Development of Novel Models to Study Deep Brain Effects of Cortical Transcranial Magnetic Stimulation

Farheen Syeda

Follow this and additional works at: https://scholarscompass.vcu.edu/etd

Part of the Bioelectrical and Neuroengineering Commons, Neurology Commons, and the Other Mechanical Engineering Commons

© The Author

Downloaded from https://scholarscompass.vcu.edu/etd/5517

This Dissertation is brought to you for free and open access by the Graduate School at VCU Scholars Compass. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.
Development of Novel Models to Study Deep Brain Effects of Cortical Transcranial Magnetic Stimulation

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

Farheen Syeda
Bachelor’s of Science
Loyola University Chicago
May 2014

Advisor: Dr. Ravi L. Hadimani
Assistant Professor
Department of Mechanical and Nuclear Engineering

Virginia Commonwealth University
Richmond, Virginia
May 2018
## Contents

1 Acknowledgments iv

2 List of Figures and Tables v

3 Abstract 1

4 Introduction 3
   4.1 Human Brain Physiology ............................................. 3
   4.2 Magnetic Resonance Imaging (MRI) ................................. 7
   4.3 Neuron Signal Processes .............................................. 12
   4.4 Short History of Bioelectrical Stimulation ....................... 18
   4.5 Brain Stimulation Modalities ........................................ 20
   4.6 Vagus Nerve Stimulation (VNS) ..................................... 20
   4.7 Transcranial Direct-Current Stimulation ......................... 21
   4.8 Electroconvulsive Therapy .......................................... 22
   4.9 Deep Brain Stimulation .............................................. 23
   4.10 Transcranial Magnetic Stimulation ................................. 24
   4.11 Knowledge Gaps ...................................................... 27

5 Modeling Approach 28
   5.1 Sim4Life Low-frequency Theory .................................... 28
      5.1.1 Decoupling Magnetic and Electric Fields .................. 29
      5.1.2 Quasi-Static Approximation .................................... 31
   5.2 Tissue Modeling ...................................................... 34
   5.3 Head Models .......................................................... 36
   5.4 TMS Coil Model ....................................................... 39
   5.5 Duke Model ........................................................... 43
   5.6 Tissue Simulation: Finite Element Analysis ..................... 47
   5.7 Simulation Steps and Parameters ................................. 48
5.7.1 Modeling .......................................................... 48
5.7.2 Simulation .......................................................... 49
5.7.3 Analysis .......................................................... 52

6 Results/Completed Projects ........................................ 56
   6.1 Effect of Anatomical Variation in TMS Response ............. 56
   6.2 Combination of DBS and TMS for Parkinson’s disease .......... 65
      6.2.1 Phase I: Direct Magnetic Field Effects .................... 65
      6.2.2 Phase II: Effects of Induced Current ..................... 73
   6.3 Spiking Neuron Network Model .................................. 86
      6.3.1 Effect of Demyelination on Neuronal Response to TMS .... 86
      6.3.2 Signal Propagation of TMS in the Motor Pathway .......... 91
   6.4 3D Fiber Tract Modeling for Finite Element Simulations ........ 102

7 Conclusions and Contributions .................................... 135
   7.1 Future Work and Recommendations ............................ 136
   7.2 Peer-Reviewed Journal Publications .......................... 137
   7.3 Conference Presentations ..................................... 138

8 Timeline .......................................................... 139
   8.1 Coursework .................................................. 139

9 References .................................................. 142

10 Vita .................................................. 155

Appendices .................................................. 158
   A Volume Stimulated Code ....................................... 158
   B Surface Stimulated Code ....................................... 161
   C Demyelinated Neurons: Electric Field and White Matter .... 164
   D Demyelinated Neurons: Electric Field, Current, and Magnetic Field 167
   E Demyelinated Neurons: Python Script ........................ 169
   F Motor Pathway Model: Python Script ......................... 173
Acknowledgments

I would like to express my gratitude to my advisor, Dr. Ravi Hadimani, for his continuous support during my graduate studies, and for encouraging me to continue whenever I felt dejected. I would also like to thank the other members of my committee, Dr. Karla Mossi, for her constant support and guidance, Dr. Jayasimha Atulasimha, for stimulating discussions, Dr. Carrie Peterson, for insightful dialogue and interesting questions, and Dr. Kathryn Holloway, for her invaluable input and asking the questions which led to much of my thesis work.

I would like to thank my labmates for their exceptional input and help over the years. They were the best coworkers I could have asked for, and even better friends. Thank you for making the lab a home.

Finally, I would like to thank my friends and family for their unconditional support and faith in my abilities, for motivating me to reach my potential, and for encouraging me always.

I would like to express all my gratitude to my parents and siblings. To my mom, who taught me the value of education and to invest in myself. To my dad, from whom I learned about the world, and how to be a good person in it. To my brother and sister, who have taught me so much about being a good friend, and who never fail to make me laugh and feel at home.

I could not have done this without the knowledge that you would all be there for me in success or failure. Thank you.
# List of Figures and Tables

## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Brain Cortex with highlighted Primary Motor Cortex and Dorsolateral Prefrontal Cortex.</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Human brain development from conception to birth.</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Evolutionary differences in brain structure between primates and humans.</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>A broad view of the MRI scanner and its multiple coils which generate not only a gradient magnetic field, but also an RF wave and a receiver coil.</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Process of MRI magnetization and how it effects proton spins and resonance.</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>Fiber Tract data visualization created using DTI.</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>Neuron Anatomy</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>Action Potential</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>Excitatory post-synaptic potentials (EPSPs) in subthalamic nucleus. Note the difference in firing pattern between tonic firing and burst firing.</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>Pathways between cortex, basal ganglia and thalamus. Note the various inhibitory (-) and excitatory (+) synapses at different locations.</td>
<td>16</td>
</tr>
<tr>
<td>11</td>
<td>Timeline of significant historical events and notable scientists in the field of bioelectrics.</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>Vagus Nerve Stimulation.</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>Schematic of transcranial direct-current stimulation.</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>Schematic of electroconvulsive therapy.</td>
<td>22</td>
</tr>
<tr>
<td>15</td>
<td>Schematic image of Deep Brain Stimulation.</td>
<td>23</td>
</tr>
<tr>
<td>16</td>
<td>NeuroStar TMS device</td>
<td>24</td>
</tr>
<tr>
<td>17</td>
<td>Transcranial Magnetic Stimulation</td>
<td>25</td>
</tr>
<tr>
<td>18</td>
<td>MRI data showing image slices.</td>
<td>34</td>
</tr>
<tr>
<td>19</td>
<td>Image of 3D brain model cortex created using Freesurfer.</td>
<td>35</td>
</tr>
<tr>
<td>20</td>
<td>Image of 3D brain model developed using FreeSurfer. Note that all anatomies are shown here: skin, skull, cerebellum, grey matter, white matter, and cerebellum.</td>
<td>36</td>
</tr>
</tbody>
</table>
21 Skull (left) and cerebrospinal fluid (right) (CSF) of healthy model developed by us. 37
22 Grey matter (GM) (left) and white matter (WM) (right) of healthy model developed by us. 37
23 Ventriles (left) and Cerebellum (right) of healthy model developed by us. 38
24 TMS single coil from Magstim. [19] 39
25 Figure-of-8 coil from Magstim. [20] 39
26 50 coil designs from Deng et. al. [21] 40
27 Field profiles of 50 coil designs from Deng et. al. [21] 41
28 Image showing Figure-of-8 coil placed beside our head model in Sim4Life. 42
29 Full-body Duke model developed by Zurich MedTech. This model is complete with full skeleton, nerves, muscles, body fat, organs, and many more complex anatomical details. 44
30 Cerebrospinal Fluid and Dura Mater in the Duke model. 45
31 Grey matter and white matter in the Duke model. 45
32 Extra anatomical structures segmented into Duke model. 46
33 Grey matter (left) shown clearly with TMS coils, and induced E-field on gray matter surface (right). 47
34 Model tab in Sim4Life with head model and Figure-of-8 coil imported. 48
35 Simulation tab in Sim4Life showing frequency in the Setup section. 49
36 Simulation tab in Sim4Life showing models imported into Materials section. 50
37 Simulation tab in Sim4Life showing coil settings. 51
38 Analysis tab in Sim4Life showing slice viewer. 52
39 Analysis tab in Sim4Life showing surface viewer for gray matter. 53
40 Analysis tab in Sim4Life showing extraction of volume stimulation data. 55
41 Analysis tab in Sim4Life showing extraction of surface stimulation data. 55
42 All head models used in this study. Top two rows show healthy models while bottom two rows show PD models. 57
43 Surface viewers (top row) and slice viewers (bottom row) in Analysis tab of Sim4Life showing induced E-field in healthy, PD, and Ella model. 58
44 Age vs. Brain-Scalp distance in our models. No clear correlation is present. 59
45 BSD vs. Volume Stimulated for each model. 59
46 BSD vs. Surface Stimulated for each model. 60
47 BSD vs. Absolute Volume Stimulated for each model. 61
48 BSD vs. Absolute Surface Stimulated for each model. 62
49 BSD vs. maximum induced E-field. 62
<table>
<thead>
<tr>
<th>Page</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Stimulation specificity, defined as Volume Stimulated/Surface Stimulated.</td>
</tr>
<tr>
<td>51</td>
<td>Stimulation specificity vs. maximum induced E-field. A clear trend is visible.</td>
</tr>
<tr>
<td>52</td>
<td>Simple DBS lead model with four conductors and long lead body with wire and surrounding insulating sleeve.</td>
</tr>
<tr>
<td>53</td>
<td>Duke model encompassed in Wire Block in the Model tab.</td>
</tr>
<tr>
<td>54</td>
<td>Maximum electric field induced on the cortex and at the site of DBS conductors in the deep brain region.</td>
</tr>
<tr>
<td>55</td>
<td>Temperature variation for all simulations in cortex (solid) and DBS contacts (dashed).</td>
</tr>
<tr>
<td>56</td>
<td>X-Ray image of patient with DBS lead. Notice extra wiring coiling around patient’s skull.</td>
</tr>
<tr>
<td>57</td>
<td>Image of DBS lead 3387/3389 schematic from Medtronic literature.</td>
</tr>
<tr>
<td>58</td>
<td>New complex DBS lead model developed in SolidWorks.</td>
</tr>
<tr>
<td>59</td>
<td>Complex DBS lead model imported into Sim4Life.</td>
</tr>
<tr>
<td>60</td>
<td>Wire details in our complex DBS lead model. Note the four individual wires, each terminating at one contact.</td>
</tr>
<tr>
<td>61</td>
<td>Coronal view of a head model with complex DBS lead model inserted and simulated TMS.</td>
</tr>
<tr>
<td>62</td>
<td>Various orientations tested in our simulations.</td>
</tr>
<tr>
<td>63</td>
<td>Current values induced in the DBS lead due to different TMS Coil orientations. Orientation (a) clearly induces the highest amount of current.</td>
</tr>
<tr>
<td>64</td>
<td>Ten PD models with DBS leads inserted. Note the slight variance in anatomy for all models.</td>
</tr>
<tr>
<td>65</td>
<td>Current induced in ten PD models and one healthy control model. Note that current never exceeds 2 µA, which is orders of magnitude below that of DBS stimulation (mA).</td>
</tr>
<tr>
<td>66</td>
<td>Surface view of temperature variation in the cortex before, during, and after 30 minutes of TMS. Note that temperature increase in all areas is negligible.</td>
</tr>
<tr>
<td>67</td>
<td>Plot of temperature variation on the cortex (solid line) as well as the deep brain region (dashed line).</td>
</tr>
<tr>
<td>68</td>
<td>Voltage variation in a single neuron given random noise input using NEST. Note that the voltage drops back to resting potential (-70 mV) when then neuron fires after reaching threshold potential (-55 mV).</td>
</tr>
<tr>
<td>69</td>
<td>Neuron with myelin wrapped around its axon. Note that the nodes, or the spaces between the axonal segments, remain free of myelin. This allows the electrical signal to jump from node to node, thus significantly increasing conduction velocity.</td>
</tr>
<tr>
<td>70</td>
<td>Electric field induced on cortical brain tissue with corresponding calculated induced current on the neuron body and magnetic field required on the TMS coil surface.</td>
</tr>
</tbody>
</table>
Neuron firing (spikes/sec) in population of 1000 neurons, with varying levels of capacitance and TMS-induced current. 

Structural model of healthy motor pathway (left) and Parkinsonian pathway (right). Blue lines correspond to excitatory connections while red lines correspond to inhibitory connections. Notice in the Parkinsonian pathway, the lack of dopaminergic input, thicker lines for increase in signal propagation and thinner lines for decrease in signal propagation.

Raster plots of GPi (healthy, PD, DBS, and 50 Hz TMS).

Raster plots of all nuclei for healthy model. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.

Raster plots of all nuclei for Parkinsonian model. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.

Raster plots of all nuclei for Parkinsonian model with DBS at GPi. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.

Raster plots of all nuclei for Parkinsonian model with cortical rTMS at 50 pulses/sec. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.

Fiber tracts developed in ExploreDTI.

Fiber tracts developed in ExploreDTI and imported into SolidWorks.

Fiber tracts developed in ExploreDTI, modeled in SolidWorks, and imported into Sim4Life as 3D models for FEA simulations of TMS. This figure shows the fiber tracts placed inside their corresponding location inside a brain tissue model.

TMS performed on frontal cortex leads to stimulation of these fiber tracts.

List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Material properties used in Sim4Life simulations.</td>
</tr>
<tr>
<td>2</td>
<td>Basic thermal properties used for DBS lead materials.</td>
</tr>
<tr>
<td>3</td>
<td>Heat transfer properties used for DBS lead materials.</td>
</tr>
<tr>
<td>4</td>
<td>Previous publications studying safety of combination TMS/DBS treatments.</td>
</tr>
<tr>
<td>5</td>
<td>Approximate firing rates found in experimental studies, which were used as known outputs for our functional motor pathway model.[24] [25] [26] [27] [28] [29] [30] [31] [32]</td>
</tr>
<tr>
<td>6</td>
<td>Poisson noise generator parameters for each nucleus.</td>
</tr>
<tr>
<td>7</td>
<td>Connection weights between nuclei and delays as found in literature. [24] [33]</td>
</tr>
<tr>
<td>8</td>
<td>Firing data for GPi in our model.</td>
</tr>
</tbody>
</table>
Abstract

DEVELOPMENT OF NOVEL MODELS TO STUDY DEEP BRAIN EFFECTS OF CORTICAL TRANSCRANIAL MAGNETIC STIMULATION

By Farheen Syeda, Ph.D.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2018

Major Director: Dr. Ravi L. Hadimani
Assistant Professor
Department of Mechanical and Nuclear Engineering

Neurological disorders require varying types and degrees of treatments depending on the symptoms and underlying causes of the disease. Patients suffering from medication-refractory symptoms often undergo further treatment in the form of brain stimulation, e.g. electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), or transcranial magnetic stimulation (TMS). These treatments are popular and have been shown to relieve
various symptoms for patients with neurological conditions. However, the underlying effects of the stimulation, and subsequently the causes of symptom-relief, are not very well understood. In particular, TMS is a non-invasive brain stimulation therapy which uses time-varying magnetic fields to induce electric fields on the conductive parts of the brain. TMS has been FDA-approved for treatment of major depressive disorder for patients refractory to medication, as well as symptoms of migraine. Studies have shown that TMS has relieved severe depressive symptoms, although researchers believe that it is the deeper regions of the brain which are responsible for symptom relief. Many experts theorize that cortical stimulation such as TMS causes brain signals to propagate from the cortex to these deep brain regions, after which the synapses of the excited neurons are changed in such a way as to cause plasticity. It has also been widely observed that stimulation of the cortex causes signal firing at the deeper regions of the brain. However, the particular mechanisms behind TMS-caused signal propagation are unknown and understudied. Due to the non-invasive nature of TMS, this is an area in which investigation can be of significant benefit to the clinical community. We posit that a deeper understanding of this phenomenon may allow clinicians to explore the use of TMS for treatment of various other neurological symptoms and conditions. This thesis project seeks to investigate the various effects of TMS in the human brain, with respect to brain tissue stimulation as well as the cellular effects at the level of neurons. We present novel models of motor neuron circuitry and fiber tracts that will aid in the development of deep brain stimulation modalities using non-invasive treatment paradigms.
Introduction

4.1 Human Brain Physiology

Figure 1: Brain Cortex with highlighted Primary Motor Cortex and Dorsolateral Prefrontal Cortex. [1]

The human brain is an exceedingly complex structure, with an estimated 100 billion neurons, and each neuron maintaining thousands of connections with surrounding neurons.[34]. These neurons are susceptible to many different variations of disease and disorder. To date neuroscience research has found numerous methods to treat patients of neurological disease. [35] [36] [37] In general, the following information about the human brain has been established. The outer layer of the brain, called the cortex, contains neuron bodies and is known as grey matter. Underneath the grey matter lie the axons of the neuron bodies with a fatty covering which appears white in color; for this reason the tissue is called the white matter. Furthermore, the human brain cortex is divided into several lobes, each of which retains primary responsibilities. Each specific action is of course governed by very refined areas of the brain, but within each lobe, neurons generally perform similar types of
tasks. TMS experts are mainly concerned with the frontal lobe, which contains the motor control area and is also responsible for many complex tasks including mood and personality.[37] Specifically, we target the Dorsolateral Prefrontal Cortex (DLPFC) and the Primary Motor Cortex (PMC), both of which are shown in Figure 1.

Although we divide the brain into primary lobes for purposes of simplification, in reality most tasks require the use of multiple cortical regions as well as deep brain nuclei. The structure of the human brain can be best understood by following its progress through fetal development. The brain is first developed in parts called the forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon). Later in development, these structures differentiate into a total of five structures called the telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon. Gestational progress can be seen in Figure 2.

Figure 2: Human brain development from conception to birth. [2]
Because of the exceedingly complex nature of the human brain, it is important to study in detail its structure and function in order to make clinical progress. However, in vivo studies are difficult to perform, even if scientists are able to receive permissions and funding. With such restrictions, it is tempting to perform parallel studies on animals whose brain structures resemble ours. While it is possible to draw some conclusions about the human brain as a result of animal studies, there are many significant characteristics which are unique to the human brain. Figure 3 shows major differences between animal and human brain structure.

Figure 3: Evolutionary differences in brain structure between primates and humans.[3]
Due to these significant differences, it is important to study the human brain to the deepest extent possible, and for this we use computational models and simulations. Simulations performed on human brain models can provide results which are good first steps for many neurological studies. It is our hope that the models and simulations presented in this thesis will add value to the clinical neurological realm.
4.2 Magnetic Resonance Imaging (MRI)

MRI is a widely-used imaging technique in clinical settings around the world. The technology is ubiquitous due to its non-invasive nature, consequent safety, and high-resolution image quality. MRI is made possible by the use of spins in unpaired protons, specifically in hydrogen atoms in the body (water). The spin of a proton in a Hydrogen atom precesses about an external magnetic field at the Larmor frequency, which can be described as follows:

\[ f = \gamma B \]  

(1)

where \( \gamma \) is the gyromagnetic ratio of the tissue in MHz/Tesla.

MRI is based on the concept of a spatially varying magnetic field creating spacially varying precession at the Larmor frequency. Separating the frequency components across the objects gives spatial information. For MRI, we use bulk precession of the water, fat, and other tissues. The consequent magnetization due to this precession is measured by a receive coil in the MRI machine. [47]

Resonance in MRI refers to matching a radiofrequency (RF) signal of an oscillating magnetic field to the precession frequency of nuclear spin. An overview of the scanner is shown in Figure 4. Magnetic moments of neutron and protons in the nucleus cancel out when the number of neutrons is equal to the number of protons, and this number is even. For unpaired protons, the magnetic moments do not exactly cancel. Only molecules whose nuclei have a net magnetic moment are able to interact with MRI magnetic fields. [48]
If rotation or spin is a first order quantity of angular momentum, and precession is the second-order quantity, then the third-order quantity is nutation, which results from forces rotating with the body’s precession. Nutation changes the angle of the object’s precession. For example, consider a precessing spinning top, and a finger pushing this top at a certain point with a certain frequency, to change the angle of the top’s precession. In MRI, a time-varying magnetic field causes nutation in biological tissue.

Static B-fields in MRI at 0.1 – 3 T correspond to 4.3 – 129 MHz Larmor frequency (precession) in hydrogen protons. Time-varying B-field on order of MHz cause nutation. Resonance happens when this frequency matches precession frequency of protons in a certain static magnetic field. These frequencies are typically on the order of radio-frequencies, so we use RF waves in MRI. Furthermore, the receiver coil generally only picks up precession wavelengths on the plane transverse to itself, so it is important to cause precession in the body on that particular plane.
When an RF wave is applied to a sample at the resonance frequency, the bulk magnetization precesses at the Larmor frequency. The intensity and time of RF radiation determines the precession angle. In this way, the RF pulse is used to bring a large number of protons in a sample in phase with each other, and this increases the bulk magnetization by aligning all the spins in the tissue. Thus, a magnetization can be applied from the sample onto the receiver coil in the transverse plane. Therefore, the static magnetic field aligns all protons in same direction, in the direction of the applied magnetic field. The addition of an RF pulse, created using a time-varying magnetic field, causes synchronized precession among all the protons in a plane (or slice) which causes a large magnetization transverse to the receive coil. This process is shown in Figure 5.

Figure 5: Process of MRI magnetization and how it effects proton spins and resonance. [5]
Switching off the RF pulse causes the protons to relax back into their original state of alignment with static magnetic field. This is called longitudinal or spin-lattice relaxation. It is also referred to the T1 relaxation time. T2 relaxation happens when the protons relax into their unsynchronized random precession. This is called spin-spin relaxation. Both T1 and T2 relaxation happen simultaneously, although T2 time is generally shorter than T1.

Different biological materials have varying T1 and T2 relaxation times. The difference between these times can be used to differentiate between different materials in the body. The reasons for differing relaxation times between materials are complex, but one factor is material viscosity. Molecules with slow-rotating spins have a greater chance for interacting with their neighbors, thus shortening their relaxation time. Furthermore, molecules with spins that happen to be rotating at the Larmor frequency have the minimum T1 relaxation times. Water molecules in different tissues have different T1 relaxation times, but often these T1 times are too long to give meaningful contrast in images. For this reason, we use contrast agents.

**Fiber Tracts**

Signals typically begin in one area of the brain and propagate through certain pathways, including cortical and deep brain regions. [49] However, many of these paths are not very well understood and difficult to study. Specific areas of the brain have been mapped out for research into certain neurological conditions, such as the hippocampus for memory deficits and the motor pathway for motor symptoms. [50] [51] [24] [52]

With new innovations in Magnetic Resonance Imaging (MRI), this infrastructure is now observable through fiber tracts, which allow visualization of the white matter fibers within the brain. Fiber tracts are visualized by using Diffusion Tensor Imaging (DTI), in which diffusion of water molecules is mapped, thus marking the direction and pathways of axons. [53]

In Diffusion MRI, the diffusion coefficient (the relationship between diffusive flux and concentration gradient) is found by using six different diffusion gradients, and the water molecule diffusion
is then modeled as a Gaussian distribution. Diffusion of water molecules in the brain is anisotropic, and so the gradient allows tracking of these pathways. The diffusion tensor is a 3x3 symmetric, positive-definite matrix. Principal direction of each tensor determines the axon’s direction, or the direction in which the water molecules diffuse fastest. The subsequent fibers are tracked throughout the 3D space of the brain.[54] [55] [56] [53] One major limitation, however, is that DTI is unable to track crossing fibers. [57] [58] [59]

Figure 6 shows a fiber tract image extracted from a functional MRI (fMRI) using DTI.

Figure 6: Fiber Tract data visualization created using DTI.[6]
4.3 Neuron Signal Processes

It is hypothesized that the adult human brain is composed of 80 to 100 billion neurons, each of which makes thousands of connections to neighboring neurons.[60][61] Furthermore, there are hundreds of neuron types with varying physiology and functions.[62] Consequently, it is an extremely complex and computationally intensive task to attempt to model the entire human brain. For this reason, single neuron and neural network models generally focus on small geometric areas of the brain with a single neuronal type. Due to the nature of the diseases we are attempting to study, we will focus on certain neuronal circuitries using the standard neuron model, from which few neuronal types deviate. It is shown in Figure 7.

