Though electrodes have been implanted in the epidural space for epidural stimulation, the electrodes were implanted in the lumbar region and only on the dorsal side of the vertebrae [52]. Thus, it may be a better option to start optimization of the actual device with increased surface area electrodes.

5.2 Limitations of the Model

The model presented incorporates more accurate representations of the vertebrae and spinal cord region than previous simulations of applied DC electric fields in the spinal cord [43, 44]. In addition to more accurate anatomy, the model also uses the exact electrode current outputs and dimensions as were used in the Phase 1 trials [37]. However, there are some limitations of the model. One such limitation is making the vertebral musculature layer one uniformly conductive layer, rather than adding all tissue materials present in the human neck. However, it has been shown that the neck region is mostly comprised of tissue materials that have similar properties, so it was appropriate for this model to use uniform conductivities for the vertebral musculature [44].

The biggest limitations arise from the assumptions made in section 2.3. Since the animal and human clinical trials showed no adverse effects of joule heating due to the implantation of the OFS, thermal mapping was not considered necessary for this study. However, bio-heat transfer solvers can be utilized to determine the changes in temperature of the tissue surrounding the electrodes. Another limitation of the model includes the lack of a time component. The OFS implantation time-period extends much longer than the *in vitro* studies by several weeks[26, 27], and the effects of a lengthened implantation time of the electrodes were not studied in this analysis.
In addition to these limitations, it is important to note that all calculated values in this study are based on approximate estimates of tissue conductivities. Though the Sim4Life solvers and the model were validated, FEM calculations are limited to the anatomical and electrical parameters set by the model.

### 5.3 Limitations of the Original OFS

The cause of sensory recovery seen in the clinical trials of the OFS could be attributed to various reasons, due to the lack of *in vivo* measurements of electric fields. Here, it is shown that the electric field strengths of the original OFS do not surpass the assumed reference value of 0.6 V/m needed for therapeutic effect. However, studies have not yet been done to measure the effect of DC electric fields on axons over a time span of weeks to months. Because the therapeutic window is so long (14 weeks), a lower field strength might suffice in enhancing axonal regeneration[2, 44, 53]. Limitations to the original OFS electrodes also include the location of the electrodes themselves, which could be another cause for lower than expected electric field values.

To address the low field strengths of the OFS, simulations were performed to see the effect on decreasing the distance between the electrodes and the spinal cord and increased surface area of electrodes for enhanced current output.

### 5.4 Future Considerations

Future work on the FEM model should consider the possibilities of contact resistance of the electrodes and effects of hydrolysis in localized tissues. This will optimize the model and account for limitations of the current model.

Sensitivity studies that test each parameter set in this model can also be computed to define the variables that cause the highest variation in results. Preliminary studies tested the effects of changing the conductivity of the region around the spinal cord, specifically the subarachnoid space. Hemorrhage to the spinal cord region is common and hemorrhaging can also occur in the subarachnoid space if contusions or lacerations to the dura are present [54]. The presence of blood instead of the CSF in the subarachnoid space will change the conductivity of that region. Thus,
A conductivity study on the subarachnoid space was performed to mimic the potential impact that SCIs can have on conductivities (Fig. 17).

**Figure 17. Effects of Conductivity Changes to the Subarachnoid Space on the Electric Fields.**

Decreasing the conductivity of the subarachnoid space led to an increase in electric field strength, with the electric field strengths being the lowest if the CSF were fully present in the subarachnoid space (1.78 S/m). The greatest change in electric field strength was 0.1 V/m, a comparatively small change, indicating that the electric field distributions seen the spinal cord are calculable, even when parameters such as the high conductivity values of the CSF and the subarachnoid space are varied.

Another experiment to consider for the future is the further validation through agar phantoms [55, 56]. Though preliminary validation studies were conducted with the use of agar phantoms, hydrolysis occurred in the agar and it was found difficult to make accurate measurements of the electric potentials and field strengths. Future studies should address this problem and hopefully fix the hydrolysis that occurs at the electrodes. The field strengths can then be compared to the field
strengths computed in this model as a form of external validation to supplement the validation for Sim4Life.

The work presented here sets a guideline for OFS placements to optimize the field distribution in the spinal cord. Using these guidelines, the OFS electrodes can be adjusted to the increased surface area and the electrode placements can be adjusted so that they are closer to the spinal cord. Future trials of the OFS should take into consideration the adjustments made to the electrodes and placements and assess the improvements in functional recovery of the patient. First, animal trials should involve the implantation of the adjusted OFS in canines with SCI as a preliminary study to assess the effects of the adjustments made to the electrodes. Second, after functional recovery has been assessed, the new device can be employed in clinical trials, which will hopefully lead to improved functional recovery and quality of life in patients with SCI.
CHAPTER 6. CONCLUSIONS

Research has shown that the application of weak, DC electric fields to the injured spinal cord helps in axonal regeneration, thus helping with functional recovery. This phenomenon has been exploited to develop the oscillating field stimulator (OFS), an implantable device that has been tested and proved to improve sensory recovery in canine and human trials. However, the biggest limitation of the device is the lack of electric field strength measurements \textit{in vivo}. Thus, we employed FEM to characterize the electric fields in the human cervical region of the spinal cord.

The main goal comprised of three aims: building an anatomically accurate model of the cervical spinal cord region, characterizing the electric fields of the OFS, and optimizing the OFS electrodes for improved field distribution. Though the original OFS electrodes showed weak field strengths in the spinal cord region, the OFS was optimized in the third aim to increase the electric fields in hopes of maximizing therapeutic effect. The recovery seen in previous clinical trials can be enhanced with increased surface area of the electrodes or closer placement of the electrodes.

Future studies can involve further optimization of electrodes and the simulation model. In addition, the electrodes of the OFS can be implanted closer to the spinal cord or be modified to have larger surface areas, in order to improve electric field distributions. Future experiments should involve the experimental testing and the assessment of functional recovery of the above-mentioned adjustments. Thus, this study has direct clinical applications that can help improve the functional recovery outcomes of the device.
REFERENCES