![Neuron Anatomy](image)

Figure 7: Neuron Anatomy [7]

The soma, or cell body, receives electrical signals which pass through the long spine, or axon, and exit via the synaptic terminals.[63] The physical location where a signal is passed from one cell to the other is known as a synapse, and the impulse passes from the pre-synaptic neuron to the post-synaptic neuron. Interestingly, it is not the electrical signal that is passed between neurons, but rather chemicals known as neurotransmitters which are released from the synaptic terminals of the pre-synaptic cell due to electric stimulation. Depending on the signal, certain ion channels
open, and the neurotransmitters then activate the receptors of the post-synaptic cell, which incites a new electrical signal within the body of the post-synaptic neuron. [64]

There are two general types of signals: excitatory, in which the neurotransmitter released excites the post-synaptic neuron, thus increasing the chances of neuron firing, and inhibitory, in which the neurotransmitter inhibits signal induction in the post-synaptic neuron. Although many synaptic connections in the brain are excitatory, it is crucial to also include inhibitory connections in order to prevent cascade effects of signal propagation, leading to over-activity in the brain. In fact, it is hypothesized that this cascade effect in the absence of enough inhibition is the cause of epileptic seizures, in which large parts of the brain begin firing in synchrony.[65] The type of signal received is dependent upon the neurotransmitter residing in that particular synapse as well as the frequency of the signal in the pre-synaptic cell. One of the most common excitatory neurotransmitter is glutamate, whereas the inhibitory chemical is usually gaba-Aminobutyric acid, commonly referred to as GABA. Dopamine can induce either excitatory or inhibitory signals, depending upon the type of receptor being targeted. [66]

Importantly, it is not enough for the soma to simply receive one or even several signals; at any given time, all input signals (excitatory and inhibitory) must sum to exceed what is called the action potential. At rest, the neuron remains at -70 mV. This voltage may increase as the soma receives signals at varying times, but the neuron will not fire until a voltage of -55 mV is reached. It is only at this point that the signal will exit the soma and travel down the axon and through the synaptic terminal. This is called the action potential, and the process is shown in Figure 8. Importantly, single signals cause very little potential change; in general one neurons typically requires thousands of signals to reach its action potential. [67]
Figure 8: Action Potential [8]

All neurons do not fire at the same frequency or rhythm. Various types of cells experience activation differently. At any given time, most neurons maintain some firing even in the absence of specific stimulation. We consider these signals as background noise, wherein the cell fires consistently without any task input; background firing can be regular or irregular, tonic (irregular pattern) or bursty (several spikes one after another followed by periods of inactivity). [68] [69]

Neuron firing is often shown as voltage spiking in the part of the brain which is being recorded. Figure 9 shows voltage differences between tonic firing and burst firing. In contrast, phasic firing occurs only when the neuron receives presynaptic input which reaches or exceeds the action potential. Phasic firing can also be bursty or tonic, depending on the incoming signal. [68] [69]
Figure 9: Excitatory post-synaptic potentials (EPSPs) in subthalamic nucleus. Note the difference in firing pattern between tonic firing and burst firing.[9]

**Motor Pathway**

We will be looking at some smaller nuclei in deeper regions in the brain, primarily the set of nuclei known as the Basal Ganglia (BG), the dysfunction of which is involved in motor disorders such as Parkinson’s Disease. Within the Basal Ganglia there exist the striatum, the globus pallidus internus (Gpi), globus pallidus externus (Gpe), substantia nigra, and subthalamic nucleus (STN), and thalamus. The neuron pathways between the basal ganglia, thalamus and cortex with respect to motor function is well-studied and modeled. One such model is outlined in Figure 10.
Figure 10: Pathways between cortex, basal ganglia and thalamus. Note the various inhibitory (-) and excitatory (+) synapses at different locations. [10]
There are two paths to observe in this paradigm. The direct pathway starts from the cortex, at the moment of movement initiation, from where an excitatory signal is passed to the striatum, which also receives dopaminergic signals from the substantia nigra pars compacta. The striatum then passes inhibitory signals to the GPi, which goes on to inhibit the ventral anterior and ventral lateral nuclei (VAVL) of the thalamus. From there, excitatory signals are passed to the motor areas of the cortex, and movement occurs.[33] [70] Due to the complex nature of this circuit, it is important to understand the role of the GPi, particularly the nature of the inhibitory signals. In a healthy brain, firing of the VAVL neurons leads to movement. However, in the absence of movement initiation, the VAVL is inhibited by the tonic irregular firing of the GPi - this process prevents unwanted movement from occurring. When a motor process is initiated, the striatum inhibits the GPi, and the lack of GPi firing then allows the VAVL to fire and cause movement. This process is called movement by disinhibition. [71] [70] It is important to note that the motor pathway does not only allow for normal movement, but also inhibition of movement at rest. We are interested in exploring this pathway at rest for the treatment of resting tremor and muscle rigidity.

One of the foci of this project is Parkinson’s Disease (PD), which is characterized by intense muscle stiffness and a shuffling walk as well as resting tremor. [72] A common treatment for these symptoms is Deep Brain Stimulation (DBS), in which a probe is surgically inserted into the BG and direct current is applied continuously to either the GPi or the STN. [73]
4.4 Short History of Bioelectrical Stimulation

Around 46-47 AD, the Roman emperor Claudius’ court physician, Scribonius Largus, inscribed hundreds of treatments to common ailments. [74] One of these treatments was the application of a fish, known as the electric ray, to the head for headache relief. [75] These fish were known to discharge electricity, and later on were also used on patients’ scalps to relieve symptoms of seizure, depression and pain. [76] [35]

In the 18th century, Luigi Galvani, a prominent scientist, showed that muscles in dead frogs could be made to move by electrically stimulating the nerves. [77] Galvani believed that there was electricity intrinsic to an animal’s nerves, and he called this phenomenon animal electricity. From these and other experiments, Galvani became the pioneer for bioelectromagnetics. His name is used today for terms such as galvanic cell and galvanic skin response (GSR).

In the 19th century, German neurologist Gustav Fritsch and anatomist Eduard Hitzig together used electrical stimulation in the motor cortex of a dog to excite the dog’s muscles. By applying an electrode directly to the exposed motor cortex of the dog’s brain, they found that different cortical regions affected various parts of the body.[78]

In the 1900’s, Sir Alan Hodgkin and Sir Andrew Fielding Huxley, both physiologists and biophysicists, developed the action potential theory which explained the initiation and propagation of neuron signals. [79] Together, they developed the Hodgkin-Huxley model of the neuron, which even today is a fundamental model for understanding the neuron. In 1963, they were awarded the Nobel Prize in Physiology for their work in neurology. Today, many computational and mathematical models of neurons and neuron networks are built on the foundation of the Hodgkin-Huxley neuron model.

These events, and more, are detailed in Figure 11, which shows some significant events in the bioelectrical realm.
Figure 11: Timeline of significant historical events and notable scientists in the field of bio-electricity. [11]
4.5 Brain Stimulation Modalities

To date, multiple brain stimulation techniques have become available for patients of neurological disease, including vagus nerve stimulation, transcranial direct-current stimulation (tDCS), electro-convulsive therapy (ECT, also known as Shock Therapy), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS).

4.6 Vagus Nerve Stimulation (VNS)

The Vagus nerve, or Cranial nerve X, is a pair of nerves, one on each side of the body, which runs from the brainstem to the heart, lungs, and digestive tract. During Vagus Nerve Stimulation, or VNS, electrodes are implanted which stimulate the vagus nerve. [80] VNS is FDA-approved for treatment of partial-onset seizures which are refractory to medication. VNS works by delivering current to the brain via the Vagus nerve. However, the exact mechanism by which VNS controls seizures is not very well understood. Figure 12

Figure 12: Vagus Nerve Stimulation. [12]
4.7 Transcranial Direct-Current Stimulation

tDCS uses low-amplitude DC current in electrodes which are placed on the patients head, as shown in Figure 13.

Figure 13: Schematic of transcranial direct-current stimulation. [13]

tDCS is relatively cheap, easy to administer, and causes minimal side effects. However, it induces spontaneous neuron firing rather than synchronous action potentials, and so may not be as effective as other neurostimulation techniques. Additionally, due to the nature of electrode placement during tDCS, current is delivered over a widespread area of the scalp rather than a small targeted region of the brain. Therefore, it is difficult to target the deficient nucleus or cortical area. [81]
4.8 Electroconvulsive Therapy

During ECT, grand-mal seizures are induced by applying high-amplitude current directly to the patient’s head. ECT has shown beneficial effects for 50% of patients of Major Depressive disorder. However, ECT requires general anesthesia, and patients have to undergo several sessions, after which they only have a 50% chance of success. Figure 14 shows a schematic of the process. [82]

![Schematic of electroconvulsive therapy](image)

Figure 14: Schematic of electroconvulsive therapy.
4.9 Deep Brain Stimulation

Patients with PD suffer from multiple symptoms including bradykinesia, resting tremor, shuffling gait, and muscle rigidity, along with non-motor symptoms including speech and swallowing difficulties. Symptoms often respond to Levodopa (L-dopa), a dopaminergic medication. However, symptoms can often become refractory, or the medication causes side effects. Patients will then undergo deep brain stimulation (DBS) surgery, wherein electrical leads deliver current directly onto deep brain nuclei called the basal ganglia. DBS is widely used to improve motor symptoms in PD and Essential Tremor (ET) patients. Figure 15 shows DBS leads inserted into the brain. DBS is a highly effective technique, but can only target deep brain nuclei which must be mapped in advance. DBS also requires invasive initial surgery for lead implantation, as well as further surgery to change the battery pack, all of which may lead to surgical complications.

Figure 15: Schematic image of Deep Brain Stimulation. [14]
4.10 Transcranial Magnetic Stimulation

In 1985, Barker et al introduced Transcranial Magnetic Stimulation (TMS) in *The Lancet* by showing the effect of a magnetic field on the motor cortex. [91] TMS is a non-invasive brain stimulation technique which is currently FDA-approved for treatment of Major Depressive disorder and is under investigation for potential treatment of other neurological conditions. It is also widely used as a diagnostic technique as well as a brain mapping tool. [92] [93] Today, there are multiple companies creating TMS devices for clinical treatment of patients. Figure 16 shows the TMS device developed by Neuronetics, Inc.

![Figure 16: NeuroStar TMS device](image)

During TMS, alternating current is pumped through a figure-of-8 coil, shown in Figure 17. The consequent time-varying magnetic field induces an electric field on the conductive tissues of the brain, thus stimulating the targeted region of the cortex. Furthermore, the brain tissue can be excited or inhibited by varying the pulse frequency of repetitive TMS (rTMS).[93] rTMS for treatment of depression targets the dorsolateral prefrontal cortex (DLPFC) and is shown to be effective in patients for which other treatments such as medication are ineffective.[94]
rTMS treatment for depression typically begin with single pulse TMS near the hand area of the motor cortex. The physician finds the corresponding scalp region when the patient’s thumb visibly twitches, then places the TMS coil 5 cm anterior, to stimulate the DLPFC. The device is then set to stimulate using pulse trains of 10 pulses per second for 30 minute sessions, 5 days/week for 4-6 weeks.[95] [96]

The magnetic field and induced electric field on conductive tissue can be calculated using Maxwell’s equations as shown below. We utilize the software known as Sim4Life by Zurich MedTech, which incorporates Maxwell’s equations into a Finite Element Analysis package and calculates E-fields induced in biological tissue by time-varying B-fields.
\[ \nabla \cdot \mathbf{E} = \frac{\rho}{\varepsilon_0} \]  \hspace{1cm} (2)

\[ \nabla \cdot \mathbf{B} = 0 \]  \hspace{1cm} (3)

\[ \nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \]  \hspace{1cm} (4)

\[ \nabla \times \mathbf{B} = \mu_0 \mathbf{J} + (\varepsilon_0 \frac{\partial \mathbf{E}}{\partial t}) \]  \hspace{1cm} (5)

where \( \mathbf{E} \) and \( \mathbf{B} \) are the electric and magnetic field vectors, respectively, \( \mathbf{J} \) is the current density vector, \( \rho \) is the charge density, and \( \varepsilon_0 \) and \( \mu_0 \) are the vacuum permittivity and permeability respectively.

Furthermore, the temperature effect of electric and magnetic fields on biological tissue can be found using the well-established Pennes Bio-heat Equation shown below.

\[ \rho c \frac{dT}{dt} = k \left( \frac{\partial^2 T}{\partial r^2} + \frac{\omega}{r} \frac{\partial T}{\partial r} \right) + q_m + \rho_b \omega_b c_b (T_{b,a} - T) \]  \hspace{1cm} (6)

where \( T \) is the local tissue temperature, \( q_m \) is the metabolic heat source term per unit volume, \( \omega \) is the perfusion rate, \( \rho_b \) is the blood density, \( c_b \) is the specific heat capacity of the blood, \( T_{b,a} \) is the blood temperature, and \( k \) is the thermal conductivity.
4.11 Knowledge Gaps

Experts in non-invasive brain stimulation agree that the “holy grail” of the field is targeted stimulation of deep regions in the brain while avoiding excess stimulation of cortical regions, which may cause unintended and potentially harmful side effects. To this end, ongoing studies observe B-fields induced by coils of various shapes, frequencies, and current amplitudes.[21] [97] [98] [99] [100] [101] [102] However, it is common knowledge that a plethora of pathways naturally exist in the brain, traveling from the cortex to deep regions. We posit that with the use of accurate models, we can begin to show exactly how these pathways can be used for non-invasive deep brain stimulation. Furthermore, we argue that by using detailed models of certain pathways, it may be possible to explore a variety of stimulation techniques in the computational realm as a first step towards animal studies and human trials for new TMS-driven deep brain stimulation modalities. In this thesis, we offer a novel motor pathway model for use in motor disorders such as Parkinson’s disease. Furthermore, we consider the use of segmented fiber tract data for study of signal propagation during TMS. We argue that this model may allow researchers to simulate specific deep brain regions stimulated when TMS is performed on any area of the cortex. We believe that the combination of this novel neuron network model and the segmented fiber tract model will be of significant benefit to researchers who wish to explore the possibility of non-invasive brain stimulation methods to treat patients with various neurological disorders.

Additionally, studies of combination DBS/TMS therapies are currently contradictory, as they are based on a variety of scenarios and parameters. We show that for a particular scenario, wherein PD patients have received medially-placed DBS leads, rTMS at the mouth motor cortex, to relieve speech and swallowing symptoms, will not cause over-stimulation.
Modeling Approach

In order to perform macroscopic field profile analysis, we need 3D models used in conjunction with Finite Element Analysis software. Here we use the FEA software Sim4Life, which has been developed by Zurich MedTech specifically to explore field profiles within biological tissue.

5.1 Sim4Life Low-frequency Theory

Maxwell’s equations in the time domain were described in Eq. 2 - 5. These can be converted to the frequency domain with assumption of harmonic oscillation $e^{j\omega t}$.

$$X(r, t) = R(e^{j\omega t}X(r))$$  \hspace{1cm} (7)

$$\frac{\partial}{\partial t} = j\omega$$  \hspace{1cm} (8)

where $X$ is a complex vector.

Then,

$$\nabla \times E = -j\omega B$$  \hspace{1cm} (9)

$$\nabla \times H = j\omega D + J$$  \hspace{1cm} (10)

$$\nabla \cdot D = \rho$$  \hspace{1cm} (11)

$$\nabla \cdot B = 0$$  \hspace{1cm} (12)

$$\nabla \cdot H = 0$$  \hspace{1cm} (13)
where \( \mathbf{E} \) is the E-field, \( \mathbf{D} \) is displacement current, \( \mathbf{B} \) is magnetic flux, \( \mathbf{H} \) is magnetic field, and \( \mathbf{J} \) is the current density field.

We also have the following constitutive laws for linear materials:

\[
\begin{align*}
\mathbf{D} &= \varepsilon \mathbf{E} \quad (14) \\
\varepsilon &= \varepsilon_0 \varepsilon_r \quad (15) \\
\mathbf{B} &= \mu \mathbf{H} \quad (16) \\
\mu &= \mu_0 \mu_r \quad (17) \\
\mathbf{J} &= \sigma \mathbf{E} + j_0 \quad (18)
\end{align*}
\]

where \( \varepsilon_0 \) is the electric permittivity of free space, \( \varepsilon_r \) is the electric permittivity of the material, \( \mu_0 \) is the magnetic permeability of free space, and \( \mu_r \) is the magnetic permeability of the material. \( \sigma \) is the ohmic loss, and \( j_0 \) is the source current.

### 5.1.1 Decoupling Magnetic and Electric Fields

Here, decoupling the magnetic field from the electric field is important using the vector potential \( \mathbf{A} \).

\[
\nabla \times \mathbf{A} = \mathbf{B} \quad (20)
\]

\[
\mathbf{E} = -j \omega \mathbf{A} - \nabla \phi \quad (21)
\]

And we separate these terms as follows:
\[ E_s = -j \omega A \] (23)
\[ E_i = -\nabla \phi \] (24)

where \( \phi \) is a scalar potential. Then we know that

\[ E = E_s + E_i \] (26)

For a solenoid,

\[ \nabla \cdot E_s = -j \omega \nabla \cdot A = 0 \] (27)

And for irrotation,

\[ \nabla \times E_i = -\nabla \times \nabla \phi = 0 \] (28)

Then, we can write:

\[ \nabla \times \frac{1}{\mu} \nabla \times A = \omega^2 \tilde{\varepsilon} A - j \omega \tilde{\varepsilon} \nabla \phi + j_0 \] (29)

where \( \tilde{\varepsilon} \) is the complex permittivity and can be defined by:

\[ \tilde{\varepsilon} = \varepsilon_r \varepsilon_0 + \frac{\sigma}{j \omega} \] (30)
5.1.2 Quasi-Static Approximation

A time-varying simulation considering Maxwell’s equations would be far too computationally intensive to perform effectively. Therefore, we use a quasi-static approximation which transforms the time-varying equations to the frequency domain.

The scaling property:

\[
\nabla \cdot \tilde{\varepsilon} \nabla \phi = O \left( \frac{\tilde{\varepsilon} \phi}{l_\phi^2} \right) \tag{31}
\]

\[
\nabla \cdot \omega \tilde{\varepsilon} A = O \left( \frac{\omega \tilde{\varepsilon} A}{l_A} \right) \tag{32}
\]

where \( O \) is the symbol for ‘on the order of’. \( l_\phi^2 \) and \( l_A \) are grid lengths. \( O(1/l) \) is the scaling derivative. For scaling of \( \phi \)-magnitude, we have

\[
\phi = O \left( \frac{\omega A l_\phi^2}{l_A} \right) \tag{33}
\]

For Ampere’s law:

\[
\nabla \times \frac{1}{\mu} \nabla \times A = O \left( \frac{A}{\mu l_A^2} \right) \tag{34}
\]

\[
\omega^2 \tilde{\varepsilon} A = O \left( \omega^2 \tilde{\varepsilon} A \right) \tag{35}
\]

\[
j \omega \tilde{\varepsilon} \nabla \phi = O \left( \frac{\omega \tilde{\varepsilon} \phi}{l_\phi} \right) = O \left( \frac{\omega^2 \tilde{\varepsilon} A l_\phi}{l_A} \right) \tag{36}
\]

Then,
\[
\frac{\omega^2 \varepsilon A}{\nabla \times \frac{1}{\mu} \nabla \times A} = O\left(\frac{\omega^2 \varepsilon \mu l_A^2}{\lambda^2}\right) = O\left(\frac{1}{\lambda^2}\right) \tag{38}
\]

\[
\frac{j \omega \varepsilon \nabla \phi}{\nabla \times \frac{1}{\mu} \nabla \times A} = O\left(\frac{\omega^2 \varepsilon \mu l_A l_\phi}{\lambda^2}\right) = O\left(\frac{l_\phi}{\lambda^2}\right) \tag{39}
\]

where

\[
\omega^2 \varepsilon \mu = k^2 \tag{40}
\]

\[
k = \frac{2\pi}{\lambda} \tag{41}
\]

where \(k\) is the wave number and \(\lambda\) is the wavelength. Then according to Ampere’s law:

\[
\left|\omega^2 \varepsilon \mu d^2\right| << 1 \tag{42}
\]

\[
\left(\frac{d}{\lambda}\right)^2 << 1 \tag{43}
\]

Which, if \(d\) becomes large enough to equal the size of the grid, can also be written as

\[
\omega^2 \varepsilon \mu d^2 << 1 \tag{44}
\]

\[
\omega \sigma d^2 << 1 \tag{45}
\]

\[32\]
In this case, Ampere’s law becomes

\[ \nabla \times \frac{1}{\mu} \nabla \times A = j_0 \quad (46) \]

The vector potential \( A \) is the magneto-static vector potential \( A_0 \). In this case, it is decoupled from \( E \), the electric field. Next, say that magnetic permeability \( \mu \) is equal to the magnetic permeability of free space \( \mu_0 \), and is constant over the entire domain. Then, using the Biot-Savart law,

\[ A_0(r) = \frac{\mu_0}{4\pi} \int_{\Omega} \frac{j_0(r')}{|r-r'|} d^3r' \quad (47) \]

where \( \Omega \) is the computational domain.

It is important to note that we do not have direct control over the software’s handling of these equations, as they are hard-coded into Sim4Life. These equations and more can be found in Sim4Life user documentation.
5.2 Tissue Modeling

We use MRI data of real patients to create 3D head and brain models. Using the software Freesurfer, along with high-resolution T1 and T2 weighted images, we can create high-resolution anatomically accurate models with differentiated skin, bones, cerebrospinal fluid, grey matter, white matter, and ventricles within the brain. The software inputs slices from MRI data such as the images shown in Figure 18.

The Freesurfer software is open-source and developed for analyzing MRI images for development of 3D models. The software inputs all MRI slices and uses contrast information to estimate anatomical boundaries, such as that between the skin and skull, or between grey matter and white matter. A 3D mesh is then created using these estimated boundaries and other geometrical information taken directly from the input MRI data. Figure 19 shows one example of a model created using Freesurfer.

Figure 18: MRI data showing image slices. [17]
It is important to note that by using Freesurfer, we are able to develop heterogeneous, anatomically-accurate brain models for use with FEA simulation software. Because we are able to not only acquire the geometrical complexities, but also assign different property values to each anatomy, we have the ability to perform simulations with much higher accuracy than previously-used spherical ball models.
5.3 Head Models

We use head models developed in our lab by Hamza Magsood, as well as those developed at Iowa State University by Erik Lee.[103] These models are created by downloading MRI data from the Human Connectome Project, which compiled MRI images from thousands of patients, including healthy people and those with neurological conditions. This MRI data is run through Freesurfer, as described in the previous section, and 3D head models are output. One of these models, imported into Sim4Life, is shown in detail below.

Figure 20: Image of 3D brain model developed using FreeSurfer. Note that all anatomies are shown here: skin, skull, cerebellum, grey matter, white matter, and cerebellum.
These anatomies can be imported separately as individual models and given different properties in the simulation domain. See separate models of all anatomies below.

Figure 21: Skull (left) and cerebrospinal fluid (right) (CSF) of healthy model developed by us.

Figure 22: Grey matter (GM) (left) and white matter (WM) (right) of healthy model developed by us.
Figure 23 shows the ventricles and cerebellum in our head model.

Figure 23: Ventricles (left) and Cerebellum (right) of healthy model developed by us.
5.4 TMS Coil Model

The standard TMS Coil has gone through some development over the years. The original coil was a simple loop of coil as shown in Figure 24.

![Figure 24: TMS single coil from Magstim. [19]](image)

Eventually, the double-coil system was introduced, and subsequently has been referred to as the figure-of-8 coil, as shown in Figure 25.

![Figure 25: Figure-of-8 coil from Magstim. [20]](image)
It was found that it is possible to induce a stronger, more focused electric field by using opposing currents in the figure-of-8 coil than by using the single loop coil.[93] Note that it is easier to create a higher-intensity electric field at a focused region with the figure-of-8 coil than with the single-loop coil. For brain stimulation purposes, this coil is much more effective at targeting a specific cortical area. Therefore, this coil has been FDA-approved for use during treatment of Depression.

Further developments in TMS research have led to multiple coil designs, with varying field effects. Figure 26 shows 50 coil designs from Deng et. al, and Figure 27 shows corresponding calculated electric field intensities.[21]
Additionally, some groups have developed new, focal coils which stimulate smaller cortical regions with higher intensity. [100]

However, in this work we model only the FDA-approved figure-of-8 coil. In this case, the current in both coils must have equal amplitude but opposite flow directions, such that the magnetic field in between the two coils adds up to a higher value than at any other point in the coil.

We model the figure-of-8 coil by creating 2 coils comprised of 9 concentric circular loops and placing them next to each other, 5 mm away from the head model’s skull, to account for distance created by the plastic insulation in a real-life clinical scenario.
Figure 28 shows our model of the figure-of-8 coil placed next to a head model in the FEA software Sim4Life.

Figure 28: Image showing Figure-of-8 coil placed beside our head model in Sim4Life.
5.5 Duke Model

Zurich MedTech, the company which developed the Finite Element Analysis software Sim4Life, has also developed a number of highly heterogeneous anatomically-accurate full-body models. Here we show the full-body model Duke, which was created using MRI images of a healthy 34-year-old male. The models created by Zurich MedTech are in some ways more detailed in their anatomical accuracy, but we are unable to emulate their procedures as their methods are proprietary.

Not only is the Duke body more anatomically meaningful, but Duke’s brain tissue is also more refined, and includes many small nuclei that we are unable to include in our own 3D models. These additional nuclei may be added by hand, but the proprietary methods by which the company creates these are unknown.

The additional small brain nuclei in Duke model include: Commissura anterior, commissura posterior, Corpus Callosum, Hippocampus, Hypophysis, Hypothalamus, Medulla Oblongata, Midbrain, Pons, and Thalamus. In addition to these, the Duke model contains the skin, bones, blood vessels, fat, larger brain tissue models (grey matter, white matter, and cerebellum), nerves, muscles, and much more. Because of these additional anatomies, the Duke model is a much more accurate representation of the body’s reaction to TMS magnetic fields.

However, we have noted that the Duke model’s calculated field profiles often contain single-pixel discontinuities in the deep brain and cortical regions, which may be due to issues importing the highly complex mesh. Nevertheless, the anatomical details of the Duke model are shown in Figure 29. Figures 30 and 31 show various brain anatomies.
Figure 29: Full-body Duke model developed by Zurich MedTech. This model is complete with full skeleton, nerves, muscles, body fat, organs, and many more complex anatomical details.
Figure 30: Cerebrospinal Fluid and Dura Mater in the Duke model.

Figure 31: Grey matter and white matter in the Duke model.
Figure 32 shows the additionally segmented nuclei and brain structures added in the Duke model that we were unable to segment into the models we developed. These include the commissura anterior, commissura posterior, Corpus Callosum, Hippocampus, Hypophysis, Hypothalamus, Medulla Oblongata, Midbrain, Pons, and Thalamus.

Figure 32: Extra anatomical structures segmented into Duke model.
5.6 Tissue Simulation: Finite Element Analysis

The Sim4Life software uses Maxwell’s equations to calculate B-fields created by AC currents and corresponding induced E-fields on biological tissue. Human models, created using MRI data of real patients, can be imported once segmented using 3rd-party software. In this project we use both models licensed by Zurich MedTech as well as models we have created in our lab using MRI data downloaded from the Human Connectome Project. Members of the group, including Hamzah Magsood, Gabrielle Jones, and Youssif Alkheder have been successful in segmenting models of healthy patients as well as those with Parkinson’s disease. The following images show Sim4Life simulations using our novel models.

![Figure 33: Grey matter (left) shown clearly with TMS coils, and induced E-field on gray matter surface (right).](image)

Figure 33: Grey matter (left) shown clearly with TMS coils, and induced E-field on gray matter surface (right).
5.7 Simulation Steps and Parameters

For a TMS simulation in Sim4Life, there are a series of steps that must be followed to ensure accurate simulation results. The following section gives information on how we conducted simulations and extracted results for analysis.

5.7.1 Modeling

Within the Model tab in Sim4Life, we first imported the head model and the Figure-of-8 coil previously created in Sim4Life as mentioned in the above section. Figure 34 shows the Model tab in Sim4Life.

Figure 34: Model tab in Sim4Life with head model and Figure-of-8 coil imported.
5.7.2 Simulation

In the Simulation tab, we first choose the type of simulation needed, the Magneto-Quasistatic Simulation. Once it is chosen, the simulation parameters are populated. We specify material parameters and grid details. In the first step shown in Figure 35, we use the Setup section to set the simulation frequency to 2500 Hz to mimic the clinical coil current frequency of 2500 Hz.

Because the simulation is Quasi-Static, we can choose the current frequency of 2500 Hz, but we cannot create a realistic scenario in which the patient is receiving 10 pulses/sec. Instead, the software effectively takes a snapshot of the induced currents and electric fields induced at a point at which the current is flowing through the coils at 2500 Hz.
Next, we add all model materials into individual folders in the Material Settings section, as shown in Figure 36. It is important to note here that Sim4Life has intrinsic properties available for biological tissue. After importing our homegrown models, we use these material properties by simply assigning the property to its respective material model. Each part of the model must be dragged from the Model Tree into its corresponding folder in the Explorer tab. Table 1 below shows the various properties used by Sim4Life.

![Simulation tab in Sim4Life showing models imported into Materials section.](image)

**Table 1: Material properties used in Sim4Life simulations.**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mass Density (kg/m³)</th>
<th>Electric Conductivity (S/m)</th>
<th>Relative Permittivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>1109</td>
<td>0.17</td>
<td>1</td>
</tr>
<tr>
<td>Skull</td>
<td>1908</td>
<td>0.32</td>
<td>1</td>
</tr>
<tr>
<td>CSF/Ventricles</td>
<td>1007</td>
<td>1.7765</td>
<td>1</td>
</tr>
<tr>
<td>Grey Matter</td>
<td>1044.5</td>
<td>0.239149</td>
<td>1</td>
</tr>
<tr>
<td>White Matter</td>
<td>1041</td>
<td>0.26507</td>
<td>1</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1045</td>
<td>0.659667</td>
<td>1</td>
</tr>
</tbody>
</table>
In addition to material properties, the software requires a current source, of which we create two. After dragging each coil to its individual source setting, we use a current value of 5000 A for one coil and -5000 A for the other. In this way, the current flow creates a Figure-of-8 path. This step can be seen in Figure 37.

![Figure 37: Simulation tab in Sim4Life showing coil settings.](image)

Any line, spline, circle, or helix created in the Model tab in Sim4Life can be used as a current source. However, note that a 3-dimensional material, either imported into the software or created in the Model tab, cannot be used as a current source. Similarly, a line, spline, circle, or helix used as a current source cannot be dragged into any material folder. If it is necessary to use a model as both a material and as a current source, the software will require two models: one to be added into a material folder, and the other (line, curve, circle, or helix) must be a 2d model used only as a current source.
5.7.3 Analysis

There are several methods of field profile analysis in Sim4Life. However, first it is important to note that while the software calculate electric fields as 3-dimensional vectors, with individual values for each axis, the E-field viewer shows the root-mean square (RMS) values for E-field. Therefore, while we can visualize TMS-induced E-fields quite easily, in-depth analysis requires extraction of raw data and independent analyses. These will be discussed in the next section.

Within Sim4Life, we require the use of two viewers: the Slice Viewer and the Surface Viewer. Figure 38 shows a head model in the analysis tab after TMS simulation. The slice viewer is clearly seen, along with a scale, units of which are in V/m.

![Figure 38: Analysis tab in Sim4Life showing slice viewer.](image)
This can be created by selecting the simulation in the Explorer window, then selecting ”Overall Field” in the Output View. A ”Sensor Extract” button will appear in the top bar. Clicking this button will result in a population of various fields in the Output View. For the most part, we are interested in the E-field. Therefore, we can select E-field and choose the Viewers button which appears in the top bar. From Viewers, we select Slice Viewer.

In Figure 38, however, we have filtered out unnecessary field profiles from the background, skin, skull, and other anatomies. To do this, we select E-field in the Output View and then click Field Data Tools in the top bar. We select Mask Filter, and in the newly-populated Properties toolbar, we simply select the anatomies to include in the filter and click Refresh.

We can also observe the E-field on the surface of any geometry. For purposes of certain analyses, we extract E-field values induced on the surface of the gray matter. Figure 39 shows the E-field surface viewer on the gray matter.

Figure 39: Analysis tab in Sim4Life showing surface viewer for gray matter.
Other surfaces, such as the skin, skull, or white matter, can also be analyzed similarly. To do this, we simply select Overall Field in Explorer, select EM E in the Output View, and drag the anatomy from the Multi-Tree into onto the Overall Field option in Explorer. Several Interpolators are then populated in Explorer. We select the bottom EM E(x,y,z,f0) Interpolator, and in the top bar click Viewers, Surface Viewer.

In both Slice Viewer and Surface Viewer, the default view is on a dB scale. To convert to a linear (log) scale, we simply click the small plot shown on the bottom left corner of the scale. It is also possible to change the scale by double-clicking on it and changing its properties in the window that pops up.

While it can be helpful to view the slice and surface viewers and find the maximum E-field on Sim4Life’s User Interface, it is often more effective to extract the raw data for analysis. Here, we show how we extracted data for Matlab analysis for brain volume and surface.

To extract volume stimulation data, we use the Slice Viewer with Mask Filter enabled, with grey matter and white matter selected for filtering. In Explorer, we right-click on EM E(x,y,z,f0) - Mask Filter, select Imp/Export on the popup window, and click MATLAB (R) Exporter. Then in Explorer, we select MATLAB (R) Exporter and in the Properties window choose a file path and click Refresh to save the Matlab data. These steps are shown in Figure 40.

We also use surface stimulation data to calculate focality or specificity of the stimulation. We define these terms to mean the surface stimulated divided by volume stimulated. This calculation is often helpful in determining how deep the stimulation goes in relation to how much of the brain surface must be targeted. To extract surface stimulation data, we follow similar steps as volume stimulation extraction. We bring up the surface viewer, and right-click on the bottommost EM E(x,y,z,f0) - Interpolator, select Imp/Export option in the pop-up window, and click MATLAB (R) Exporter. In the same way as for volume extraction, we choose a file path in the newly-populated Properties window and click Refresh to save the data file. These steps are shown in Figure 41.
Figure 40: Analysis tab in Sim4Life showing extraction of volume stimulation data.

Figure 41: Analysis tab in Sim4Life showing extraction of surface stimulation data.
Results/Completed Projects

6.1 Effect of Anatomical Variation in TMS Response

The first project we undertook was based on the fact that each TMS patient requires an individualized approach to TMS treatment. The hypothesis was that this is likely due to differing brain geometry and/or size, but more specifically, age-related efficacy has been observed in the past. [104] We wanted to verify or deny this claim by performing simulations of TMS on models of various ages and calculating induced electric field. We obtained MRI data of adult patients between the ages of 25 and 65, created 3D head models using Freesurfer and Simnibs, and imported these models into Sim4Life for TMS simulations. Figure 42 shows the models that were used for this study.

We simulated TMS with coils positioned directly above the models’ heads as shown in Figure 42. We used healthy and Parkinsonian models downloaded from PPMI database, as well as the Duke and Ella models developed by the company IT’IS, which creates models for Zurich MedTech. Figure 43 shows analysis of these models.

We exported stimulation data and ran it through our Matlab programs (Attached in appendix) to calculate brain volume and surface stimulated. These programs effectively find the fraction of the brain volume/surface which has been stimulated above a certain threshold. In the past, stimulation threshold has been a function of the maximum E-field induced in each individual model. [103] However, because this maximum E-field is variable depending on the model, we introduce an additional ”absolute threshold” which simply finds the fraction of the brain volume/surface above a specified numerical value. Matlab code analyzing volume stimulated and surface stimulated can be found in Appendix A and Appendix B, respectively.
We started by finding the brain-scalp distance (BSD) for each model in order to find any correlation between age and BSD. It has been suggested in the past that the lower efficacy in elderly patients may be due to brain atrophy and subsequent larger BSD as age increases. Higher BSD increases the distance between the TMS coils and cortical surface. However, the following plot in Figure 44, which shows our models’ ages and BSD, shows that there is not necessarily any correlation between age and BSD. Healthy patient MRI data is downloaded from the Human Connectome Project (HCP), and Parkinson’s patient MRI data is downloaded from the Parkinson’s Progression Markers Initiative (PPMI).

We believe that the lack of correlation between age and BSD is due to the fact that we are observing data across a population. While it is true that for individuals, BSD likely increases over time as the brain atrophies, there is not necessarily a decrease in brain volume across a population. In
other words, while a patient’s brain does atrophy as they age, it may still have a larger volume than another younger individual’s brain. This variation is most likely caused by differences in genetics, environment, and lifestyle.

Because we do not observe a correlation between age and BSD, we base the rest of our data not on age but on BSD. After performing simulations, we plot the stimulation analyses against BSD. As in previous literature, we use a stimulation threshold of $\frac{E_{\text{max}}}{2}$ such that if a cell’s E-field value is calculated to be equal to or greater than half of that particular model’s maximum induced E-field, we consider that cell to be stimulated. However, because each individual patient’s $E_{\text{max}}$ is different, it is difficult to find any correlation between BSD and Volume Stimulated. This plot is shown in Figure 45 below.

Similarly, we do not necessarily see any correlation between Brain-Scalp Distance and Surface Stimulated in Figure 46.
Figure 44: Age vs. Brain-Scalp distance in our models. No clear correlation is present.

Figure 45: BSD vs. Volume Stimulated for each model.
However, if we use a particular numerical value to designate stimulation, we can observe a clear trend between BSD and Volume and Surface Stimulated, as seen in Figures 47 and 48. Note also that while the healthy patient data we downloaded was that of younger patients, and the older patient data was that of Parkinson’s patients, there is no clear correlation between PD and BSD or, in the case of Figures 47 and 48, between PD and TMS stimulation.

We also observed the maximum E-field induced in each patient and compared against the brain-scalp distance. There seems to be some correlation, as seen in Figure 49.

Finally, we calculate “stimulation specificity” or the ratio of volume to surface stimulated, by taking the number of volume stimulated fraction of each model and dividing by surface stimulated fraction. Once again, it is difficult to observe any clear correlation when using individualized stimulation parameters. This can be seen in Figure 50. However, we also observed the correlation between specificity and maximum induced E-field in each model, and find an interesting trend, as seen in Figure 51. It is clear that as $E_{max}$ increased, the specificity of stimulation increases as well.
Interestingly, there seems to be a higher variation between the older, Parkinson’s models than with the younger healthy models.
Figure 48: BSD vs. Absolute Surface Stimulated for each model.

Figure 49: BSD vs. maximum induced E-field.
Figure 50: Stimulation specificity, defined as Volume Stimulated/Surface Stimulated.

Figure 51: Stimulation specificity vs. maximum induced E-field. A clear trend is visible.
We can conclude from this work not only the more obvious result, that in our models, age is not necessarily correlated to brain stimulation, but also that the somewhat common notion among TMS clinicians, that older patients generally require higher stimulation thresholds, may not hold true. We posit that it is more beneficial for the patient’s health to find the brain-scalp distance using the individual’s MRI data, and set stimulation thresholds accordingly. It is clear from our data that many elderly patients retain the same high brain volume, and subsequently, low BSD, as many younger patients. Therefore, stimulation at unnecessarily high thresholds may cause negative side effects such as seizures in elderly patients.

Similarly, it is clear that many younger patients may have surprisingly high BSD and low brain volume, and so lower stimulation thresholds generally used for younger patients may not have the required efficacy needed for treatment. Therefore, we argue that it is crucial for TMS clinicians to understand individual patients’ brain volume and brain-scalp distance to provide effective TMS treatment.

See attached publication on our study of the effects of anatomical variability on TMS treatment. [105] Results showed that although brain atrophy for individuals is well-studied, brain-scalp distance (BSD), and thus motor threshold (MT), cannot be predicted by age alone. Furthermore, while induced E-field is a function of BSD, there is no direct correlation between induced E-field and patient age.
6.2 Combination of DBS and TMS for Parkinson’s disease

6.2.1 Phase I: Direct Magnetic Field Effects

Based on discussions with Dr. Kathryn Holloway from the Neurosurgery Department of Virginia Commonwealth University Health Systems, we were interested in exploring the implications of combining TMS with Deep Brain Stimulation (DBS). Parkinson’s Disease patients often exhibit motor symptoms such as hypophonia and dysphagia, even after receiving DBS. [72] [83] [84] Unfortunately, DBS has been unable to address these symptoms, and we argue that they may be improved by stimulating the cortical region of the brain which is responsible for motor-related tasks (M1 or Motor Cortex). TMS is easily able to stimulate areas of the cortex. However, it is possible that time-varying magnetic fields from TMS may induce eddy currents on the surface of the conductive parts of the DBS leads. While the issue of combining DBS with TMS has been addressed by a few studies in the past, we argue that the head models used in these studies were not sufficiently complex to find accurate induced electric and magnetic fields.[106] [107]

For this project, we calculated induced electric and magnetic fields in the deep brain region in the presence of conductors and a long cylindrical body, which was composed of a conductive wire wrapped in an insulating sleeve. We used Sim4Life v3, which was the most up-to-date version of the software at the time, with the complex, heterogeneous Duke model developed by IT’IS. At this time, we were unable to develop a highly complex and accurate DBS lead model, so we focused primarily on calculating induced E-field in the deep brain region due to the presence of conductors in the area and TMS coils at the motor cortex.

Simulation technique for these simulations differentiated from the regular simulations done for previous work. Due to the presence of the conductors, we first performed a Static Vector Potential simulation as a first step, to calculate the induced E-field on the conductors. Then, using results from the Static Vector Potential simulation as the source input for the Magneto Quasi-Static Vector Potential simulation, we found the induced E-field on the biological tissue. Finally, because we
were interested in studying potential temperature increase in the brain tissue, we used results from the Magneto Quasi-Static simulation as source input for a Transient Thermal simulation.

The first deviation from a traditional Sim4Life simulation was in the Modeling tab. As usual, we import our biological model, in this case the Duke model, as well as our Figure-of-8 Coil. We also create a simple DBS lead model, with 4 conductors and a long lead body comprised of a conductive wire (cylinder) and insulating sleeve (hollow cylinder surrounding the wire model). This simple lead model can be seen in Figure 52. Note that due to some instabilities in this older version of Sim4Life, we were unable to position the conductors close enough together to resemble an accurate DBS lead.

Figure 52: Simple DBS lead model with four conductors and long lead body with wire and surrounding insulating sleeve.
Next, to perform the Static Vector Potential calculation correctly, the Duke model and lead model needed to be encompassed in a “Wire Block”. In the Model tab, we simply clicked on the Duke model in Explorer, and in the top bar select Extract, Wire Block. This gives us a large wire frame in which the whole Duke model is encompassed, as shown in Figure 53.

Figure 53: Duke model encompassed in Wire Block in the Model tab.
Next, we switched to the Simulation tab and created a new Static Vector Potential Simulation. We used frequency 2500 Hz, and in the Materials section added the Duke model with all separate anatomies populated automatically with their properties. To add the DBS lead model, we created two different material settings – Insulators (modeled as PVDF) and Conductors (modeled as Platinum). All conductive parts of the lead, including the conductors and wire, were placed into this material folder and set as a PEC, or Perfect Electrical Conductor. This ensured that the materials were modeled as metallic and not dielectric. The insulating sleeve was placed into the Insulators materials folder and and the settings were as follows: Dielectric, Mass Density 1780 kg/m$^3$, and Conductivity 0.2 S/m. The Figure-of-8 coil was used as the current source as usual. All other simulation settings were set similarly to the regular Magneto Quasi-Static simulation.

After the Static Vector Potential simulation was complete we created a new Magneto Quasi-Static simulation. All settings were set as usual, with the exception of the Source folder, for which we created a new Vector Potential Source folder. To use the previous simulation’s results as the input, we dragged the Vector Potential simulation’s Sensors folder into the newly-created Vector Potential Source folder. All other settings were set as usual and the simulation was performed.

We performed these simulations for a range of TMS coil currents in order to ascertain the differences between induced E-field in the deep brain regions from varying the TMS intensity. We used TMS coil current of 1000 A, 3000 A, and 5000 A. After performing the simulations, we found maximum induced E-field in the area of the cortex closest to TMS coils and DBS conductors. These induced E-fields are shown in Figure 54. It is clear that induced E-field at the site of electrodes is much lower than at the cortex, and far too low to cause neuron stimulation.
Finally, we were interested in analyzing the temperature variation in the brain tissue as a result of the combination treatments. For this, we created a new Thermal Transient simulation. The settings for this simulation are described below.

Setup: Pennes

Time: 10,000 sec

Time Step Factor: 1 sec

The Materials section was populated as described above, but the thermal simulation requires thermal properties to be specified for each material. The Duke model’s properties were automatically supplied, and the material properties we used for the DBS lead are described in the following tables.

Heat generation properties were constant for all materials:

Type: Constant
Table 2: Basic thermal properties used for DBS lead materials.

<table>
<thead>
<tr>
<th>Material</th>
<th>Mass Density ($\text{kg/m}^3$)</th>
<th>Specific Heat Capacity ($\text{J/kgK}$)</th>
<th>Thermal Conductivity ($\text{W/mK}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrodes (Platinum)</td>
<td>21450</td>
<td>133</td>
<td>72</td>
</tr>
<tr>
<td>Insulators (PVDF)</td>
<td>1780</td>
<td>1200</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Heat Generation Rate: $0 \text{ W/kg}$

Heat Generation Interval: Whole Simulation Time

The following table gives heat transfer properties for each DBS lead material, calculated using the material property and geometry of the particular material.

Table 3: Heat transfer properties used for DBS lead materials.

<table>
<thead>
<tr>
<th>Material</th>
<th>Type</th>
<th>Heat Transfer Rate ($\text{W/m^2K}$)</th>
<th>Convective Temperature (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrodes (Platinum)</td>
<td>Constant</td>
<td>3.97487E6</td>
<td>37</td>
</tr>
<tr>
<td>Wire (Platinum)</td>
<td>Constant</td>
<td>453828</td>
<td>37</td>
</tr>
<tr>
<td>Wire Insulation (PVDF)</td>
<td>Constant</td>
<td>1048.45</td>
<td>37</td>
</tr>
<tr>
<td>Small Insulators (PVDF)</td>
<td>Constant</td>
<td>11041.3</td>
<td>37</td>
</tr>
<tr>
<td>Long Insulators (PVDF)</td>
<td>Constant</td>
<td>488.858</td>
<td>37</td>
</tr>
</tbody>
</table>

Initial conditions were set as follows:

Initialization: Fixed Value

Overall Temp: 25 °C

A new Initial Conditions settings folder was created, in which Duke was placed. For this new folder, the Overall Temp was set at 37 °C.

The Source was input from the Sensors folder of the completed Magneto Quasi-Static simulation.

Frequency: 2500 Hz

Interpolation: Energy Preserving

Interval Mode: User Defined Interval

Start Time: 5000 sec
Stop Time: 6000 sec

Boundary Conditions: Mixed

Outside Temp: 25 °C

Heat Transfer Coefficient: $5 \, \frac{W}{m^2 K}$

Heat Flux: $0 \, \frac{W}{m^2 K}$

Sensors: Whole Simulation Time

Max. No. Samples: 100

Figure 55 shows the temperature variation in the TMS-targeted cortex as well as the DBS contacts in the deep brain region. Note that temperature does not increase more than 0.5 °C in any region of the brain.

![Temperature Variation in Brain Tissue](image)

Figure 55: Temperature variation for all simulations in cortex (solid) and DBS contacts (dashed).
See attached publication on the first phase of combination of TMS and deep brain stimulation (DBS) for treatment of mouth/throat symptoms in PD patients. [108] A highly simplified DBS lead model was created for use in this project, and only the effects of direct induced E-field on the lead conductors was observed. We found that there was insufficient E-field, induced from direct applied B-field, in the deep brain region to induce stimulation from a combination of TMS and DBS. Furthermore, there is a negligible temperature increase (\(\leq 0.5 \degree C\)) in both the cortex and deep brain region.
6.2.2 Phase II: Effects of Induced Current

Next, we were interested in studying the effects of any TMS-induced current in the top of the DBS lead which would propagate down to the contacts and thus cause stimulation in the deep brain region. To answer this question, it was necessary to develop a new, accurate, complex DBS lead model, which was not possible in the simple geometries of Sim4Life. Therefore, an undergraduate student in our lab, Ciro Alcoba Serrate, used SolidWorks to develop a highly-accurate and complex DBS lead model.

Furthermore, it is important to include extra wiring that coils around the patient’s skull, as there may be current induced in these parts of the wire from cortical TMS. An example of this type of DBS coil winding is shown in Figure 56 below. To create accurate geometry, we followed MedTech literature for DBS lead 3387/3389, as shown in Figure 57.

Figure 56: X-Ray image of patient with DBS lead. Notice extra wiring coiling around patient’s skull. [22]
Figure 57: Image of DBS lead 3387/3389 schematic from Medtronic literature. [23]
The introduction of DBS wiring, particularly that which is winding around the patient’s skull, will be crucial in determining any current which may be induced by TMS and travel down to the lead contacts in the deep brain region. Importantly, this consideration adds a new dimension to this project; in the previous publication, we were only accounting for induced E-field caused in the deep brain region by any magnetic fields which may have propagated to that region. With the new complex DBS lead, we are able to calculate any current induced in the DBS wires close to the TMS coils. Additionally, we will consider the possibility of TMS-induced current in the proximal contacts which are placed near the back/side of the head to connect the lead wire to the battery pack or IPG. Because these contacts are conductive, it is important to place the TMS coil close to these proximal contacts to calculate potential currents induced at that location. Figure 58 shows our new, complex, highly accurate DBS model developed in SolidWorks, complete with full lead body, wire, wire insulation, and proximal and distal contacts. We were able to import this model into Sim4Life to perform simulations. Figure 59 shows details of the imported DBS lead model in Sim4Life.

Note that this model includes detailed wiring, with 4 separate wires coiling around each other to end at one conductor each, as is the case with real DBS leads. This is important to note because although each wire terminates at an individual contact, the 4 wires coil together throughout most of the lead body, and each wire has the potential to carry any TMS-induced current to its respective lead, thus stimulating the deep brain nuclei it targets. This particular detail can be seen in Figure 60.
Figure 58: New complex DBS lead model developed in SolidWorks.

Figure 59: Complex DBS lead model imported into Sim4Life.
Figure 60: Wire details in our complex DBS lead model. Note the four individual wires, each terminating at one contact.

In this project, we were interested in studying a specific scenario, as specified by our collaborator Dr. Kathryn Holloway, in which patients who have received DBS leads, placed medially in the head, also exhibit speech and swallowing symptoms. Stimulation of the inferior region of the M1, or Motor Cortex is thought to improve these symptoms. Therefore, we placed our leads relatively medially in each model’s head, although anatomical differences prevented the lead from fitting perfectly in each model in the same location. Furthermore, we targeted the inferior-most part of the M1 in an effort to stay true to the given scenario. Literature search shows that some studies have been done in the past to address the possibility of combining TMS with DBS treatment. The results, however, have been mixed, and we posit that this is due to significant variations in both lead and head model accuracy, as well as location of DBS and TMS relative to the brain. Table 4 addresses these previous studies as well as our particular case.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Methods</th>
<th>Current Induced in DBS Leads</th>
<th>Results/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et. al. 1999 [106]</td>
<td>Homogeneous phantom head model. TMS at 100% intensity performed 1 cm above leads. Voltage measured between contacts.</td>
<td>70 - 125 $\mu$A</td>
<td>Induced current significantly lower than DBS stimulation.</td>
</tr>
<tr>
<td>Shimojima et. al. 2009 [107]</td>
<td>Homogeneous phantom head model. TMS applied at various locations along head model Impedance used: 1162 $\Omega$</td>
<td>&gt;20 $\mu$C/cm²/phase</td>
<td>Charge density too high for stimulation to be safely performed.</td>
</tr>
<tr>
<td>Kuhn et. al. 2011 [109]</td>
<td>TMS at 100% intensity with DBS ON at 4V. Voltage measured between contacts.</td>
<td>0.2 - 2.8 V</td>
<td>Voltage does not exceed DBS stimulation and TMS duration is too short to cause stimulation.</td>
</tr>
<tr>
<td>Deng et. al. 2010 [110]</td>
<td>Created full circuit from contacts to chest IPG. Did not use full DBS lead geometry. 1.2 k$\Omega$ resistor with contacts.</td>
<td>Up to 83 mA. If DBS is OFF, current is only possible at $V&gt;5V$.</td>
<td>Induced current too high for stimulation to be safely performed.</td>
</tr>
<tr>
<td>Kuhn et. al. 2002 [111]</td>
<td>Clinical investigation of 5 patients with bilateral DBS and TMS in the Motor Cortex.</td>
<td>N/A</td>
<td>Contralateral and ipsilateral motor-evoked potentials were induced in 3/5 patients from TMS. No other complications reported.</td>
</tr>
<tr>
<td>Hidding et. al. 2006 [112]</td>
<td>Clinical investigation of 8 Parkinson’s patients with DBS, and mono pulse TMS in the Motor Cortex.</td>
<td>N/A</td>
<td>MEP latencies were significantly shortened, possibly due to current induced from TMS. No other complications reported.</td>
</tr>
<tr>
<td>Current work</td>
<td>Computational simulations with full heterogeneous head models and complex DBS lead model. TMS is at mouth motor cortex and medially positioned DBS is OFF.</td>
<td>&lt;2 $\mu$A.</td>
<td>Induced current lower than DBS stimulation.</td>
</tr>
</tbody>
</table>
We attempted to calculate induced E-field at various regions in the brain, but the Sim4Life software was unable to handle some of complexities of the DBS lead. One of the biggest issues we faced was the creation of discontinuities at various points in the DBS lead model. We were able to recognize these as discontinuities as they were single-pixel errors of extremely high E-field values at regions of relatively low E-field, and the associated induced current was not on par with the high E-field value at the same cell. For this reason, we continued with the paper with only induced current rather than E-field. Figure 61 shows an example of induced E-field calculations using the complex DBS lead.

Figure 61: Coronal view of a head model with complex DBS lead model inserted and simulated TMS.
We were first interested in studying the effect of different orientations with regards to the TMS coils and DBS lead. Because we were looking for the worst-case scenario, it was important to find the orientation which would lead to the highest induced current. We would then perform further simulations on all other models using the highest-current orientation. Therefore, we performed simulations using a variety of coil orientations near the M1 region, at the top of the head closest to the DBS lead, and at the back of the head closest to the proximal conductive contacts which would connect the wire to the battery pack or IPG. Additionally, for each of these setups we also rotated the TMS coil by 90 degrees from its normal position, in order to account for the well-observed phenomenon of angle-dependent E-field induction by TMS in the cortex. Figure 62 shows the various orientations we used for the healthy model.

![Figure 62: Various orientations tested in our simulations.](image)

Figure 62: Various orientations tested in our simulations.
It is important to note here that Sim4Life calculates current density rather than current. To calculate current, we found the highest current density value induced in the DBS lead wires and multiplied by the cross-section of the wire. Current density was in units of $\frac{A}{m^2}$, so we multiplied this value by $\pi r^2$ where $r = 0.05\text{mm}$, for the radius of the DBS wires. Then, of the various orientations and locations tested, we found that the highest induced current in the DBS leads was caused by orientation (a). This is most likely due to the orientation and location of the magnetic field relative to that of the four DBS wires in the lead body. The current values are plotted in Figure 63.

Figure 63: Current values induced in the DBS lead due to different TMS Coil orientations. Orientation (a) clearly induces the highest amount of current.
After finding that the highest induced current was caused by orientation (a), we positioned the TMS coil similarly in all other models. We also inserted DBS leads in all these PD head models as medially as the anatomy would allow. Note that it was crucial to position the DBS lead such that no part of the lead was extending through the model’s skin; in such instances, the E-field and induced current at these points jumped significantly in these cells, signaling a software glitch. For this reason, it was necessary to trim the lead to exclude the proximal lead contacts in order to fit the lead into each PD patient. Because the proximal leads did not cause higher induced current than orientation (a), this decision did not effect the outcome of the study. Figure 64 shows all ten PD models used in these simulations with inserted DBS leads.

Figure 64: Ten PD models with DBS leads inserted. Note the slight variance in anatomy for all models.

Once we had placed the leads inside each model and positioned the TMS coil in orientation (a), we performed the simulations and analyzed induced current values in the DBS leads. We found that none of the models’ current values exceeded 2 µA, while normal DBS stimulation currents are on the order of mA. This data is shown in Figure 65.
Figure 65: Current induced in ten PD models and one healthy control model. Note that current never exceeds 2 µA, which is orders of magnitude below that of DBS stimulation (mA).

Note that each patient, due to varying anatomy, has different stimulation requirements to reach stimulation threshold. For example, patients with higher brain-scalp distance tend to require higher stimulation current in order for their cortex to receive high enough B-field for stimulation. Similarly, our models all require different TMS current in order to reach the stimulation threshold of 150 V/m on their cortex due to anatomical variations in each head model. We found these TMS currents and stimulated each model at its respective current to ensure that each brain was receiving stimulation.
We also calculated the temperature variation in the control model for orientation A during and after 30 minutes of TMS stimulation, which is typically the time it takes to perform clinical TMS. We found the temperature in the cortex and DBS contact does not exceed $34.5 \degree C$, which is a negligible increase. The variation can be seen in Figures 66 and 67.

Figure 66: Surface view of temperature variation in the cortex before, during, and after 30 minutes of TMS. Note that temperature increase in all areas is negligible.

The following is the latest version of our publication of Phase II of the DBS project (in-progress), in which we have studied propagation of TMS-induced current on any part of the lead. We find
Figure 67: Plot of temperature variation on the cortex (solid line) as well as the deep brain region (dashed line).

that for our particular clinical scenario of TMS in the mouth motor region while DBS leads are placed medially in the head, there is some induced current in the DBS wires. However, this current is orders of magnitude lower than normal DBS stimulation. Therefore, our simulations suggest that for our scenario with DBS leads in the OFF state, the combination TMS/DBS treatment may not cause over-stimulation of the deep brain regions.
6.3 Spiking Neuron Network Model

6.3.1 Effect of Demyelination on Neuronal Response to TMS

In addition to studying the macroscopic tissue effects of TMS, we were interested in observing TMS stimulation on a neuronal level. Neuron physiology is complex, and there are certainly stimulation effects that we cannot observe by using Finite Element Analysis. Neuron modeling allows for study of not only single neurons, but also entire neuron populations as well as networks, in which populations of neurons are interconnected. To do this, we turned to neuron modeling using the Python package called NEST. While there are several neuron and neural network softwares available today, NEST allows for observation of whole networks rather than focusing on individual neuron physiology. Many neuron modeling softwares tend to focus on the effects of stimulation of individual neurons rather than an entire system. Generally, neural network softwares are used for machine-learning algorithm development, and so do not use accurate neuron physiology information and do not allow for observation of actual neural signals. Furthermore, NEST is a package of modules for the computational language Python, so we are not constrained by the rules of a traditional software using Graphical User Interface (GUI) for user communication. It is possible to write the program to perform using our specifications, and any modeling, simulation, and analysis details can be added easily by simply writing the corresponding code in Python. Using NEST, we can observe voltage and signal changes in single neurons as well as neuron populations. NEST allows for modeling of several types of neurons, each with its own benefits and constraints. For our simulations, we use the integrate-and-fire (iaf) neuron model, which integrates all incoming signals and fires, or passes on the signal, once it reaches the threshold potential of -70 mV. Figure 68 shows the voltage change in a single neuron given a random (Poisson) input signal. Note that the neuron starts at resting potential of -55 mV. We can not only deliver random noise to each neuron, we can also specify its frequency and connection weight. Furthermore, we can create our own stimulation generators, such as a TMS or DBS signal generator.
Figure 68: Voltage variation in a single neuron given random noise input using NEST. Note that the voltage drops back to resting potential (-70 mV) when then neuron fires after reaching threshold potential (-55 mV).

Note that although in reality, the voltage of a firing neuron will often reach up to +40 mV, the integrate-and-fire neuron in NEST simply comes back down to resting potential. Using entire populations of these single neurons, we can observe larger system effects of stimulation. Here, we were interested in the effects of TMS on abnormal neurons, specifically those that have been demyelinated.

Myelin is a fatty layer which surrounds the axon of many different types of neurons and allows for fast signal conductivity. Although myelin itself is an insulating substance, its presence on the neural axon causes electrical signals to jump from node to node, rather than to travel down the entire length of the long axon. In certain neurodegenerative diseases, however, neurons begin to undergo destruction of the surrounding myelin. This is called demyelination, and leads to slower conduction velocity across the neuron body, and thus may be a cause of some pathological symptoms. Demyelination has been shown to occur in Multiple Sclerosis (MS), Guillain-Barre Syndrome (GBS), and multiple other diseases. [113] [114] [115] The process of demyelination is shown in Figure 69.
Figure 69: Neuron with myelin wrapped around its axon. Note that the nodes, or the spaces between the axonal segments, remain free of myelin. This allows the electrical signal to jump from node to node, thus significantly increasing conduction velocity.

We were interested in the possibility of performing TMS on demyelinated cortical neurons, such as those of a Multiple Sclerosis patient. To do this, it was first necessary to establish the stimulation threshold in terms of TMS current. We created a TMS model in NEST by using an ac-generator function with frequency of 2500 Hz and 10 pulses per second, following clinical parameters. Because the TMS model in NEST needed to be a current generator rather than a voltage generator, it was necessary to find the current induced on the body of a cortical neuron during clinical TMS. Neuron physiology can be quite variable depending on the type of neuron and the part of the brain, so we used typical values of cortical neuron physiology, which we found in literature. The values were: diameter 1 µm, axon length 10 mm, resistance 32 Ω. [116] [117] [67] Using these values, we calculated corresponding necessary E-field by using the following formula:

\[
E\text{-field Value} \left( \frac{V}{m} \right) = \frac{IR}{\text{Area}} = \frac{\text{Induced Current (A)} \times \text{Resistance (Ω)}}{\text{Axon Diameter (m)}} \quad (48)
\]

Because the TMS stimulation threshold is typically assumed to be 150 V/m, we wanted to apply the corresponding induced current to the neurons in the simulation. We were also interested in finding the corresponding magnetic field induced on the surface of the TMS coil, which we did by using the FEA software Sim4Life. Demyelination occurs not on the grey matter (soma), but
the white matter (axon), so here we are only concerned with E-field induced on the white matter. Figure 70 shows our results comparing E-field induced on cortical white matter, current induced on neuron body, and B-field on the surface of TMS coils. Raw data for this plot can be found in Appendix C and Appendix D.

![Electrical Parameters for TMS on Cortical White Matter](image)

Figure 70: Electric field induced on cortical brain tissue with corresponding calculated induced current on the neuron body and magnetic field required on the TMS coil surface.

By iterating through the simulation with increasing TMS-induced current amplitude, we found that NEST neurons react with significantly increased synaptic activity when stimulated with current of 40,000 pA. As can be seen in the above figure, this value is very close to the 150 V/m threshold, and so we find our NEST neuron model and TMS generator validated.

Next, to simulate demyelination, we slowly increase the neurons’ capacitance, thus decreasing the conduction velocity and modeling a decrease in myelin. In NEST, the iaf neuron’s default capacitance is set at 250 pC. We increase this capacitance until we see an almost complete lack of signaling in the population, at 290 pC, at which we assume complete demyelination. We use a population
size of 1000 neurons and introduce a noisy background current. Then, we add TMS stimulation current and increase this value to observe differences in neuron firing. Figure 71 shows the observed firing rate for the neuron population of 1000 neurons, with varying capacitance values (demyelination) and TMS-induced current values. We found that relatively demyelinated neurons can be stimulated with clinical TMS parameters, and that highly demyelinated neurons require higher amounts of TMS current, which would likely be too high for FDA-approved treatment. Python script for this project can be found in Appendix E.

Figure 71: Neuron firing (spikes/sec) in population of 1000 neurons, with varying levels of capacitance and TMS-induced current.

See attached publication on our project modeling the effect of TMS on neuron populations with varying degrees of demyelination. [118]
6.3.2 Signal Propagation of TMS in the Motor Pathway

Although we had studied the effects of TMS on DBS leads, it was unclear what the effects of TMS may be on the actual deep brain nuclei with regards to signal propagation in the motor pathway from the cortex to the basal ganglia. We were interested in a potential TMS treatment that may help treat PD in a similar manner to DBS. To study these deep brain effects of Parkinson’s Disease, DBS, and TMS, it was necessary to observe neuron firing in the motor circuitry. For this purpose, we created a new neuron network model using NEST, complete with basal ganglia nuclei and the network complexities present. The motor pathway has been well-studied and the structural pathways and connections have been mapped by various groups. [24] [119] We used these models to create a complex, connected circuit of nuclei in NEST. Each nucleus was created separately using 800 neurons, which we found to give us the optimum balance of accuracy and computational time. Each nucleus was given some random noise in a given range, based on in-vivo studies which have observed background neuron firing in the basal ganglia. [24] [25] [26] [27] [28] [29] [30] [31] [32] We use the following initialisms for the nuclei:

Cortex = CTX; Striatum = STR; Striatum D1 neurons = STRD1; Striatum D2 neurons = STRD2; Substantia Nigra pars compacta = SNC; Globus Pallidus externus = GPe; Globus Pallidus internus = GPi; Subthalamic Nucleus = STN.

Table 5 outlines experimentally-found neuron firing values that were used as guidelines for our model’s signal output.

Table 5: Approximate firing rates found in experimental studies, which were used as known outputs for our functional motor pathway model.[24] [25] [26] [27] [28] [29] [30] [31] [32]

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Healthy Firing (Hz)</th>
<th>Parkinsonian Firing (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX</td>
<td>5</td>
<td>N/A</td>
</tr>
<tr>
<td>STR</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>SNC</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>GPe</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>STN</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>GPi</td>
<td>70</td>
<td>90</td>
</tr>
</tbody>
</table>
All excitatory and inhibitory connections between nuclei were made, and connection weights were specified based on known signal output data. We first created a healthy model and verified correct output signals for all nuclei. We then modeled a Parkinsonian circuitry by severing the connection between the SNc and Striatum, thus eliminating dopaminergic input from SNc to STRD1 and STRD2. Figure 72 shows our structural model of the motor pathway, developed using the cited literature, for both healthy and Parkinsonian/Dystonic circuitry. Notice that with the dopaminergic input removed, signals decrease in the Striatal D1 neurons and they increase in the Striatal D2 neurons. These disturbances then cause further downstream effects, leading to well-established increase in burstiness, or synchrony. It has been theorized that this synchrony is the cause for motor symptoms in PD and Dystonia. [120] [121] We are therefore interested in studying methods of decreasing the level of synchrony in these nuclei.

Figure 72: Structural model of healthy motor pathway (left) and Parkinsonian pathway (right). Blue lines correspond to excitatory connections while red lines correspond to inhibitory connections. Notice in the Parkinsonian pathway, the lack of dopaminergic input, thicker lines for increase in signal propagation and thinner lines for decrease in signal propagation.
Through trial-and-error, we were able to find the optimum background noise range for each nucleus, as well as connection weights between the nuclei shown in Figure 72, such that the output signals were accurate; when dopaminergic input was removed from the Striatum, the resulting neuron firing rates were also true to experimentally-found firing rates in Parkinsonian basal ganglia nuclei. Details of background noise and connection weights between noise generators and nuclei are given in Table 6. Connection weights and delays between nuclei are given in Table 7.

Table 6: Poisson noise generator parameters for each nucleus.

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Excitatory Conn.</th>
<th>Inhibitory Conn.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>1.1</td>
<td>-1.28</td>
</tr>
<tr>
<td>Striatum (D1)</td>
<td>1.0</td>
<td>-1.1</td>
</tr>
<tr>
<td>Striatum (D2)</td>
<td>1.0</td>
<td>-0.85</td>
</tr>
<tr>
<td>SNe</td>
<td>1.0</td>
<td>-0.9</td>
</tr>
<tr>
<td>GPe</td>
<td>1.3</td>
<td>-0.5</td>
</tr>
<tr>
<td>STN</td>
<td>1.15</td>
<td>-0.9</td>
</tr>
<tr>
<td>GPi</td>
<td>1.1</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

Table 7: Connection weights between nuclei and delays as found in literature. [24] [33]

<table>
<thead>
<tr>
<th>Nuclei Connected</th>
<th>Exc.(+) or Inh. (-)</th>
<th>Weight</th>
<th>Delay (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX - STN</td>
<td>+</td>
<td>1.0</td>
<td>5.9</td>
</tr>
<tr>
<td>CTX - STR</td>
<td>+</td>
<td>0.1</td>
<td>5.1</td>
</tr>
<tr>
<td>SNe - STRD1</td>
<td>+</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>SNe - STRD2</td>
<td>-</td>
<td>-5.0</td>
<td>0.5</td>
</tr>
<tr>
<td>STRD1 - GPi</td>
<td>-</td>
<td>-2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>STRD2 - GPe</td>
<td>-</td>
<td>-5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>GPe - STN</td>
<td>-</td>
<td>-0.3</td>
<td>4.0</td>
</tr>
<tr>
<td>STN - GPi</td>
<td>+</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>STN - GPe</td>
<td>+</td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Using these parameters, we were able to model healthy and Parkinsonian firing rates, which matched those found in past experimental studies. Next, we modeled the signal from a DBS lead and connected it directly to the GPi to model a PD patient receiving DBS to the GPi. DBS current parameters were modeled with frequency 185 Hz, pulse width 0.09 ms, and current amplitude 0.1 mA. These DBS parameters matched those used by our collaborator, Dr. Kathryn Holloway in clinical DBS treatment of PD patients.

Because we were also interested in studying downstream effects of TMS, we modeled TMS in this...
simulation similarly to that used in the demyelination project. TMS-induced current was modeled with frequency of 2500 Hz, pulse frequency varying between 10 and 60 pulses/sec, pulse width 0.4 ms, and current amplitude 40,000 pA.

To quantify synchrony $S$, we use the following method. Assume that a nucleus is firing in complete synchrony, with $N$ neurons, either firing simultaneously or remaining silent. Assume that the neurons fire at every other timestep. Then, given an array of timesteps and signals recorded during those timesteps, we would see half the timesteps with signal count 0, and the other half with signal count $N$. In this case, the mean $\mu = N/2$, and the standard deviation $\sigma = N/2$. Maximum signal frequency at any given point would be $f_{\text{max}} = N$ and minimum signal frequency would be $f_{\text{min}} = 0$. The range of the data is $f_{\text{max}} - f_{\text{min}}$. We can then classify synchrony as

$$S = \frac{2\sigma}{f_{\text{max}} - f_{\text{min}}}$$

(49)

For a neuron population with complete synchrony, we see

$$S = \frac{2\sigma}{f_{\text{max}} - f_{\text{min}}} = \frac{2(N/2)}{N} = 1$$

(50)

As the nucleus becomes less and less synchronous, we begin to see the firing frequency approach the mean, with about half of the neurons firing at any given timestep, and the standard deviation begins to decrease. Then if $\sigma$ approaches 0,

$$S = \frac{2\sigma}{f_{\text{max}} - f_{\text{min}}} = \frac{2(0)}{f_{\text{max}} - f_{\text{min}}} = 0$$

(51)

Therefore, we can say that with this method of synchrony quantification, a nucleus with complete asynchrony gives $S = 0$, and one with complete synchrony gives $S = 1$. We measure these values in our model; Table 8 gives firing data found for the GPi. It is clear from our measurements that the healthy GPi has a low synchrony of $S = 0.08$. In the Parkinsonian state, this synchrony increases
significantly to 0.52. This result serves to further validates our model, as the transition to highly bursty firing in the basal ganglia is well-established in the field.[120] [121]

With the addition of DBS, both the firing rate and synchrony increase, with \( S = 0.62 \). In the past, it was theorized that DBS causes a lesioning effect in the basal ganglia, thus minimizing firing in the targeted nuclei. [122] However, more recent publications have brought forward the idea that the effect of DBS may have both excitatory and inhibitory effects, depending on the orientation of the neurons relative to the DBS contact, and other variable parameters. [123] In any case, some experts theorize that it may be the interruption of pathological discharge in the basal ganglia that decreases motor symptoms. In our model, DBS significantly increases firing rate, and because the signal is directly connected to the neurons in the GPi, we assume that this is the correct result.

We then wanted to observe the effects of cortical rTMS in deep brain regions, so we added TMS and connected it to the CTX nucleus. From Table 8, it is clear that TMS can decrease Parkinsonian synchrony with \( S = 0.26 \) for clinical TMS of 10 pulses/sec. By further increasing the TMS frequency, we see even lower levels of synchrony; 50 Hz TMS gives synchrony levels very close to that of a healthy GPi, with \( S = 0.09 \).

Thus, our model suggests that clinical TMS on the M1 region at 50 pulses/sec can lower the synchrony level of the GPi close to that of a healthy GPi nucleus. Raster plots of the GPi can be seen in Figure 73. We conclude that this new model showed a potentially viable non-invasive alternative to DBS therapy using high-frequency rTMS. This phenomenon should be studied in animal models as a next step.

The following pages show supplementary raster plots for visualization of changes in the motor pathway nuclei firing for healthy, PD, DBS, and TMS models. Full Python code for this project can be found in Appendix F. Also see the latest version of our manuscript below, which has been submitted to *IEEE Transactions on Biomedical Engineering*. 
<table>
<thead>
<tr>
<th>Model</th>
<th>Standard Deviation</th>
<th>$f_{avg}$ (impulses/sec)</th>
<th>$f_{min}$ (impulses/timestep)</th>
<th>$f_{max}$ (impulses/timestep)</th>
<th>Synchrony S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>5.68</td>
<td>72</td>
<td>144</td>
<td>128</td>
<td>0.08</td>
</tr>
<tr>
<td>Parkinsonian</td>
<td>37.30</td>
<td>82</td>
<td>800</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>DBS @ GPi</td>
<td>248.39</td>
<td>122</td>
<td>80</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>TMS(10 Hz)</td>
<td>25.26</td>
<td>80</td>
<td>240</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TMS(20 Hz)</td>
<td>26.88</td>
<td>80</td>
<td>233</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>TMS(30 Hz)</td>
<td>25.29</td>
<td>80</td>
<td>236</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>TMS(40 Hz)</td>
<td>15.00</td>
<td>87</td>
<td>230</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>TMS(50 Hz)</td>
<td>9.78</td>
<td>87</td>
<td>230</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>TMS(60 Hz)</td>
<td>16.64</td>
<td>82</td>
<td>239</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>
Figure 73: Raster plots of GPi (healthy, PD, DBS, and 50 Hz TMS).
Figure 74: Raster plots of all nuclei for healthy model. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.
Figure 75: Raster plots of all nuclei for Parkinsonian model. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.
Figure 76: Raster plots of all nuclei for Parkinsonian model with DBS at GPi. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.
Figure 77: Raster plots of all nuclei for Parkinsonian model with cortical rTMS at 50 pulses/sec. Red arrows indicate inhibitory connections while blue arrows indicate excitatory connections.
6.4 3D Fiber Tract Modeling for Finite Element Simulations

The final step in this project was creating a segmented fiber tract model in which each tract bundle is developed as a separate model piece. The hypothesis is that by using a high conductivity value to model axonal conduction velocity, it may be possible to apply TMS on any part of the cortex and observe signal propagation through the fiber tracts. Using these models, it may be possible to observe stimulation of deep brain regions with cortical TMS. Past studies have shown that it is possible to segment fiber tracts manually as well as by use of software. [56] [124] [125] However, these models were limited to M1 fiber tracts and focused on characterizing the signal propagation through these tracts. We were interested in developing a method to create fiber tracts from various parts of the brain such that we could perform FEA simulations to visualize cortical/subcortical and cortical/deep brain region paths.

We used the software ExploreDTI to find targeted fiber tracts which propagate from cortical to deep brain regions. Figure 78 shows an example of some fibers created using Diffusion MRI data from a healthy male patient in ExploreDTI. We were then able to export the vector data for these fiber tracts, and, after some analysis, import this vector data into SolidWorks. Figure 79 shows these fiber tracts imported into SolidWorks. Finally, we performed the sweep function for these tracts to export them as solid 3D models, after which we were able to import these models into Sim4Life and perform TMS to the cortical end of the tracts, as shown in Figure 81.

Because we now have this method of creating fiber tracts for FEA simulations, we can easily create hundreds or even thousands of tracts for analysis from any part of the brain. This work will be helpful in understanding which deep brain regions are affected by TMS on any part of the cortex.

We are grateful to Jennifer Mak and Paxton O’Bryen for their invaluable contributions in creating these fiber tract models.
Figure 78: Fiber tracts developed in ExploreDTI.

Figure 79: Fiber tracts developed in ExploreDTI and imported into SolidWorks.
Figure 80: Fiber tracts developed in ExploreDTI, modeled in SolidWorks, and imported into Sim4Life as 3D models for FEA simulations of TMS. This figure shows the fiber tracts placed inside their corresponding location inside a brain tissue model.

Figure 81: TMS performed on frontal cortex leads to stimulation of these fiber tracts.
Effect of anatomical variability in brain on transcranial magnetic stimulation treatment

F. Syeda,1 H. Magsood,1 E. G. Lee,2 A. A. El-Gendy,1 D. C. Jiles,3 and R. L. Hadimani1,a

1Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, Virginia 23284, USA
2Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
3Department of Electrical and Computer Engineering, Iowa State University, Ames, Iowa 50011, USA

(Presented 2 November 2016; received 23 September 2016; accepted 31 October 2016; published online 24 January 2017)

Transcranial Magnetic Stimulation is a non-invasive clinical therapy used to treat depression and migraine, and shows further promise as treatment for Parkinson’s disease, Alzheimer’s disease, and other neurological disorders. However, it is yet unclear as to how anatomical differences may affect stimulation from this treatment. We use finite element analysis to model and analyze the results of Transcranial Magnetic Stimulation in various head models. A number of heterogeneous head models have been developed using MRI data of real patients, including healthy individuals as well as patients of Parkinson’s disease. Simulations of Transcranial Magnetic Stimulation performed on 22 anatomically different models highlight the differences in induced stimulation. A standard Figure of 8 coil is used with frequency 2.5 kHz, placed 5 mm above the head. We compare cortical stimulation, volume of brain tissue stimulated, specificity, and maximum E-field induced in the brain for models ranging from ages 20 to 60. Results show that stimulation varies drastically between patients of the same age and health status depending upon brain-scalp distance, which is not necessarily a linear progression with age. © 2017 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/). [http://dx.doi.org/10.1063/1.4974981]

INTRODUCTION

Transcranial Magnetic Stimulation (TMS) uses external time-varying magnetic fields to induce electric fields within the brain to downregulate or upregulate targeted brain tissue. Although TMS is currently only FDA approved to treat depression and migraine, it is also a promising treatment for certain symptoms of Parkinson’s disease (PD), Schizophrenia, Obsessive Compulsive disorder, and other neurological conditions.1,2 We use data obtained from the Human Connectome Project (HCP), a study sponsored by the National Institute of Health which gathered a large amount of Magnetic Resonance Images (MRI) from real individuals.3 In previous studies, we have shown Transcranial Magnetic Stimulation induced in models developed using data from the HCP.4 Here, we introduce models of Parkinson’s patients created using data obtained from the Parkinson’s Progression Marker’s Initiative (PPMI), a project which collected MRI images of patients with Parkinson’s disease.5 We created head models of PPMI patients with the goal of comparing effects of TMS on healthy individuals and those with Parkinson’s disease. It is well known that the structure of the brain in Parkinson’s patients can vary drastically, depending on disease progression, due to lesions which form on white matter surface.6,7 Furthermore, it is well known that brain volume generally decreases with age as the brain shrinks, but this fact is variable with genetics and lifestyle.8 We
assert that these structural differences may influence the stimulation of the brain during TMS. To study these effects and draw relationships between brain structure and stimulation effects, we compare results of TMS simulations on models of healthy individuals (henceforth referred to as HCP models) and Parkinson’s patients (PPMI models) of varying ages. We also include the highly heterogeneous models known as Duke and Ella, developed by the IT’IS Foundation using MRI data of healthy individuals. We compute maximum E-field ($E_{\text{max}}$) induced in the brain as well as total volume and surface of the brain which receives stimulation as well as the specificity of the induced E-field. We compare these effects for patients of varying ages and discuss the implications for brain stimulation.

**SETUP AND CALCULATIONS**

Simulations include commercial TMS Figure-of-8 coil run using current of 5000 Amps at a frequency of 2.5 kHz. The TMS coils are situated 5 mm above the surface of the head in each case, as shown in Figure 1. To find optimum power required to stimulate each patient’s brain tissue, clinicians find the motor cortex area of the brain and induce enough stimulation to obtain a visible motor reaction (twitching of the hand), and this is called the motor threshold (MT). 120% of MT is then used as the stimulation parameter in the targeted region of the brain. To mimic clinical TMS, we define our stimulation threshold as half of the maximum E-field induced in a particular model, which is close to MT for a healthy individual. Because $E_{\text{max}}$ in each model varies, we also define an absolute stimulation threshold of 50 V/m for purposes of comparison. Then, we analyze the amount of brain volume stimulated, surface stimulated, and specificity, a measure of how focused the E-field diffusion is in the brain tissue. We compute specificity by dividing volume stimulated by surface stimulated. We show the results of both nominal stimulation, which varies for each model, as well as stimulation above the absolute threshold of 50 V/m, for purposes of clarity and comparison. Surface stimulation and specificity do not include the Duke and Ella models due to IT’IS licensing restrictions. Biot-Savart Law and Maxwell’s equations are used to calculate H-field, B-field, and E-field induced in the tissues, similar to our previous publications.9–11

**RESULTS AND DISCUSSION**

Figure 2 shows electric field induced in two HCP models and two PPMI models. We compare the induced electric field by analyzing the number of cells which receive stimulation above the given
threshold, both throughout the brain (volume stimulated), and on the surface of the grey matter (surface stimulated). Stimulation threshold is first taken as $E_{\text{max}}/2$ and then as 50 V/m, for separate comparisons.

A significant cause of stimulation variability is the distance between the brain and the scalp, which increases with age. It is unclear how Parkinson’s disease affects this process, as it is possible that the disease may cause structural differences in brain tissue. Figure 3 shows how the brain-scalp distance varies with age in our models. The trend is much clearer with the younger healthy individuals than for Parkinson’s patients. For this reason, we will compare all parameters using brain-scalp distance, rather than age, as the independent variable. Figure 4 shows the maximum E-field values induced in all models as brain-scalp distance varies. It is clear that in general, as the brain-scalp distance increases, a lower maximum E-field value is induced in the brain tissue, in both HCP and PPMI models. Because $E_{\text{max}}$ varies for each model, and our stimulation threshold is generally dependent on $E_{\text{max}}$, it is important to also choose an unconditional threshold to decipher any trends between stimulation and brain-scalp distance. We take this absolute threshold as 50 V/m, because each model receives at least that value of stimulation. When this absolute threshold is used, we use the phrase “absolute stimulation”. Figure 5 shows volume and surface stimulation in each model as a function of brain-scalp distance. Relationships are much more obvious in the plots utilizing the absolute threshold of 50 V/m. It is shown that as the brain-scalp distance increases, volume stimulation and surface stimulation both decrease, which is intuitive given that the magnetic field decays as $1/r^3$, and any increase in the distance between the brain and the coil would reduce the induced E-field significantly. Furthermore, we calculate specificity (volume stimulated divided by surface stimulated) as a function of distance (Fig 6(a)), as well as a function of $E_{\text{max}}$. 

![FIG. 2. Two models demonstrating orientation of TMS coils.](image)

![FIG. 3. Brain-Scalp Distance as a function of age, with blue data points representing healthy individuals and red data points indicating Parkinson’s patients.](image)
Specificity as a function of distance does not show much of a trend, once again due to the variability of $E_{\text{max}}$ in each model. For this reason, then, we consider specificity as a function of $E_{\text{max}}$, and discover a clear monotonically increasing relationship which seems to differ between HCP and PPMI models. Models with high maximum E-field values also receive higher specificity of stimulation.

FIG. 4. Maximum E-field values induced in each model as a function of brain-scalp distance.

FIG. 5. Volume of brain tissue and grey matter surface stimulated as a function of brain-scalp distance. 5a and 5b show volume stimulated, 5c and 5d show surface stimulated.
CONCLUSION

While the volume, surface, and specificity vary drastically with between models, we are able to discern clear trends when we observe these same parameters using the constant stimulation threshold of 50 V/m. While general trends have been observed in the past between the patient’s age and brain-scalp distance, these trends can differ drastically between healthy individuals and Parkinson’s patients. In PPMI models, the variability in brain-scalp distance was much greater than in the HCP models. This may be due to the disease or to age, both of which can alter brain structure. Furthermore, maximum induced E-field can vary between patients of the same age. As $E_{\text{max}}$ increases, the specificity is monotonically increasing for both HCP and PPMI models. From these data, it is clear that stimulation effects can vary drastically between patients of similar age and health status. The causes for this discrepancy may be numerous, but we can infer from our results that stimulation effects are more far more dependent upon brain-scalp distance than upon age and health. This implies that in order to accurately determine TMS parameters for a particular patient, it is crucial to determine the brain-scalp distance using MRI.

ACKNOWLEDGMENTS

Data were provided [in part] by the Human Connectome Project, WU-Minn Consortium funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University, and from the Parkinson’s Progression Marker’s Initiative (PPMI) database (www.ppmi-info.org/data). We are grateful to Gabrielle Briana Marie Jones for helpful comments.

Computational analysis of transcranial magnetic stimulation in the presence of deep brain stimulation probes

F. Syeda,1 K. Holloway,2 A. A. El-Gendy1 and R. L. Hadimani1,a
1Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, Virginia 23284, USA
2Department of Neurosurgery, School of Medicine, Virginia Commonwealth University, Richmond, Virginia 23284, USA

(Presented 1 November 2016; received 19 September 2016; accepted 26 October 2016; published online 11 January 2017)

Transcranial Magnetic Stimulation is an emerging non-invasive treatment for depression, Parkinson’s disease, and a variety of other neurological disorders. Many Parkinson’s patients receive the treatment known as Deep Brain Stimulation, but often require additional therapy for speech and swallowing impairment. Transcranial Magnetic Stimulation has been explored as a possible treatment by stimulating the mouth motor area of the brain. We have calculated induced electric field, magnetic field, and temperature distributions in the brain using finite element analysis and anatomically realistic heterogeneous head models fitted with Deep Brain Stimulation leads. A Figure of 8 coil, current of 5000 A, and frequency of 2.5 kHz are used as simulation parameters. Results suggest that Deep Brain Stimulation leads cause surrounding tissues to experience slightly increased E-field ($\Delta E_{\text{max}} = 30 \text{ V/m}$), but not exceeding the nominal values induced in brain tissue by Transcranial Magnetic Stimulation without leads (215 V/m). The maximum temperature in the brain tissues surrounding leads did not change significantly from the normal human body temperature of 37 °C. Therefore, we ascertain that Transcranial Magnetic Stimulation in the mouth motor area may stimulate brain tissue surrounding Deep Brain Stimulation leads, but will not cause tissue damage. © 2017 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/). [http://dx.doi.org/10.1063/1.4974062]

INTRODUCTION

Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique which utilizes external time-varying magnetic fields to induce electric fields within the conductive tissues of the brain, thus downregulating or upregulating targeted regions. TMS is currently FDA-approved for treatment of depression, but shows promise for treating Parkinson’s disease (PD), Schizophrenia, Obsessive Compulsive disorder, and a variety of other neurological conditions.1 A primary concern for clinicians when considering TMS therapy is the risk of tissue damage and seizure from over-stimulation. In addition, for PD and Essential Tremor (ET) patients, a widely used treatment for tremor control is Deep Brain Stimulation (DBS), in which one (unilateral) or two (bilateral) leads are placed inside the brain to deliver current directly to the globus pallidus internus (GPi) or subthalamic nucleus (STN).2,3 These leads are comprised of four electrodes, insulating material, and a wire running through the center of the lead body. DBS is a reliable and successful treatment for controlling tremor; however, PD patients often suffer from other symptoms, such as difficulty with speech and swallowing, which are caused by dysfunction in the mouth motor area of the brain, which is not accessible to DBS leads.4,5

1rhadimani@vcu.edu
In these cases, supplementary TMS treatment to the mouth motor area can be a significant benefit to the patient’s quality of life. It has been unclear in the past, however, whether the E-field induced from TMS would stimulate GPi and STN due to the conductive material within the lead. DBS provides sufficient stimulation to these regions, therefore additional stimulation from TMS may be hazardous to the patient’s health. Therefore stimulation in tissues surrounding DBS lead in the presence of TMS must be considered. Limited work has been done to study these effects, with results indicating that tissue damage may occur.\textsuperscript{6,7} However, we posit that the models used in these studies did not possess the complexity needed to replicate the human brain, and that simulation with a heterogeneous head model with accurate parameters may give dissimilar results. We use Sim4Life, a finite element analysis software developed by Zurich MedTech, to perform such simulations. Additionally, while various coil shapes and designs have been proposed in the past for increased focality and optimization, we use a model of the commercial, FDA-approved Figure-of-8 coil to simulate a more realistic scenario.\textsuperscript{8}

**SETUP**

Protocol for the desired results requires accurate, anatomically realistic head models and quasi-static solvers suitable for low frequency stimulation parameters. This study used the “Duke” model, which has been developed by Zurich MedTech from MRI data of a real patient. This model includes full heterogeneity, including a variety of brain tissues such as grey matter, white matter, cerebrospinal fluid, and thalamus, with best estimates of density, conductivity, and permittivity parameters obtained by Zurich MedTech.\textsuperscript{5} A frequency of 2500 Hz was used for a Figure-of-8 coil, which was operated at currents ranging from 1000 to 5000 Amps and situated near the mouth motor area of the brain. A Deep Brain Stimulation probe model was developed and simulated as “off”, with no current running through the lead. Figure 1 shows a visualization of the setup and a comparison of the full and simplified probe models.

![Figure 1](image-url)

FIG. 1. (a) Figure-of-8 coil positioned 5 mm away from model’s head, by mouth motor area. (b) DBS probe visibly propagating through grey matter. (c) Full probe model with insulators (blue) and conductors (pink). (d) Simplified probe model in which conductors and insulators are placed further apart for simulation ease. (e) Wire and wire insulation (green), which is included in both full and simple probe models.
simplified DBS probe models. We model conductors in the probe as Perfect Electrical Conductors in E&M simulations and as pure platinum in thermal simulations.

**CALCULATIONS**

Vector Potential, decoupled from the E-field, is calculated using the Biot-Savart Law, and Maxwell’s equations are used to calculate H-field, B-field, and E-field induced in the tissues similar to our previous publications.\(^8\)\textsuperscript{--}\textsuperscript{10} Previous work has cited charge density as a means of determining the occurrence of tissue damage.\(^6\) However, current density is generally computed using time and pulse durations. Our electromagnetic simulation is quasi-static, and we do not use discrete pulses but rather a continuous source of current. Therefore, rather than using current density, we will instead consider tissue damage as a function of heat.

We use the Transient Thermal Simulation allows to compute time-varying temperature distribution in tissue. This solver uses the Pennes Bio-Heat Equation, finds heat generation and heat transfer in the time domain. Table I gives our referenced thermal values for probe materials.\(^7\)\textsuperscript{,}\textsuperscript{11}\textsuperscript{,}\textsuperscript{12}

**RESULTS AND DISCUSSION**

We compute magnetic field, induced electric field and temperature in brain tissue surrounding DBS lead to determine if presence of DBS lead will cause health issues in the patient. Excessive E-field will lead to over-stimulation and consequently adverse effects such as motor contractions, tingling, and mood changes, while excessive heat in brain tissue will cause tissue damage. Figure 2 shows major results from simulations run using 5000 Amps. Increased E-field and temperature can be observed in mouth motor area due to placement of the Figure-of-8 TMS coil. We position the DBS lead along the z-axis, from cortex to basal ganglia, as is the case for patients with PD. Figure 2c shows a sagittal slice in close proximity to DBS lead, and stimulation in tissues surrounding DBS lead can be observed. E-field and time-varying temperature have been calculated and shown in Figures 3 and 4. Note that in Figure 3, the maximum E-field induced in brain tissue is a linear function of the current value in the coils. While the presence of DBS lead increased E-field induced by TMS in the surrounding tissue, the values were smaller than the E-field induced in the mouth motor region of the brain. Therefore, in our simulations the presence of DBS lead does not cause excessive stimulation in surrounding tissue. Additionally, because PD patients receive electrical stimulation in the basal ganglia from DBS, clinicians must be certain that no additional stimulation is provided to basal ganglia area from TMS. Figure 3 shows that the E-field induced in basal ganglia tissue of the model is too low to cause stimulation. Finally, Figure 4 shows time-varying temperature distribution in brain tissue. We first allowed the brain model 5000 seconds to reach steady-state, then applied TMS from 5000 seconds to 6000 seconds, and finally we allowed a second rest period to observe heat diffusion. Total simulation time was 10000 seconds. Maximum temperature in the model’s brain in all cases remained below 37.35 °C. Because the overall typical body temperature is 37 °C, this variation can be considered negligible, especially when considering heat diffusion in the body over time. Furthermore, while tissue surrounding DBS lead can be seen to increase slightly in the presence of TMS, these temperatures remain below 37.15 °C in all cases. Simulations were performed on the model of a healthy patient with normal vasculature and blood flow; therefore, the effect of decreased vasculature and blood flow is not shown here.
FIG. 2. (a), (b) Induced E-field on grey matter surface; scale: 0 – 213 V/m. (c) E-field through coronal slice; scale: 0 – 50 V/m. (d) Temperature of grey matter surface at 5900 sec; scale: 37 – 37.4 °C.

FIG. 3. Maximum values for E-field in motor mouth (MM) area, brain tissue surrounding DBS lead, and tissue in basal ganglia (BG) area for various current values.
CONCLUSION

In the recent past, studies have analyzed, either computationally or using simple physical models, the effect of TMS on brain tissue. However, very few of these studies have replicated the presence of Deep Brain Stimulation (DBS) leads in a brain which receives TMS treatment. Those that have done so have used simple spherical head models and non-commercial circular coil shapes. We use a complex, heterogeneous, anatomically correct head model with a commercial double coil design, as well as a DBS lead modeled using standard, commercial-grade DBS leads. We use the Finite Element Analysis software, Sim4Life, to solve highly refined grids for electric field and time-varying temperature distribution in brain tissue. Analysis of these simulations suggest that while the presence of DBS leads may slightly increase the induced electric field in surrounding tissues, no overstimulation or overheating occurs. Therefore, our computations indicate that while DBS is switched off, Parkinson’s patients may safely receive TMS treatment in the motor mouth area for treating speech and swallowing impairment.

ACKNOWLEDGMENTS

We are grateful to Dr. Deepak Kumbhare for helpful comments.

Computational Safety Study of Combination Treatment: Deep Brain Stimulation and Transcranial Magnetic Stimulation

F. Syeda, Student Member, IEEE, C. A. Serrate, H. Magsood, Student Member, IEEE, K. Holloway, R. L. Hadimani, Senior Member, IEEE

Abstract—Patients with advanced Parkinson’s Disease often receive deep brain stimulation treatment, in which conductive leads are surgically implanted in the brain. While DBS treats tremor and rigidity, patients often continue to suffer from speech and swallowing impairments, which involve cortical regions of the brain. Because DBS is unable to treat these symptoms, the addition of transcranial magnetic stimulation may be beneficial. However, the potential electromagnetic interactions of the strong magnetic fields from TMS on the conductive leads is unknown. Objectives: To calculate induced current in DBS lead due to magnetic fields from TMS. Methods: We have created a novel complex 3D model of a deep brain stimulation lead, along with 10 heterogeneous, anatomically accurate head models of Parkinson’s patients and one healthy control. We used Finite Element Analysis to perform simulations of Transcranial Magnetic Stimulation of these 11 models with the complex lead implanted in the brain. Results: Simulations show that transcranial magnetic stimulation will induce current values lower than normal DBS stimulation current. Thermal analysis shows that there is a maximum increase of 0.25°C after 30 minutes of stimulation at motor threshold stimulation strengths. Conclusion: Our computational simulations using complex models and clinical settings suggest that combination TMS/DBS treatment will not cause over-stimulation in the brain. Significance: The potential combination of TMS and DBS for patients of Parkinson’s disease will not cause over-stimulation in the deep brain nuclei, and so may be safe for combination use. Physical phantom trials are necessary to validate the computational simulations.

I. INTRODUCTION

Patients of Parkinson’s Disease (PD) suffer from debilitating symptoms and complications, including bradykinesia, resting tremor, shuffling gait, and rigidity as well as non-motor symptoms including speech and swallowing difficulties. Although the symptoms initially respond to Levodopa, a dopaminergic medication, symptoms can often become refractory, or side effects can cause additional symptoms. In these cases, physicians recommend deep brain stimulation (DBS) surgery, in which one or two electrical leads are inserted into the subthalamic nucleus (STN) or globus pallidus internus (GPI), and current is continuously delivered to these nuclei from a battery pack inserted into a chest pocket. DBS has been shown to effectively eliminate motor symptoms in patients of both PD as well as Essential Tremor. However, one of the more crippling symptoms of PD that is not treated by DBS is hypophonic speech and swallowing difficulty (dysphagia). Not surprisingly, hypophonia and dysphagia can seriously deteriorate quality of life and cause complications such as weight loss, isolation and depression. Importantly, these symptoms typically present well after the other motor symptoms have become problematic, thus most patients with speech and swallowing symptoms will have received DBS by the time of onset. The mouth motor area of the primary motor cortex is thought to play a role in the pathophysiology of these symptoms, and manipulation of this cortex through repetitive Transcranial Magnetic Stimulation (rTMS) has been proposed as a treatment option. rTMS is a non-invasive neuromodulation therapy which utilizes time-varying magnetic fields to induce electric fields in the patient’s brain, thus stimulating neurons in the targeted region. However, the potential for electromagnetic interference from the magnetic fields of rTMS with the conductive leads of DBS has prevented serious consideration of the combination therapy. Primarily, there is concern regarding eddy currents, which are induced on conductive surfaces caused by time-varying magnetic fields. It is hypothesized that B-fields from rTMS may induce such currents on the surface of any conductive part of the lead, and this current would travel along the lead down to the contacts, in turn stimulating the deep brain nuclei which the contacts target. We posit that this issue has yet to be studied with accurate models and parameters. In the past, studies have considered the implications of combining DBS with TMS, but we argue that these studies are quite limited. Some have underestimated and oversimplified the geometrical complexities of the lead and biological tissue. Other studies have not used clinical parameters of rTMS (current frequency, motor threshold) or considered induced current due to TMS B-fields on the conductive parts of the DBS lead. In addition, we are not aware of any studies as of yet which have used the heterogeneous head models to study the effects of TMS on full, implanted DBS leads. These studies present mixed results, with a variety of stimulation methods and scenarios. Here, we present our calculations for a very specific situation – TMS performed on the Mouth Motor Cortex with ipsilateral medially inserted
DBS lead. A brief literature review outlining differences between these publications and our present work, including general methods and findings, is presented in Table 1.

We have previously studied the effects of TMS on a conductive cylinder and individual lead contacts in deep brain regions. We focused on the E-field induced in the brain tissues surrounding the conductive probe and found that although there was some slight increase in E-field in the tissues surrounding the lead, E-field values did not come close to the stimulation threshold.[31] However, that study did not include the geometrical complexities of DBS wires within the lead; these model details would enable a more comprehensive study of TMS-induced current inside the lead body. While E-field at the contact locations may not have reached stimulation threshold, it is crucial to determine the current induced in the conductive wires, as this current would potentially lead to deep brain stimulation. In this study we introduce a complex DBS lead model implanted into newly-created anatomically accurate heterogeneous head models of PD patients. We utilized a TMS coil model, based on the FDA-approved coil, to explore the interference of TMS B-fields on the DBS lead wire. Because we have in the past studied E-field induced in the brain due to implanted conductive materials, in this study we have focused only on calculating the induced current in the lead wire, as well as subsequent temperature variation in the brain tissues.

### A. Deep Brain Stimulation

DBS leads are comprised of four electrodes which lie at the site of stimulation, with four separate wires capable of delivering current to each contact. Each wire is wrapped in insulation so as to avoid interference with the other wires, and there is further insulation that comprises the entirety of the probe body. We based our DBS lead model on the commercial Medtronic 3387 lead used across the board in DBS surgeries. [32] Another issue that needs to be addressed is the temperature variation along the lead and surrounding the tissues when rTMS is administered for durations such as those used in clinical settings. Earlier studies have reported thermal analysis in simple spherical phantoms that use brine solution to represent conductivity of the grey and white matter.[2] Here, we report analysis of thermal simulations using anatomically accurate models of PD patients with inserted DBS lead.

### TABLE I

<table>
<thead>
<tr>
<th>Publication</th>
<th>Methods</th>
<th>Current Induced in DBS Leads</th>
<th>Results/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et. al. 1999 [1]</td>
<td>Homogeneous phantom head model. TMS at 100% intensity performed 1 cm above leads. Voltage measured between contacts.</td>
<td>70 - 125 µA</td>
<td>Induced current significantly lower than DBS stimulation.</td>
</tr>
<tr>
<td>Shimojima et. al. 2009 [2]</td>
<td>Homogeneous phantom head model. TMS applied at various locations along head model Impedance used: 1162 Ω</td>
<td>&gt;20 µC/cm²/phase</td>
<td>Charge density too high for stimulation to be safely performed.</td>
</tr>
<tr>
<td>Kuhn et. al. 2011 [3]</td>
<td>TMS at 100% intensity with DBS ON at 4V. Voltage measured between contacts.</td>
<td>0.2 - 2.8 V</td>
<td>Voltage does not exceed DBS stimulation and TMS duration is too short to cause stimulation.</td>
</tr>
<tr>
<td>Deng et. al. 2010 [4]</td>
<td>Created full circuit from contacts to chest IPG. Did not use full DBS lead geometry. 1.2 kΩ resistor with contacts.</td>
<td>Up to 83 mA. If DBS is OFF, current is only possible at V&gt;5V.</td>
<td>Induced current too high for stimulation to be safely performed.</td>
</tr>
<tr>
<td>Kuhn et. al. 2002 [5]</td>
<td>Clinical investigation of 5 patients with bilateral DBS and TMS in the Motor Cortex.</td>
<td>N/A</td>
<td>Contralateral and ipsilateral motor-evoked potentials were induced in 3/5 patients from TMS. No other complications reported.</td>
</tr>
<tr>
<td>Hidding et. al. 2006 [6]</td>
<td>Clinical investigation of 8 Parkinson’s patients with DBS, and mono pulse TMS in the Motor Cortex.</td>
<td>N/A</td>
<td>MEP latencies were significantly shortened, possibly due to current induced from TMS. No other complications reported.</td>
</tr>
</tbody>
</table>

Current work

Computational simulations with full heterogeneous head models and complex DBS lead model. TMS is at mouth motor cortex and medially positioned DBS is OFF.

<2 µA. Induced current lower than DBS stimulation.
B. Transcranial Magnetic Stimulation

rTMS is currently FDA-approved for treatment of drug-resistant Major Depressive disorder, but has shown beneficial effects for symptoms of other neurological conditions.[25][33][34][35] During TMS, alternating current is run through a figure-of-8 coil, which causes a time-varying magnetic field. This B-field then propagates through the patient’s skull and onto the brain cortex, where an electric field is induced and neurons in the targeted cortical region are depolarized.[25][33][36] rTMS in the mouth area of the primary motor cortex may help relieve hypophonia and dysphagia by similarly induced plasticity.[20][21][22] Therefore, we targeted the inferior primary motor cortex in our model, hereafter known as the mouth motor area of the cortex.[37][38]

C. Electromagnetic Issues

Because TMS induces a time-varying magnetic field, it is important to consider the effects of TMS on conductive DBS leads. From Faraday’s law of induction, it is clear that any time-varying magnetic field will induce an electric field on a conductive substance. It is possible that this B-field will induce an E-field and subsequent eddy currents on the conductive surfaces of the lead wires. In this study, we explore factors which mediate the intensity of this current.

II. Computational Models

A. DBS Lead

We have developed a novel, highly complex DBS lead in SolidWorks, using parameters from commercially available Medtronic lead 3387.[32] This model includes the entire lead length coursing over the skull towards the burr hole where it dives deep into the brain parenchyma. It is composed of the insulating sleeve, four independent wires with wire insulation, and 4 contacts at the lead tip. Figure 1 below shows details of the probe model.

![Figure 1](image1.png)

Figure 1. Detailed view of novel lead model. Note the insulating sleeve (red) and separate wires (yellow) ending at each contact (purple).

Generally clinicians use either bipolar configuration or unipolar configuration of DBS. In the bipolar configuration, current is delivered to one contact such that the voltage difference between the contact and its neighboring contact creates a sphere of potential at the stimulation location. In the unipolar configuration, the generator case is the positive and a single contact is negative. [39][40][41] The current induced in either of these configurations, on the order of mA, must be compared against current induced due to TMS B-fields. Therefore, we have simulated these leads in the "OFF" position, with no direct current applied to the leads.

Furthermore, location of the lead tip is typically at similar sites in each patient, at the Globus Pallidus internus (GPi) or Subthalamic Nucleus (STN). However, it is also important to note that the course of the additional lead body lying on the surface of the skull is closest to the TMS coil. Therefore, it is important to consider the distance between the lead and TMS coil, as well as the orientation of the TMS coil, to correctly calculate induced eddy currents on the DBS lead wire. In this study, we have assumed that the surgeon has tunneled the lead directly posteriorly towards the vertex so that the subgaleal lead is relatively medial, while the TMS coils are placed laterally and inferiorly to access the ipsilateral mouth motor cortex. This setup is shown in Figure 2.

![Figure 2](image2.png)

Figure 2. Setup of lead placement on skull surface.

It is important to note that due to excess model complexity, we were unable to create a longer DBS lead model which extends down to the patient’s chest area for connection with a battery pack. However, we posit that this issue will not cause significant changes in terms of electromagnetic calculations, as the maximum induced current in the lead will occur in the brain, closest to TMS coils.

B. Human Models

In the past, computational TMS studies have used simple, homogeneous, spherical models to represent the human head.[28][42] While these studies have been beneficial for understanding general E-field induction in conductive material, we posit that a more heterogeneous and complex model is necessary. In this study, we have used newly-developed head models created using MRI images of real PD patients, downloaded from the online database ADNI PPMI. These models include separate geometries for grey matter, white matter, cerebrospinal fluid, skin, skull, and cerebellum, similar to models developed in our previous reports.[43][44][45]

III. Simulations

We used the Finite Element Analysis software known as Sim4Life, which has been developed by Zurich Medtech.
(www.zurichmedtech.com) for the purposes of simulating the effects of EM fields on biological tissue. Figure 3 shows the simulation setup of a model with the figure-of-8 TMS coil. Note that the coil has been placed with the highest intensity of B-field aimed at the mouth-motor area of the primary motor cortex. We used the same setup for the newly-developed Parkinson’s models and the healthy model.

The coils were modeled after commercial figure-of-8 coil by creating 9 concentric circular coils for each half. Additionally, to model the current directions, the two halves of the coils were given equal amplitude current in opposite directions.

A. Low Frequency Vector Potential Simulation

Eddy currents were analyzed using vector potential calculations. [46] [47] [48] Therefore, the first step in simulating this paradigm in Sim4Life was an Low Frequency (LF) Vector Potential (VP) simulation, which allows for the insertion of conductive materials within the brain tissue. This simulation utilized the figure-of-8 coil as a source, with frequency 2500 Hz. This AC current then induced a time-varying magnetic field, at which point the software calculated induced current on the conductive surface of the DBS lead.

B. Low Frequency Magneto Quasi-Static Simulation

Next, the LF Magneto Quasi-Static simulation was used by sourcing the results of LF VP simulation. The software calculated induced E-field on all biological tissue due to TMS B-fields. Additionally, induced currents from the DBS lead were utilized to find effects on the surrounding tissue.

C. Thermal Analysis

Finally, we used Sim4Life’s Thermal Simulation to find heating effects in the brain tissue. Sim4Life uses the well-established Pennes Bio-heat equation, shown below, to calculate temperature variation due to electric fields and cooling rate due to blood perfusion. [49] [50] [51]

\[
\rho c \frac{\partial T}{\partial t} = \nabla (k \nabla T) + \rho Q + \rho S - \rho_b c_b \rho \omega (T - T_b)
\]

where \( k \) is the thermal conductivity, \( Q \) is the specific metabolic heat generation rate, \( S \) is the specific absorption rate, \( \omega \) is the perfusion rate, and \( \rho \) is the medium density. \( \rho_b \), \( c_b \), and \( T_b \) are the density, specific heat capacity, and temperature of the blood, respectively.

D. Motor Threshold

Clinical rTMS requires the establishment of each patient’s motor threshold (MT), i.e. the stimulation current at which the patient’s motor evoked potential (MEP) is reached. [52] [53] [54] Varying stimulation parameters are required due to each patient’s varying anatomy, such as the brain-scalp distance. [43] [55] [56] Generally, MT is established when the physician uses the TMS coil to target, to best estimation, the hand region of the primary motor cortex, then sweeps through a range of currents until the patient’s thumb visibly twitches. In the case of rTMS for treatment of Major Depressive disorder, the physician will then shift the coils 5 cm anterior, attempting to target the left Dorsolateral Prefrontal Cortex (DLPFC). [57] [58] [59] In our models, MT was established by directly targeting the primary motor cortex and computing the E-field induced on the cortex. Similar to the clinical setting, varying anatomy in our models caused varying MT values across the model population. The current at the primary motor cortex was increased until the well-established threshold of 150 V/m was reached. [60] [61] [62]

E. Simulation Steps

For purposes of consistency, we stimulated each model at its MT value, ensuring that the stimulation value at primary motor cortex was 150 ± 1 V/m across the model population. To do so, we performed a primary simulation without inserting the DBS lead. Once MT was established for the model, we inserted the DBS lead and performed a Vector Potential simulation to compute induced current on DBS lead due to TMS at that particular model’s MT. The results of this simulation were used as input for the EM quasi-static simulation. Finally, the results of the EM simulation were used as input for the thermal simulation.

F. Parkinson’s Patient Models

Due to the lead wire’s conductive nature, current induced on any region of the wire will travel to the lead contacts. For this reason we concerned ourselves with the location of the lead wire with respect to the TMS coils. We targeted each model’s left hemisphere for both DBS and TMS, and placed the DBS lead at a medial location to maintain clinical consistency. All PD models with implanted DBS lead can be seen in Figure 4.
G. Power Analysis

We performed a power analysis to determine the number of patient samples needed with use of the following parameters: power of 0.8, null hypothesis 1 mA, with standard deviation of 0.5, so that the expected hypothesis is that the induced current will be near the level of DBS stimulation. Finally, we used 0.1 as the alternative hypothesis, to represent anything below DBS stimulation current. This power analysis gave a required sample size of \( n = 5 \) models. In our study, combination DBS/TMS treatment was simulated for 10 PD models and 1 healthy control model. These additional models gave us a power of 0.999.

H. Coil Orientations

Finally, we staged various scenarios in which the TMS coils were positioned at various orientations with respect to the lead. The reasoning for these additional simulations was that if in all cases the induced current values were also on par with DBS stimulation current, then results would suggest that combination TMS/DBS therapy is not safe for any setup. These orientations are shown in Figure 5.

IV. RESULTS AND DISCUSSION

After performing TMS on the mouth area of the primary motor cortex for all models, and subsequently finding Motor Threshold, we inserted the DBS lead model and performed a second simulation at MT. Importantly, it is the induced current, rather than the E-field, which propagates through the lead body and out to the tissue. Hence, we focused on induced current in the lead wire. Sim4Life can also calculate induced current density on all surfaces, and we deduced the total current value by multiplying current density in the wire (\( A/m^2 \)) by the wire’s cross-section, using 0.05 mm as the wire radius.

It is important to note that we were not able to directly compare either induced E-field or current density between the lead and cortex. Due to complex geometries of the lead model, Sim4Life could not accurately calculate E-field on the lead body without discontinuities. On the other hand, calculated current density on the cortex was meaningless, as Sim4Life uses bulk conductivity value of grey matter for calculations, rather than current induced on neuron bodies, which is the contributing factor for neuron depolarization. Therefore, we compared current induced in the DBS lead wire to current supplied to DBS lead during constant current stimulation, which is typically on the order of mA. [63]

It is important to consider the orientation of the B-field with respect to the DBS lead. Therefore, we tested the effects of placing TMS coils parallel and perpendicularly to the lead body, as well as targeting the second set of conductors which connect the lead wires to the battery pack. After performing simulations and analyzing results, we found that orientation (a) in Figure 5 induced the highest amount of current, most likely due to the parallel nature of the lead wires with the magnetic field; this orientation is similar to an inductive coupling set-up. Additionally, we have two segments of the lead at essentially right angles to each other - the segment targeting the deep brain nuclei, and the segment which lies on the skull. However, it is only the segment with the exposed lead contacts which is clinically significant due to its interaction with TMS at the mouth motor region. A schematic of the magnetic field in this orientation can be found in the appendix. Induced current results can be seen in Figure 6.

Figure 4. 10 PD models with DBS lead inserted in the deep brain region close to the hypothesized area of GPi/STN. Insertion regions differ slightly depending on anatomical differences.

Figure 5. Various TMS coil orientations being tested on healthy model with DBS Lead inserted. (a) and (d) show coil set parallel to intraparenchymal lead. (b) and (e) show coil set perpendicular to lead. (c) and (f) show coil placed close to second set of conductive extensions that connect the lead to the generator.

Figure 6. Current induced in lead wire for 6 orientations shown in Fig. 5. Note that maximum current was induced
The overall goal of this project was to compare any stimulation from TMS-induced current in the lead with DBS stimulation parameters. To account for the worst-case scenario, we used orientation (a) in Figure 5, which induced the highest current value compared to all other orientations, most likely due to the orientation of the B-field with respect to the DBS wire loops. We used current density calculations from Sim4Life simulations and converted to current in the cross section of the lead wire by multiplying by \( \pi r^2 \), with \( r = 0.05 \text{mm} \). These calculations equaled the maximum current induced at any point in the DBS wires and into the lead conductors. Calculated current values for all models can be seen in Figure 7. Note that for all models, the current values are on the order of \( \mu \text{A} \), orders of magnitude below the constant current values used for DBS (mA). For this reason, it is clear that our simulations show that for a DBS lead positioned medially in the patient’s head, TMS in the mouth area of the primary motor cortex will not cause over-stimulation.

Finally, thermal simulations were performed for \( t > 30 \text{ min} \), with TMS in the “on” state from \( t = 20 \) to \( 50 \text{ min} \). Initialization time of 20 min was given to bring all tissue to their respective initial conditions, which placed various parts of the brain between 37 and 37.3° C. TMS was then switched on, and left on for 30 minutes, until \( t = 50 \text{ min} \). Cooldown was then observed. The results show that although there is slight increase in temperature in the tissue close to TMS coils \( (T_{\text{max}} = 37.45° \text{ C}) \) as well as the DBS lead \( (T_{\text{max}} = 37.3° \text{ C}) \), maximum temperature does not exceed 37.45° C in any part of the brain, which is a negligible increase in temperature. Temperature variation over time on the gray matter surface can be seen in Figure 8.

Finally, thermal simulations were performed for \( t > 30 \text{ min} \), with TMS in the “on” state from \( t = 20 \) to \( 50 \text{ min} \). Initialization time of 20 min was given to bring all tissue to their respective initial conditions, which placed various parts of the brain between 37 and 37.3° C. TMS was then switched on, and left on for 30 minutes, until \( t = 50 \text{ min} \). Cooldown was then observed. The results show that although there is slight increase in temperature in the tissue close to TMS coils \( (T_{\text{max}} = 37.45° \text{ C}) \) as well as the DBS lead \( (T_{\text{max}} = 37.3° \text{ C}) \), maximum temperature does not exceed 37.45° C in any part of the brain, which is a negligible increase in temperature. Temperature variation over time on the gray matter surface can be seen in Figure 8.

Thus, our simulations found that while performing TMS in the presence of DBS leads, there is no significant temperature
increase in any part of the brain.

We believe that our simulations show a distinct lack of over-stimulation due primarily to the scenario presented. Because we model DBS leads placed medially in the brain, and TMS performed at the inferior motor cortex, there is significant distance between the TMS coils and DBS leads, particularly at the orientation which causes highest induced current. Additionally, we use heterogeneous, highly accurate head models, which have not been used in the past, as well as clinical TMS parameters and a full DBS lead model complete with wire insulation. It is important to note that while our simulations show low induced current, they are only relevant for the particular patient scenario presented in this work.

V. Conclusion

We have developed a complex Deep Brain Stimulation lead model with all conductive parts, wires, and insulating body included. We inserted this model into 10 newly-developed heterogeneous, anatomically accurate head models of Parkinson’s patients as well as one healthy control model. Using Finite Element Analysis with a model of FDA-approved TMS coil, we performed simulations of TMS at the inferior motor cortex on brain models which have DBS lead inserted medially in the brain. We then calculated induced currents on DBS wires due to time-varying B-field from TMS. To account for anatomical variability across patient populations, differences in DBS lead placement, and variability of TMS treatments, we tested multiple coil orientations. We found that for all models and coil orientations tested, induced current in the DBS lead was in all cases orders of magnitude below clinical stimulation current parameters (mA). This induced current will not cause deviations from the patient’s normal clinical TMS parameters and a full DBS lead model complete for the particular patient scenario presented in this work.

VI. Acknowledgments

We are thankful to Dr. Deepak Kumbhare for helpful comments and consultation.

VII. References

References

Effect of Transcranial Magnetic Stimulation on Demyelinated Neuron Populations

F. Syeda, Student Member, IEEE, A. Pandurangi, A. A. El-Gendy, Member IEEE, R. L. Hadimani, Senior Member, IEEE

Abstract—Transcranial Magnetic Stimulation is non-invasive neuromodulation therapy which uses time-varying magnetic fields to induce electric fields within the patient’s brain, thus allowing for neural stimulation of the targeted region. While past studies have used Finite Element Analysis to model the effects of stimulation in brain tissue, there have been limited studies which analyze the effects of the same stimulation on the neuron responses. We use a python package called NEST to model populations of neurons which are healthy as well as those that have diminished or absent myelin sheath. We model diminished myelin sheath by increasing the capacitance of the neuron. We study the effects of Transcranial Magnetic Stimulation on the synaptic activity of these populations by utilizing clinical parameters specific to Transcranial Magnetic Stimulation. Furthermore, we compare our results to models of brain tissue stimulation using the Finite Element Analysis software Sim4Life. Our results indicate that all neuron populations, regardless of their myelination state, retain some stimulation threshold which increases discretely as the myelin sheath diminishes. Using tissue analysis, we also computed the range of TMS current necessary to reach these stimulation thresholds for demyelinated populations. Furthermore, we find that the maximum induced E-field on the cortical surface does not exceed 220 V/m for stimulation of highly demyelinated neuron populations. Therefore our study finds that although demyelinated neurons exhibit much lower synaptic activity than healthy neurons, they are nevertheless responsive to Transcranial Magnetic Stimulation, and these stimulation thresholds can be reached without inducing an unsafe maximum E-field on the cortex.

Index Terms—Transcranial Magnetic Stimulation, Neuron Modeling, Brain Stimulation, Neuron Demyelination

I. INTRODUCTION

TRANSCRANIAL Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique which is currently FDA-approved for treatment of major depression. TMS also shows beneficial effects for treatment of additional disorders of the brain, such as Alzheimer’s and Parkinson’s disease, but further research is required to fully understand its effects.[1][2] During TMS, a coil is placed near the surface of the patient’s head. An AC current flows through the coil, and a subsequent time-varying magnetic field is induced, which then propagates through the head and onto the surface of the brain. This B-field in turn induces an electric field in the conductive parts of the brain, which serves to excite neurons in the targeted area of the cortex. The particular location of this targeted region can vary depending upon the particular disorder being treated. While TMS is currently FDA-approved for limited usage, it is believed within the field that further research will enable clinicians to utilize TMS for treatment of a wide variety of neurological conditions. In the recent past, studies have shown the effects of TMS on brain tissue using simulations in Finite Element Analysis software and heterogeneous head models developed from MRI images of real patients [3],[4],[5],[6]. These studies have improved the understanding of TMS on the brain with respect to safety, with regards to overstimulation or overheating in the brain. However, the mechanism behind TMS in the stimulation of the neurons, is little understood, despite its wide clinical use. While there have been groups who have modeled neurons in the past, there have been no studies that we are aware of which compute activity in neuron populations during Transcranial Magnetic Stimulation. We posit that a study of the neuronal activity during TMS would be beneficial to the basic understanding of brain stimulation.

One of the wide variety of physiological issues that can cause neurological disorders is demyelination of neurons. The myelin sheath in healthy neurons encloses the neuron shaft and aids in the propagation of electrical signals through the neuron body. Presence of myelin increases the voltage difference between the two ends of the long neuron body, thus allowing the electrical signal to jump across. When the myelin sheath begins to disintegrate, as is the case in Multiple Sclerosis (MS), Guillain-Barré Syndrome (GBS), and a number of other diseases, the neuron capacitance increases, thus slowing down the signal propagation. With enough myelin disintegration, the signal is unable to pass on to the adjacent neuron.[7] This structure is shown in Figure 1.[8][9]

In this study, we use a python-based neuron modeling software package called NEST to model neuron populations and study the effect of direct active stimulation on healthy and demyelinated neurons. Because TMS is performed on the cerebral cortex, we use parameters from past literature corresponding to cortical neurons in order to correlate induced E-field and current on the neuron. [10]–[14] We then compare this data to analysis of tissue stimulation using the Finite
Element Analysis software called Sim4Life, which has been used in past literature.

II. MODELING AND SIMULATIONS

In NEST[15] all default settings for modeling simple, healthy neurons were utilized, then capacitance was gradually increased to model demyelination. As a first step, we simulated a single neuron with nominal incoming noise modeled by a Poisson (random noise) generator, which is commonly used to model normal neural activity.[16] Figure 2 shows the activity of a single healthy neuron in the presence of this Poisson noise.

![Neuron structure (left) and disintegration of myelin (right) [7, 8].](image1)

Figure 1: Neuron structure (left) and disintegration of myelin (right) [7, 8].

For modeling of TMS in NEST, we used stimulation current frequency of 2500 Hz and pulse width of 0.4 milliseconds for a total of 10 pulses per second. Note that the current frequency of 2500 Hz differs from the pulse frequency of 10 pulses/second. These parameters correlate to both past TMS models for brain tissue, as well as clinical constraints.[3] We model populations of 10,000 neurons, stimulating for a total of 10 pulses, or 1 second. Lastly, to account for demyelination, we gradually increase the neuron capacitance from its nominal value of 250 pF until the non-stimulated synaptic activity had decreased to less than 0.01%, which we consider to be demyelinated, at 290 pF.

![Calculated E-field values required to induce varying levels of current on cortical white matter.](image2)

Figure 3: Calculated E-field values required to induce varying levels of current on cortical white matter.

Note that the resting potential of neurons is -70 mV, and only after reaching a potential of -55 mV does the neuron fire, i.e., the voltage immediately drops back to its resting potential. Furthermore, in MS, it is mainly axons in the cortical region (near the surface of the brain) that undergo demyelination, therefore we will be focusing on the electric and magnetic field properties at the cortical region of the brain.[17]

Electrical modeling of neurons can be quite variable as resistance values and axon sizes can significantly differ between neurons, thus significantly altering the current induced in the neuron membrane. For this study we use typical values of cortical neuron electrophysiology found in literature: diameter 1 µm, axon length 10 mm, and resistance 32 Ω.[10]–[12] Utilizing these values, we calculated the E-field required to induce varying amounts of current in the axons. For additional calculations, we utilize a Finite Element Analysis software, Sim4Life, which is commonly used to calculate electric and magnetic fields in human tissue.[3], [4]. We utilize Sim4Life to find correlations between E-field induced on the cortical white matter (axonal) surface and B-field on the surface of the TMS coil. These calculations are presented in Figure 3.

![The Duke model (left) and images of grey and white matter (right).](image3)

Figure 4: The Duke model (left) and images of grey and white matter (right).
The FEA software Sim4Life has been developed by Zurich MedTech for analysis of field profiles in biological tissue in the presence of electric and magnetic fields. Past studies have used Sim4Life to analyze the effects of TMS on brain tissues using heterogeneous and anatomically accurate head models.\[3\], \[4\] Zurich MedTech has developed and licensed these models using MRI data from real patients. We utilize Sim4Life and the model known as Duke, shown in Figure 4, and compare the results of the neuron model to the field profiles present in brain tissue.

### III. RESULTS AND DISCUSSION

After simulating TMS with the above-mentioned clinical parameters, we find clear spikes in neuronal activity, which represent the stimulation threshold of these populations. To validate the accuracy of our model, we can compare the stimulation threshold of the healthy population to the established stimulation threshold of 150 V/m.\[4\], \[18\] Figure 4 shows that by using the stated axonal parameters, our healthy neuron population displays a spike in activity at 40,000 pA. Figure 3 correlates this current value to an induced E-field on the white matter surface of around 130 V/m, which validates the relative accuracy of this neuron model.

We then gradually increase the capacitance of the neuron population, from 250 pF to 290 pF, at which point the activity decreases to a total of 1 impulse per second, from the original value of ~85,000 total impulses per second for the population of 10,000 neurons.

It is clear from Figure 5 that marginally demyelinated neuron populations (255-265 pF) retain the same stimulation threshold as that of the healthy population at around 40,000 pA. However, at 270 pF, a higher stimulation threshold of 50,000 pA is required, and for highly demyelinated neuron populations, those with capacitance greater than 280 pF, stimulation current of 60,000 pA is required, with overlapping data points for 285 pF and 290 pF.

The neural activity shown in Figure 5 is a suitable representation of what is currently known about brain stimulation. As stimulation current is increased, synaptic activity remains constant until the stimulation threshold is reached, at which point there is a clear spike in neural activity. Additional current does not induce any further spikes in activity. This data shows clear stimulation thresholds for healthy and demyelinated populations.

Additionally, the change in number of impulses is closely related to the natural, non-stimulated, firing rate of the neuron populations, which varies with neuron type, but this study does not reach the extent of varying natural firing rates. Therefore, we can safely state that the clear increase in activity represents neuron stimulation, and although this preliminary model is useful for a basic understanding of the subject matter, the exact values of impulses needs further study if we want a more accurate, clinical understanding of the effects of TMS on neuron populations.

![Synaptic Activity During TMS](image-url)

*Figure 5: Number of Impulses observed in each population as a function of increasing stimulation current.*
Next, we utilize Sim4Life to calculate the electric field profiles that are required to reach these threshold current values. The data shown in Fig. 3 establishes that for values of 40,000 pA, 50,000 pA, and 60,000 pA, the required E-field values are 128 V/m, 160 V/m, and 192 V/m. Figure 6 shows the induced E-field on the cortical grey matter (GM) and white matter (WM) surfaces of the model known as Duke.

![Figure 6: Induced E-field on grey matter (left) and white matter (right) for TMS coil current 10,000 Amps, as performed on Duke.](image)

It is important to note that because grey matter surrounds white matter, the induced E-field on grey matter surface is significant to ascertain the safety of these stimulation parameters. Due to the nature of the B-field, very small distances can cause large drops in field strength. For this reason, it is important to calculate the difference in induced E-field between white matter and grey matter. There is a clear variation in induced E-field values between the (surrounding) grey matter and (encased) white matter surface in Figure 7, which shows these calculated E-field values, as well as associated TMS coil current amplitudes.

![Figure 7: Maximum induced E-field values on grey matter (GM) and white matter (WM) cortical surfaces.](image)

It is crucial to note that the horizontal axis in Figure 7 represents the current in the TMS coil rather than the current induced in the neuron population. Due to anatomical variation, the TMS coil currents for nominal stimulation can vary significantly between patients.[4] Thus, the initial current value in Fig 7 is less significant than the current range of 5000 Amps. The data shows that between 134 V/m (~threshold 1) and 161 V/m (~threshold 2) in the white matter, an additional 2000 Amps are needed in the TMS coil. Another 2000 Amps are required to induce an E-field of 188 V/m (~threshold 3) in the white matter.

These values signify the difference in TMS coil current required to stimulate healthy and demyelinated neurons, as shown in Figures 3 and 5. Our data shows that, in the above-stated cases, the maximum E-field on the grey matter cortical surface does not exceed 220 V/m, which is generally considered a safe dosage.

**IV. CONCLUSION**

Transcranial Magnetic Stimulation is a widely-utilized treatment for major depression, and has shown beneficial effects for treatment of other neurological conditions. Although there have been some studies in the recent past calculating E-field in human brain tissue as a result of TMS, the actual mechanism behind neural stimulation is not well-understood. We have developed a simple neuron population model using the python package NEST, and modeled the application of Transcranial Magnetic Stimulation to this population. We looked at healthy neurons as well as those that have undergone mild to severe demyelination as a result of demyelinating disorders such as Multiple Sclerosis. Our study correlated the induced electric field on the cortical white matter surface to the current induced on the axons. We then verified the accuracy of our model by comparing the resultant stimulation threshold in our model to the known stimulation threshold of 150 V/m, and we further found the stimulation thresholds in a variety of demyelinated neuron populations. We found that all populations, including completely demyelinated neurons, retain the ability to fire during TMS, albeit at a higher stimulation threshold. We calculated this threshold for each neuron population and showed correlated induced E-field on brain tissue as well as B-field required on TMS coil. We find that the necessary induced E-field values on the cortex for stimulation of demyelinated neuron populations does not exceed 220 V/m. Therefore, our study indicates that Transcranial Magnetic Stimulation can be applied effectively on demyelinated neuron populations with an increased stimulation threshold, and will result in a dramatic surge in synaptic activity during stimulation.
REFERENCES


A Novel Computational Model to Study the Effects of Non-Invasive Brain Stimulation on the Parkinsonian Motor Pathway

F. Syeda, Student Member, IEEE, D. Kumbhare, M. S. Baron, R. L. Hadimani, Senior Member, IEEE

Abstract—Parkinson’s disease is a motor disorder affecting millions of people. Patients with medication-refractory symptoms often receive deep brain stimulation, a surgical procedure in which current is delivered to deep brain nuclei. It may also be possible to alter neuronal firing in these nuclei by performing non-invasive repetitive transcranial magnetic stimulation, although downstream neuronal effects are difficult to observe experimentally.

Objectives: To create a computational model of the basal ganglia motor pathway and observe downstream neuronal effects of rTMS.

Methods: We modeled healthy nuclei with background noise and connection weights, then simulated parkinsonism by removing dopaminergic input to the striatum. We modeled DBS current delivery to the GPi in a parkinsonian brain. rTMS at various frequencies was simulated at the level of the motor cortex, and we observed predicted downstream firing rate effects and synchrony at GPi.

Results: We have created an accurate basal ganglia motor pathway model, with firing rates and patterns matching those found in literature for both healthy and parkinsonian circuitry. We performed DBS at the GPi and cortical rTMS at various frequencies. Cortical rTMS at 50 pulses/sec led to desynchronous firing rates and patterns at the level of the GPi.

Conclusion: Our simulations suggest that cortical, non-invasive rTMS at 50 pulses/sec may have beneficial downstream desynchronous effects in the deep brain nuclei which closely match those seen in a healthy GPi.

Significance: This computational study suggests that rTMS at certain frequencies may be a viable alternative to DBS surgery for patients with Parkinson’s disease.

I. INTRODUCTION

Parkinson’s disease (PD) affects roughly 10 million people worldwide.[1] Symptoms such as resting tremor, hypokinesia, and rigidity can cause a drastic decrease in quality of life, and in late stages of the disease, PD-related complications can be fatal.[2][3][4] For treatment of medication-resistant motor symptoms, physicians often recommend deep brain stimulation (DBS), an invasive procedure wherein a lead is inserted into either the subthalamic nucleus (STN) or the globus pallidus internus (GPI). Programmable current is provided to these nuclei via the lead, which is connected to a battery pack implanted in the patient’s shoulder/chest area. [5] [6] [7] DBS has been shown to ameliorate tremor, bradykinesia, and rigidity in PD patients, and is also used to treat essential tremor (ET). [5] [7] [8] While this technology has undoubtedly changed lives, the invasive nature and cost of the procedure can invoke major burdens for patients. We posit that if the neuronal circuitry involved in these deficits can be traced, modeled, and simulated, then non-invasive treatments may be explored.

In particular, we are interested in the effects of repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique which is currently FDA-approved for treatment of major depressive disorder (MDD), as well as symptoms of migraine. [9][10][11] TMS uses alternating current in a Figure-of-8 coil to create a time-varying magnetic field. This magnetic field then propagates through the patient’s skull and onto the surface of the brain, where due to the brain tissue’s inherent conductivity, an electric field is induced, and neurons in the targeted region are depolarized. [12] [13] [14]

One major limitation of TMS is that only cortical areas can be directly targeted. Due to the rapidly-decreasing nature of the magnetic field, deeper nuclei are out of reach if safe parameters are upheld. On the other hand, TMS is a completely non-invasive outpatient procedure with the potential to indirectly manipulate deep structures. Currently, MD patients undergo TMS therapy for five days a week, 30 minute sessions for 4-6 weeks. With these parameters TMS has been shown to significantly improve symptoms which were previously medication-resistant.[12] [13] [15]

While TMS is clearly effective in the treatment of some neurological conditions, the exact mechanism by which it works is poorly understood. It is clear that cortical neuron stimulation leads to activation of neurons in deeper regions, but the details of this mechanism are unclear. Single neuron and neural network models have been developed in the past, but as far as we know, none have been created for the purpose of studying the effect of TMS on deep regions of the brain. Here, we introduce a neuron network model using the software package called NEST.[16] This model incorporates the basal ganglia motor pathway which is thought to cause motor symptoms in PD. We created a model of a healthy motor pathway by using background signal and connection data found during in vivo studies.[17] We simulated PD by removing dopaminergic input to the striatum (STR), and the resulting simulated circuitry showed indications of neuropathophysiology matching that which has been seen during in-vivo parkinsonian/dystonic...
humans and monkeys. [17] Next, to observe simulated local and downstream neuronal effects of DBS, we modeled DBS current input to the GPi in a parkinsonian brain. Finally, we modeled current from TMS input to the cortex (CTX) and observed this signal propagation along the basal ganglia motor pathway.

II. BASAL GANGLIA CIRCUITRY AND PD PATHOLOGY

There are three pathways to consider in the modeling of basal ganglia motor circuitry (Figure 1). These are the ‘direct’ pathway, thought to facilitate voluntary movement, and the ‘indirect’ pathway, thought to suppress involuntary movement, and the 'hyperdirect' pathway, which connects the cortex directly to the subthalamic nucleus. [17] [18] The motor pathway contains multiple inhibitory and excitatory connections, and has been modeled and studied in depth. We use these previously developed structural models to develop our own functional computational model with accurate connections.

In the parkinsonian state, dopaminergic neurons present in the SNc are destroyed, significantly limiting dopaminergic input to the striatal dopaminergic D1 and D2 neurons. Following the inhibitory and excitatory connections of the basal ganglia shows that while some signals would be decreased, others increase due to disinhibition, which is caused by suppression of inhibitory signals, thus increasing the signal output. This chain of events leads to a change in GPi output signals, and these too have been recorded experimentally and reported in past literature. [19] [20] [18]

Here, we present a computational open-loop motor pathway model, the structure of which is based on the structural circuitry shown in Figure 1. We study the effects of TMS on parkinsonian pathology using simulations of this model. Our results show that our model is, for the most part in agreement with previous in-vivo studies in its firing and connection weights, as is discussed in detail in the next section. Additionally, we are largely interested in the downstream effects of cortical TMS, and for this purpose, an open-loop model gives good accuracy.

III. NEURON MODELING

NEST has been developed to focus primarily on modeling neuron networks rather than individual neurons with variable morphologies. [16] Hence, we use the simple leaky integrate-and-fire neuron model to explore individual nuclei in the circuitry. Using a single-cell model we can observe the electrical behavior of the neurons. Figure 2 shows a single neuron in NEST, receiving randomly-generated noise as input. This plot shows clearly that the neuron fires only after reaching a membrane potential of -55 mV. Here, the integrate-and-fire neuron model’s voltage simply falls back to resting potential after firing, rather than reaching the maximum voltage value of 40 mV. However, in this study we are interested in the firing patterns rather than voltage potential, therefore this model is effective for our simulations. In order to simulate self-pacing neurons, we additionally add current generators to model background noise for each nucleus.

![Fig. 1. Structural model of healthy basal ganglia motor pathway (left) and parkinsonian pathway (right). Blue lines correspond to excitatory connections while red lines correspond to inhibitory connections. Notice that in the parkinsonian condition with reduced dopaminergic input, thicker lines depict increases in signal propagation and thinner lines depict decreases in signal propagation.](image-url)
Fig. 2. Single neuron response to randomly generated Poisson noise input. Note that in NEST, the integrate-and-fire neuron does not exceed a voltage value higher than -55 mV. Therefore, after firing, the voltage falls back to resting potential rather than reaching the maximum 40 mV as is often seen.

Using NEST, modeling single neurons is relatively simple; it is the connection between populations that becomes complex. The type of connection, or synapse, between two neurons is governed by the neurotransmitter present at the synapse site. Glutamate is one of the neurotransmitters responsible for excitatory synapses, while γ-aminobutyric acid, or GABA, is one of the major inhibitory neurotransmitters. In NEST, and therefore in this computational model, connections are specified as simply excitatory or inhibitory. Additionally, neural networks require synaptic weight inputs to determine the connection strength between two populations. In neural networks developed for machine learning, these weights are “learned” by the program based on some previously-determined output. Similarly, we hard-code synaptic weights between populations based on the nominal values of impulse frequency found in past literature.

### IV. Modeling Parameters

The NEST software requires hard-coded values of synaptic weights, and these weights, along with any background noise introduced to the neurons, directly influence the firing behavior of any given neuron. We found firing rates of each relevant nucleus found in experimental studies, given in Table I. We then found that the optimum number of neurons per nucleus was 800, as less than 800 neurons did not provide enough connections, and more than 800 did not change the response, but did increase computational time. Additionally, we found background noise and connection weights which give output signals closest to those found in the literature. The weights used are those that give accurate output signals.

### TABLE I

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Healthy Firing (Hz)</th>
<th>Parkinsonian/Dystonic Firing (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX</td>
<td>5</td>
<td>N/A</td>
</tr>
<tr>
<td>STR</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>SNc</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>GPe</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>STN</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>GPi</td>
<td>70</td>
<td>90</td>
</tr>
</tbody>
</table>

Once each nucleus was given a background signal, we created the necessary connections between the nuclei in accordance with the motor pathway model shown in Figure 1. We found the following connection weights to be optimum. We also modeled DBS current with frequency 185 Hz, pulse width 0.09 ms, and current amplitude 0.1 mA as per parameters used at the VCU Medical Center as well as those found in literature. TMS-induced current was modeled as with frequency 2500 Hz, pulse frequency varying between 10 and 60 pulses/sec, pulse width 0.4 ms, and current amplitude 40,000 pA. In the past, we have found this parameter to be the most accurate representation of current induced on the neuron body by TMS.

### V. Results and Discussion

Using the above-discussed parameters, we first ran the simulation with healthy circuitry to observe firing rates and patterns. To model Parkinsonian pathology, we simply removed the connection between the dopaminergic input from...
the SNc to STR. The resulting firing output in the GPi was drastically changed for much of the circuitry. Parkinsonian GPi output became highly synchronous and bursty, in contrast to the random asynchronous firing observed in the healthy model.

The transition from asynchronous healthy to bursty PD GPi firing has been observed in experiments from various studies in the past. [19] [20] Thus, this finding helped to validate the connection weights for our model. However, it was still crucial to compare the firing rates of all nuclei in our model to those observed experimentally, as well as to quantify the burstiness and synchrony of our neuronal populations. To observe the average firing rates for each nucleus, we took the total number of impulses recorded for each nucleus and divided by the total number of neurons (800). Although each iteration gave slightly variable firing rates ($\pm 10\%$), the mean for healthy and parkinsonian/dystonic outputs are given in Table IV, along with values from Table I, firing rates found in experimental studies.

We also quantify the population’s synchrony, or the tendency of the neurons to fire simultaneously at any given timestep. We calculate the synchrony $S$ of the system such that if $S = 1$, the populations is completely synchronized, whereas $S = 0$ means complete asynchrony. For a population of $N$ neurons firing in complete synchrony, the firing rate at any given timestep would be either $N$ or $0$. Assume then that the mean firing frequency $\mu = N/2$. Then the minimum signal frequency, $f_{\text{min}} = 0$, while the maximum signal frequency $f_{\text{max}} = N$, and thus the standard deviation $\sigma = N/2$. The range, $f_{\text{max}} - f_{\text{min}} = N$. In this case, then,

$$\frac{2\sigma}{f_{\text{max}} - f_{\text{min}}} = \frac{2(N/2)}{N} = 1$$  \hspace{1cm} (1)

On the other hand, for a completely asynchronous system, we assume $\mu = N/2$. Then, $\sigma$ would approach zero, and therefore,

$$\frac{2\sigma}{f_{\text{max}} - f_{\text{min}}} = 0$$  \hspace{1cm} (2)

In turn, we quantify the system’s synchrony as follows:

$$S = \frac{2\sigma}{f_{\text{max}} - f_{\text{min}}}$$  \hspace{1cm} (3)

with $S = 0$ for complete asynchrony and $S = 1$ for complete synchrony.

It is important to note that while we modeled all nuclei discussed above as part of the motor pathway, we will be discussing results primarily for the GPi nucleus. We model DBS as applied to the GPi as a treatment for PD, therefore we will observe changes in the GPi. Using the above-discussed quantification system, we perform simulations for motor pathways that are healthy, parkinsonian, receiving DBS stimulation, and receiving hypothetical downstream effects of cortical rTMS at various pulse frequencies. We quantify the synchrony of the GPi for each scenario. Table V shows firing rate and synchrony data for the GPi in our model. Note also that for modeling accuracy, we allow the model 0.5 seconds to initialize, then run the simulation for an additional second.

Using our synchrony quantification, it is clear that naturally, a healthy GPi in our model is mostly asynchronous, with $S = 0.08$. The onset of PD, however, heavily synchronizes the neurons, with $S = 0.52$. This is a well-observed phenomenon, which we can now quantify with our model and synchrony calculation. Next, applying DBS directly to the parkinsonian GPi increases the total firing rate but also the synchrony to $S = 0.62$. The effect of DBS on surrounding neurons has been a subject of debate among experts. Many researchers argue that DBS inhibits local neurons, the equivalent of lesioning the nucleus. [35] [36] [37] More recent work has found that DBS

<table>
<thead>
<tr>
<th>Model</th>
<th>Standard Deviation $\sigma$</th>
<th>$f_{\text{avg}}$ (impulses/sec)</th>
<th>$f_{\text{min}}$ (impulses/timestep)</th>
<th>$f_{\text{max}}$ (impulses/timestep)</th>
<th>Synchrony $S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>5.68</td>
<td>72</td>
<td>1</td>
<td>128</td>
<td>0.08</td>
</tr>
<tr>
<td>Parkinsonian</td>
<td>37.30</td>
<td>82</td>
<td>1</td>
<td>144</td>
<td>0.52</td>
</tr>
<tr>
<td>DBS @ GPi</td>
<td>248.39</td>
<td>122</td>
<td>1</td>
<td>800</td>
<td>0.62</td>
</tr>
<tr>
<td>TMS(10 Hz)</td>
<td>25.26</td>
<td>80</td>
<td>1</td>
<td>240</td>
<td>0.21</td>
</tr>
<tr>
<td>TMS(20 Hz)</td>
<td>26.88</td>
<td>80</td>
<td>1</td>
<td>233</td>
<td>0.23</td>
</tr>
<tr>
<td>TMS(30 Hz)</td>
<td>25.29</td>
<td>80</td>
<td>1</td>
<td>236</td>
<td>0.21</td>
</tr>
<tr>
<td>TMS(40 Hz)</td>
<td>15.00</td>
<td>87</td>
<td>1</td>
<td>230</td>
<td>0.13</td>
</tr>
<tr>
<td>TMS(50 Hz)</td>
<td>9.78</td>
<td>87</td>
<td>1</td>
<td>230</td>
<td>0.09</td>
</tr>
<tr>
<td>TMS(60 Hz)</td>
<td>16.64</td>
<td>82</td>
<td>1</td>
<td>239</td>
<td>0.14</td>
</tr>
</tbody>
</table>
may cause a combination of excitation and inhibition. In our model, the addition of DBS increases the firing rate and synchrony, and so we assume that given our parameters, this is an accurate representation. It is also possible that by stimulating these neurons at roughly double their normal firing rate, they may become over-discharged with signals and essentially "turn off". While this phenomenon needs more study, our model simply shows a much higher firing rate, possibly because this phenomenon is not included within NEST. Next, we see that removing DBS and applying cortical rTMS gives interesting results, as the level of synchrony naturally depends on the pulse frequency of TMS. Downstream effects of clinical rTMS at 10 Hz seems to actually decrease the synchrony of the GPi, with $S = 0.21$. Further increasing the pulse frequency gives slightly varying results, with 50 Hz giving the lowest amount of asynchrony ($S = 0.09$), very close to natural healthy asynchrony ($S = 0.08$). However, by increasing TMS pulse frequency even further, we begin to see synchrony increasing again. Therefore, our simulations suggest that clinical rTMS may have synchrony-decreasing effects on the GPi up to a certain frequency, and furthermore, rTMS at 50 pulses/sec may bring the GPi to an asynchrony level very close to that of a healthy GPi. We have created raster plots to demonstrate neuron firing for a total of 1 second, between 0.5 seconds to 1.5 seconds. GPi raster plots for healthy, PD, DBS, and cortical TMS at 50 Hz can be seen in Figure 3. Raster plots for other nuclei can be found in the appendix.

**G Pi Raster Plots**

![Raster plots of healthy, PD, DBS, and 50 Hz TMS. Note the increased synchrony in PD GPi, and the higher asynchrony with downstream effects of 50 Hz rTMS.](image-url)
VI. CONCLUSION

We have developed a new computational model for an open-loop basal ganglia motor pathway, with M1 cortical and basal ganglia nuclei. We used experimentally-measured firing rates for healthy and parkinsonian/dystonic nuclei and connection delays, from previous literature, to validate our model. Each nucleus was initialized to its correct background activity with connections of varying levels of random noise. We suppressed the connection between dopaminergic input from SNC to STR and verified that the resulting firing rates and patterns matched those found in parkinsonian (and dystonic) nuclei. This verification also validated the connection weights between all nuclei. With the verified parkinsonian pathway, we then added a DBS signal connected directly to the GPi to model DBS treatment and measured the firing rates and synchrony within the GPi. Finally, to model cortical rTMS, we removed DBS and applied rTMS signal to the cortex, at clinical frequency of 10 pulses/sec, as well as increasing frequencies up to 60 pulses/sec. Our simulations found that DBS increases the firing rate but also the synchrony of the GPi nucleus, while downstream effects of clinical rTMS may illicit lower levels of synchrony; furthermore, higher frequency rTMS of 50 pulses/sec may cause asynchrony very close to that of a healthy GPi nucleus. We argue that this investigation may have opened up an opportunity to study a non-invasive alternative to DBS for patients with PD.

VII. ACKNOWLEDGMENTS

We are grateful to Dr. Kathryn Holloway, Shane Harstad, and Hamza Magsood for helpful discussions.

REFERENCES


Conclusions and Contributions

Our work in macroscopic brain tissue simulations aided in answering some important questions about TMS field profiles in patients of varying ages and brain volumes. The two-phase DBS lead model project showed that for certain patients with implanted DBS leads, cortical TMS at the mouth motor region may benefit treatment of speech and swallowing symptoms without over-stimulating the deep brain regions and negatively impacting DBS treatment. Our new, neuron-based motor pathway model provided some very significant insights regarding the effect of M1 rTMS in the basal ganglia nuclei. Simulations showed that high-frequency rTMS may have beneficial effects for motor symptoms in Parkinson’s Disease. Because rTMS has been shown to induce more long-term plasticity than DBS, this study may be a starting point for animal studies showing the potential use of rTMS as a non-invasive alternative to DBS. Finally, our new method of creating 3D models of fiber tracts will be helpful in studying the potential deep brain effects of various TMS modalities. The addition of fiber tracts in a 3D head model during FEA simulation will give much more significant data regarding signal propagation rather than simple tissue stimulation information. The combination of brain tissue, neuron network, and fiber tract models will allow for significantly deeper understanding of the mechanisms behind Transcranial Magnetic Stimulation and enable clinicians to make more informed decisions about patient treatment. Furthermore, our novel studies of motor pathway stimulation and deep brain effects of TMS will enable translational researchers to develop new non-invasive treatments for specific deep brain regions. TMS is capable of inducing synaptic plasticity, but at the moment, a lack of understanding prevents the treatment from reaching its full potential for patients of other neurological conditions. This project will contribute to the clinical field by allowing development of new non-invasive brain stimulation treatments through a greater understanding of the effects of cortical TMS on deep brain regions.
7.1 Future Work and Recommendations

Because this thesis project was purely computational, there is much work that can be done to follow up on simulation results. An anatomically-accurate, heterogeneous brain phantom should be developed to compare with Sim4Life simulation results. A real DBS lead can be inserted into such a phantom and TMS can be performed on the phantom’s cortical region, and the amount of current induced in the DBS lead can be measured directly.

The next steps in our motor pathway model require animal studies, using animals with similar motor pathway layout as humans. These animal’s deep brain regions can be lesioned to induce dystonia or PD, as is currently done in Parkinson’s Disease studies. Then, rTMS should be performed at the M1 region for these animals, and motor symptoms should be monitored over the course of the treatment. If the animal studies show an improvement in motor symptoms through TMS-induced plasticity and basal ganglia asynchrony, then this finding would be a breakthrough in PD treatment research.

Finally, our method for developing 3D fiber tract models should be used to develop a variety of fiber tracts from all cortical areas. Once developed, these models can be used in FEA simulations of TMS to either study how certain treatments may cause signal propagation to various parts of the deep brain region, or conversely, to find the cortical regions which should be targeted to stimulate certain deep brain areas non-invasively.
7.2 Peer-Reviewed Journal Publications

1. Effect of anatomical variability in brain on TMS treatment

2. Computational analysis of transcranial magnetic stimulation in the presence of deep brain stimulation probes

3. Effect of Transcranial Magnetic Stimulation on Demyelinated Neuron Populations


5. Submitted: Novel Disease-State Motor Pathway Model to Study Deep Brain Effects of Transcranial Magnetic Stimulation in Parkinson’s Disease.
7.3 Conference Presentations


8.1 Coursework

Fall 2015

EGMN 503 MNE Continuum ................................................................. A
EGMN 504 MNE Analysis ................................................................. B
EGMN 690 MNE Seminar ............................................................... S
GRAD 614 Intro to Grant Writing ..................................................... S

Spring 2016

EGMN 510 Probabilistic Risk Assessment ........................................... A
EGMN 603 MNE Dynamic Systems ..................................................... A
EGMN 604 MNE Materials ............................................................... B
EGMN 690 MNE Seminar ............................................................... S

Fall 2016

EGMN 610 Topics in Nuclear Engineering ......................................... B
PHYS 576 Electromagnetic Theory .................................................... A
EGMN 690 MNE Seminar ............................................................... S
Spring 2017

ANAT 608 Functional and Clinical Neuroanatomy ........................................ A
EGMN 690 MNE Seminar ................................................................. S

Fall 2017

EGMN 570 Effective Technical Writing ................................................. A
EGMN 691 Nanomagnetic Devices ....................................................... A
EGMN 690 MNE Seminar ................................................................. S
EGRB 690 BME Seminar ................................................................. S

Spring 2018

EGMN 560 Monte Carlo Simulations .................................................... A
EGMN 690 MNE Seminar ................................................................. S
EGRB 690 BME Seminar ................................................................. S
Timeline

Core Courses
Electives
Qualifying Exam
Project 1 (DBS/TMS I)
Project 2 (Varying Anatomy)
Project 3 (Demyelination)
Project 4 (DBS/TMS II)
Project 5 (Motor Pathways)
Project 6 (Fiber Tracts)
Proposal Defense
Dissertation Defense
References


145


Vita

Farheen Syeda

Education
Ph.D, Mechanical and Nuclear Engineering, 2015 – Present, Virginia Commonwealth University
B.S., Physics, 2014, Loyola University Chicago

Research
02/2016 – 06/2018 Doctoral Research in Brain Modeling and Simulations of Transcranial Magnetic Stimulation. Mechanical and Nuclear Engineering, VCU
Advisor: Dr. Ravi Hadimani

Publications

Professional Presentations


Teaching Experience
08/2015 – Present Graduate Teaching Assistant. Various Subjects. VCU.
06/2016 – 07/2016 Supervisor for Mayor’s Youth Academy Summer Intern, VCU.
05/2012 – 05/2014 Undergraduate Teaching Assistant. Various Subjects. Loyola University.

Volunteer Work
08/2016 – Present Secretary, IEEE Magnetic Society, Richmond Chapter
05/2012 – 06/2013 Secretary, Physics Club, Loyola University Chicago

Awards/Recognitions/Scholarships
07/2017 NIH NCAN Summer Course Scholar
04/2017 IEEE Intermag 2017 Conference Travel Award Recipient
08/2013 – 05/2014 Mulcahy Research Scholarship
05/2013 – 08/2013 NSF Research Experience for Undergraduates Scholar
11/2013 APS Division of Fluid Dynamics Travel Grant Recipient
01/2011 – 05/2014 Loyola University Academic Scholarship

Membership in Professional Societies
IEEE; IEEE Magnetics Society
American Physical Society (APS)

Programming Languages/Computer Competencies
Sim4Life, Matlab, Simulink, LabVIEW, C#, C++, Python, Interactive Data Language (IDL)
Appendices

Volume Stimulated Code

The following pages show the Matlab code we have written to calculate the amount of cells in the brain tissue which are stimulated above a given threshold. We use the volume stimulation data extracted from a Mask Filter from Sim4Life as imported data.
Volume Stimulated Calculations for Sim4Life simulations of TMS
Farheen Syeda
August 2016

This script takes input data from Sim4Life and finds the volume stimulated
in a brain model after TMS simulations. Take the final output and multiply
by 100 to get the percent stimulated.

To find volume stimulated for each model, follow these instructions:
Perform Sim4Life simulation with grid priorities set to 0 to ensure
each grid is same size. When the simulation is complete, in the
analysis tab, create a Mask Filter which includes only the brain tissue,
make sure to hit refresh, and export it as a matlab file. Then, import
the file into matlab. During import, deselect Axes 1-3, and rename
"Snapshot0" to "testmodelSnapshot0" or "NameofModelSnapshot0".
If model name is numeric, add "M" in front of name to avoid issues.
Finally, copy and paste "testmodel" section below, and find and replace
each instance of "testmodel" with the new model name.

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%% DO NOT GET RID OF OR REPLACE THE TESTMODEL SECTION
%%COPY AND PASTE IT INSTEAD
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%% If you have any questions about these instructions, I can be reached
at syedaf2@vcu.edu
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%% COPY AND PASTE THE BELOW SECTION. REPLACE 'testmodel' WITH the model
name.
%testmodel
%set waitbar
h = waitbar(0,'Calculating for testmodel ...');

%Convert E-field data to RMS
Snapsize = size(testmodelSnapshot0,1);
Avg = ones(Snapsize,1);
for i = 1:size(testmodelSnapshot0,1)
    Avg(i) = sqrt((testmodelSnapshot0(i,1)^2 +
    testmodelSnapshot0(i,2)^2 + testmodelSnapshot0(i,3)^2)/2);
    waitbar(i / Snapsize)
end

close(h);

ImagAvg = imag(Avg);

% find max e-field value
m = max(ImagAvg);
testmodelm = m;

% Declare thresholds
t = 100;
t2 = 150;

% Find total number of cells above threshold
count = 0;
count2 = 0;
for i = 1:size(ImagAvg)
    if ImagAvg(i) >= t
        count = count + 1;
    end
    if ImagAvg(i) >= t2
        count2 = count2 + 1;
    end
end
testmodelVS = count / Snapsize;
testmodelVS50 = count2 / Snapsize;
clear i Avg count count2 ImagAvg Snapsize m t t2 h

disp('testmodel Completed...')

Published with MATLAB® R2015a
Surface Stimulated Code

We have written the following Matlab code to calculate the amount of cells on the gray matter surface which are stimulated above a given threshold. We import surface stimulation data extracted from Surface Viewer in Sim4Life.
% Farheen Syeda
% Surface Stimulation Calculations
% Varying MRI Paper 2016
% September 12, 2016

% Surface for testmodel

% set waitbar
h = waitbar(0, 'Calculating for testmodel...');

% Convert E-field data to RMS
Snapsize = size(testmodelSnapshot0,1);
Avg = ones(Snapsize,1);
for i = 1:size(testmodelSnapshot0,1)
    Avg(i) = sqrt((testmodelSnapshot0(i,1)^2 +
                   testmodelSnapshot0(i,2)^2 + testmodelSnapshot0(i,3)^2)/2);
    waitbar(i / Snapsize)
end

close(h);

ImagAvg = imag(Avg);

% Pull up max data
m = testmodelm;

% Declare thresholds
t = m/2;
t2 = 50;

% Find total number of cells above threshold
count = 0;
count2 = 0;
for i = 1:size(ImagAvg)
    if ImagAvg(i) >= t
        count = count+1;
    end
    if ImagAvg(i) >= t2
        count2 = count2+1;
    end
end

SurfacetestmodelVS = count/Snapsize;
SurfacetestmodelVS50 = count2/Snapsize;

clear i Avg count count2 ImagAvg Snapsize m t t2 h

disp('testmodel Completed...')
%Record Data to Excel Sheet

VSdata =    { 'Model' , 'Volume Stimulated (%)' ;
    'Model M198451'  SurfaceM198451VS;};

VS50data =    { 'Model' , 'Volume Stimulated (%)' ;
    'Model M198451'  SurfaceM198451VS50;};

filename = 'Varying MRI Surface Data.xlsx' ;
xlswrite(filename,VSdata,1)
xlswrite(filename,VS50data,2)

Published with MATLAB® R2015a
Demyelinated Neurons: Electric Field and White Matter

The following pages show Sim4Life calculations of electric field values on the cortical surface and corresponding magnetic field on TMS coil surface.
<table>
<thead>
<tr>
<th>Max E-field on WM Surface</th>
<th>B-field on Coil Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3.36</td>
<td>0.0572</td>
</tr>
<tr>
<td>6.72</td>
<td>0.114</td>
</tr>
<tr>
<td>10.1</td>
<td>0.172</td>
</tr>
<tr>
<td>13.4</td>
<td>0.229</td>
</tr>
<tr>
<td>16.8</td>
<td>0.286</td>
</tr>
<tr>
<td>20.2</td>
<td>0.343</td>
</tr>
<tr>
<td>23.5</td>
<td>0.4</td>
</tr>
<tr>
<td>26.9</td>
<td>0.458</td>
</tr>
<tr>
<td>30.2</td>
<td>0.515</td>
</tr>
<tr>
<td>33.6</td>
<td>0.572</td>
</tr>
<tr>
<td>36.952</td>
<td>0.629283636</td>
</tr>
<tr>
<td>40.31090909</td>
<td>0.686494545</td>
</tr>
<tr>
<td>43.66981818</td>
<td>0.743705455</td>
</tr>
<tr>
<td>47.02872727</td>
<td>0.800916364</td>
</tr>
<tr>
<td>50.38763636</td>
<td>0.858127273</td>
</tr>
<tr>
<td>53.74654545</td>
<td>0.915338182</td>
</tr>
<tr>
<td>57.10545455</td>
<td>0.972549091</td>
</tr>
<tr>
<td>60.46436364</td>
<td>1.02976</td>
</tr>
<tr>
<td>63.82327273</td>
<td>1.086970909</td>
</tr>
<tr>
<td>67.18218182</td>
<td>1.144181818</td>
</tr>
<tr>
<td>70.54147186</td>
<td>1.201392727</td>
</tr>
<tr>
<td>73.9004329</td>
<td>1.258603636</td>
</tr>
<tr>
<td>77.25939394</td>
<td>1.315814545</td>
</tr>
<tr>
<td>80.61835498</td>
<td>1.373025455</td>
</tr>
<tr>
<td>83.97731602</td>
<td>1.430236364</td>
</tr>
<tr>
<td>87.33627706</td>
<td>1.487447273</td>
</tr>
<tr>
<td>90.6952381</td>
<td>1.544658182</td>
</tr>
<tr>
<td>94.05419913</td>
<td>1.601869091</td>
</tr>
<tr>
<td>97.41316017</td>
<td>1.65908</td>
</tr>
<tr>
<td>100.7721212</td>
<td>1.716290909</td>
</tr>
<tr>
<td>Value</td>
<td>Value</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>104.131</td>
<td>1.7735</td>
</tr>
<tr>
<td>107.490</td>
<td>1.8307</td>
</tr>
<tr>
<td>110.849</td>
<td>1.8879</td>
</tr>
<tr>
<td>114.207</td>
<td>1.9451</td>
</tr>
<tr>
<td>117.567</td>
<td>2.0023</td>
</tr>
<tr>
<td>120.925</td>
<td>2.0596</td>
</tr>
<tr>
<td>124.285</td>
<td>2.1167</td>
</tr>
<tr>
<td>127.644</td>
<td>2.1739</td>
</tr>
<tr>
<td>131.002</td>
<td>2.2312</td>
</tr>
<tr>
<td>134.362</td>
<td>2.2884</td>
</tr>
<tr>
<td>137.721</td>
<td>2.3456</td>
</tr>
<tr>
<td>141.079</td>
<td>2.4028</td>
</tr>
<tr>
<td>144.436</td>
<td>2.4600</td>
</tr>
<tr>
<td>147.796</td>
<td>2.5172</td>
</tr>
<tr>
<td>151.156</td>
<td>2.5744</td>
</tr>
<tr>
<td>154.515</td>
<td>2.6316</td>
</tr>
<tr>
<td>157.875</td>
<td>2.6888</td>
</tr>
<tr>
<td>161.234</td>
<td>2.7460</td>
</tr>
<tr>
<td>164.592</td>
<td>2.8033</td>
</tr>
<tr>
<td>167.951</td>
<td>2.8605</td>
</tr>
<tr>
<td>171.310</td>
<td>2.9177</td>
</tr>
<tr>
<td>174.669</td>
<td>2.9749</td>
</tr>
<tr>
<td>178.028</td>
<td>3.0321</td>
</tr>
<tr>
<td>181.387</td>
<td>3.0893</td>
</tr>
<tr>
<td>184.746</td>
<td>3.1465</td>
</tr>
<tr>
<td>188.105</td>
<td>3.2038</td>
</tr>
<tr>
<td>191.464</td>
<td>3.2609</td>
</tr>
<tr>
<td>194.823</td>
<td>3.3182</td>
</tr>
<tr>
<td>198.182</td>
<td>3.3754</td>
</tr>
<tr>
<td>201.541</td>
<td>3.4326</td>
</tr>
</tbody>
</table>
Demyelinated Neurons: Electric Field, Current, and Magnetic Field

The following page shows calculations of electric field on cortical white matter, induced current on neuron bodies, and corresponding magnetic field on TMS coil surface. Induced current was calculated by using Eq. 48, and magnetic field was calculated using interpolation of previously shown data.
<table>
<thead>
<tr>
<th>E-field required on axons</th>
<th>Current (pA)</th>
<th>B-field on Coil Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>10000</td>
<td>0.545176471</td>
</tr>
<tr>
<td>64</td>
<td>20000</td>
<td>1.089987178</td>
</tr>
<tr>
<td>96</td>
<td>30000</td>
<td>1.6350106</td>
</tr>
<tr>
<td>128</td>
<td>40000</td>
<td>2.180004189</td>
</tr>
<tr>
<td>160</td>
<td>50000</td>
<td>2.724988439</td>
</tr>
<tr>
<td>192</td>
<td>60000</td>
<td>3.26997269</td>
</tr>
<tr>
<td>224</td>
<td>70000</td>
<td>3.814956941</td>
</tr>
<tr>
<td>256</td>
<td>80000</td>
<td>4.359941191</td>
</tr>
<tr>
<td>288</td>
<td>90000</td>
<td>4.904925442</td>
</tr>
<tr>
<td>320</td>
<td>100000</td>
<td>5.449909692</td>
</tr>
</tbody>
</table>
Demyelinated Neurons: Python Script

The following pages include the python script from this project.
# Farheen Syeda
# NEST Neural Simulator

#add path where nest module is located to allow importing
import sys
sys.path.append('/Users/hadimanilab/opt/nest/lib/python2.7/site-packages')

import matplotlib
matplotlib.use('TKAgg')
import pylab
import nest
import nest.topology as topp
import numpy as np
import array
import matplotlib.pyplot as plt
import matplotlib.animation as animation
import mpl_toolkits.mplot3d.axes3d as p3

nest.ResetKernel()

# define all constants here
popnum = 1000  # number of neurons in stimulated population
noise_ex_rate = 80000.0  # rate of incoming excitatory signal
noise_in_rate = 15000.0  # rate of incoming inhibitory signal
noise_ex_weight = 1.2  # synaptic weight of excitatory signal(pA)
noise_in_weight = -2.0  # synaptic weight of inhibitory signal(pA)
normal_V = -70.0  # normal resting potential of neurons (V)
normal_E = -70.0  # normal starting potential of neurons (V)
normal_C = 250.0  # normal capacitance of neurons (pF)
sampling_resolution = 1.  # for voltmeter (ms)
stimamp = 0.0  # amplitude of stimulating current for TMS
stimfreq = 2500.0  # frequency of TMS current (Hz)

# Define stimulation parameters and create neurons
normparams = {'C_m': normal_C}

pop1 = nest.Create('iaf_neuron', popnum, normparams)
pop2 = nest.Create('iaf_neuron', popnum, normparams)
pop3 = nest.Create('iaf_neuron', popnum, normparams)

vm_pars = {
    'record_to': ['memory'],
    'withtime': True,
    'withgid': True,
    'interval': sampling_resolution
}

# Create devices for signal measurement
vm = nest.Create('voltmeter', 1, vm_pars)
spikedetector = nest.Create('spike_detector',
                          params={'withgid': True, 'withtime': True})  # record spiking events
vm2 = nest.Create('voltmeter', 1, vm_pars)
spikedetector2 = nest.Create('spike_detector',
                         params={'withgid': True, 'withtime': True})  # record spiking events
vm3 = nest.Create('voltmeter', 1, vm_pars)
spikedetector3 = nest.Create('spike_detector',
    params={'withgid': True, "withtime": True})  # record spiking events

# Create stimulation device
# Each pulse lasts for 0.4 milliseconds
stim = nest.Create('ac_generator', params = {
    'amplitude': stimamp,
    'frequency': stimfreq,
    'start': 0.,
    'stop': 0.4,
    'origin': 0.})

# Create poisson generator (generally used to model noisy neuron signals)
noise_ex = nest.Create('poisson_generator')
noise_in = nest.Create('poisson_generator')
nest.SetStatus(noise_ex, {'rate': noise_ex_rate})
nest.SetStatus(noise_in, {'rate': noise_in_rate})

# Make noise connections to all populations
nest.Connect(noise_ex, pop1, syn_spec={'weight': noise_ex_weight})
nest.Connect(noise_in, pop1, syn_spec={'weight': noise_in_weight})
nest.Connect(noise_ex, pop2, syn_spec={'weight': noise_ex_weight})
nest.Connect(noise_in, pop2, syn_spec={'weight': noise_in_weight})
nest.Connect(noise_ex, pop3, syn_spec={'weight': noise_ex_weight})
nest.Connect(noise_in, pop3, syn_spec={'weight': noise_in_weight})

# Connect stimulation sources to populations
nest.Connect(stim, pop1)
nest.Connect(stim, pop2)
nest.Connect(stim, pop3)

# Connect sources to readers
nest.Connect(vm, pop1)
nest.Connect(pop1, spikedetector)
nest.Connect(vm2, pop2)
nest.Connect(pop2, spikedetector2)
nest.Connect(vm3, pop3)
nest.Connect(pop3, spikedetector3)

# Simulate 10 times for 100 ms each
# 10 pulses, 1000 ms = 1 second
for k in range(10):
    nest.Simulate(100)
    print k + 1
    print "..."

# Signal analysis
Vm = nest.GetStatus(vm, 'events')[0]['V_m']
times = nest.GetStatus(vm, 'events')[0]['times']
senders = nest.GetStatus(vm, 'events')[0]['senders']
dSD = nest.GetStatus(spikedetector, keys="events")[0]
```python
evs = dSD['senders']
ts = dSD['times']

Vm2 = nest.GetStatus(vm2, 'events')[0]['V_m']
times2 = nest.GetStatus(vm2, 'events')[0]['times']
senders2 = nest.GetStatus(vm2, 'events')[0]['senders']
dSD2 = nest.GetStatus(spikedetector2, keys='events')[0]
evs2 = dSD2['senders']
ts2 = dSD2['times']

Vm3 = nest.GetStatus(vm3, 'events')[0]['V_m']
times3 = nest.GetStatus(vm3, 'events')[0]['times']
senders3 = nest.GetStatus(vm3, 'events')[0]['senders']
dSD3 = nest.GetStatus(spikedetector3, keys='events')[0]
evs3 = dSD3['senders']
ts3 = dSD3['times']

#ts contains a list of all the timesteps in which a spike is recorded
#the length of ts tells us the total number of impulses recorded
print len(ts)
print len(ts2)
print len(ts3)
```
Motor Pathway Model: Python Script

The following pages include the python script for the motor pathway model.
#Farheen Syeda
#NEST Neural Simulator
#Motor Pathway model
#Last Modified April 13, 2018 by Farheen Syeda

#add path where nest module is located to allow importing
import sys
sys.path.append('/Users/hadimanilab/opt/nest/lib/python2.7/site-packages')
import matplotlib
matplotlib.use('TKAgg')
import pylab
import nest
import nest.topology as topp
import numpy as np
import array
import nest.voltage_trace
import random
import pylab as plt
import csv
import nest.raster_plot
import matplotlib.pyplot as plt
import matplotlib.animation as animation
import mpl_toolkits.mplot3d.axes3d as p3
from random import randint
from collections import Counter

#Reset simulations
nest.ResetKernel()
nest.ResetNetwork()

#Define Constants
popnum = 10 #Number of neurons we want to follow through circuit
iterations = 1 #Number of iterations for simulation to run
simtime = 1500 #time in ms for simulation to run
n = 8 #total number of neural layers in circuit

#Create arrays for data storage
pop = [0]*n
multimeter = [0]*n
spikedetector = [0]*n
dmm = [0]*n
Vms = [0]*n
tss = [0]*n
Vm = [0]*n
times = [0]*n
senders = [0]*n
dSD = [0]*n
evs = [0]*n
ts = [0]*n
ts10 = [0]*n
lentsarray = [0]*iterations
tsarray = [[] for i in range(n)]
poisson_ex = [0]*10
poisson_in = [0]*10

# Create TMS model
TMSstimfreq = 2500.0  # frequency of TMS current (Hz)
TMSfreq = 10  # number of pulses/sec
TMSpulsewidth = 0.4  # pulse width in ms
TMS = [0]*TMSfreq  # Create array for data storage
b = simtime/TMSfreq
TMSpause = b*1.0  # pause between TMS pulses (ms)
stimamp = 40000.0  # amplitude of stimulating current for TMS

# DBS Probe Model
DBSfreq = 185.0  # frequency of DBS current pulses/sec
DBSfreqint = int(DBSfreq)
DBSpulsewidth = 0.09  # pulse width (milliseconds)
DBSamp = 100000000.0  # amplitude of DBS current (pA)
pausetime = simtime/DBSfreq  # time of pause between pulses
DBS = [0]*DBSfreqint

# Start loop
for i in range(iterations):
    # reset simulations for cleanliness
    nest.ResetNetwork()
    nest.ResetKernel()

    # Create TMS simulator
    for t in range(0,TMSfreq):
        starttimeTMS = t*(TMSpause)
        stoptimeTMS = starttimeTMS + TMSpulsewidth
        TMS[t] = nest.Create('ac_generator', params = {
            'amplitude':stimamp,
            'frequency':TMSstimfreq,
            'start':starttimeTMS,
            'stop':stoptimeTMS,
            'origin':0.})

    # Create DBS simulator
    for d in range(0,DBSfreqint):
        starttime = d*(DBSpulsewidth+pausetime)
        stoptime = starttime + DBSpulsewidth
        DBS[d] = nest.Create('dc_generator', params = {
            'amplitude': DBSamp,
            'start':starttime,
            'stop':stoptime})

# Create devices for signal measurement
for p in range(0,n):
    multimeter[p] = nest.Create("multimeter")
    # record each sampling with time and decide which variables to record
    nest.SetStatus(multimeter[p],{"withtime":True,
                                 "record_from":["V_m"]})
    # record spiking events
    spikedetector[p] = nest.Create("spike_detector",
                                 params={"withgid":True,
                                         "withtime":True})

# Create neuron populations
pop[0] = nest.Create("iaf_neuron",800)
pop[1] = nest.Create("iaf_neuron",800)

# Rename populations
CTX = pop[0]
STRD1 = pop[1]
STRD2 = pop[2]
SNc = pop[3]
GPi = pop[4]
GPe = pop[5]
STN = pop[6]
THL = pop[7]

# Create noise generators
for p in range(0,10):
    poisson_ex[p] = nest.Create('sinusoidal_poisson_generator',
                               params={"rate": random.uniform(8300.0, 8500.0),
                                       "amplitude": 50.0,
                                       "frequency": 1.0, 'phase': 0.0,
                                       'individual_spike_trains': True})
    poisson_in[p] = nest.Create('sinusoidal_poisson_generator',
                                params={"rate": random.uniform(2000.0, 2100.0),
                                        "amplitude": 50.0,
                                        "frequency": 1.0, 'phase': 0.0,
                                        'individual_spike_trains': True})

# Connect all random noise generators to each neuron in each population
for c in range(0,10):
    nest.Connect(poisson_ex[c], STN, {'rule': 'fixed_indegree', 'indegree': 1},
                  syn_spec = {"weight":1.15})
    nest.Connect(poisson_in[c], STN, {'rule': 'fixed_indegree', 'indegree': 1},
                  syn_spec = {'weight':-0.9})
    nest.Connect(poisson_ex[c], SNc, {'rule': 'fixed_indegree', 'indegree': 1},
                  syn_spec = {"weight":1.0})
    nest.Connect(poisson_in[c], SNc, {'rule': 'fixed_indegree', 'indegree': 1},
                  syn_spec = {"weight":-0.92})
nest.Connect(poisson_ex[c], STRD2, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': 1.0})

nest.Connect(poisson_in[c], STRD2, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': -0.85})

nest.Connect(poisson_ex[c], STRD1, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': 1.0})

nest.Connect(poisson_in[c], STRD1, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': -1.1})

nest.Connect(poisson_ex[c], GPe, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': 1.3})

nest.Connect(poisson_in[c], GPe, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': -0.5})

nest.Connect(poisson_ex[c], GPi, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': 1.1})

nest.Connect(poisson_in[c], GPi, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': -1.4})

nest.Connect(poisson_ex[c], CTX, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': 1.1})

nest.Connect(poisson_in[c], CTX, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': -1.28})

nest.Connect(poisson_ex[c], THL, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': 1.97})

nest.Connect(poisson_in[c], THL, {'rule': 'fixed_indegree', 'indegree': 1},
            syn_spec = {'weight': -1.0})

#Connect DBS to GPi
#Uncomment this section to connect DBS to GPi
print "DBS Connected..."
for d in range(0, DBSfreqint):
    nest.Connect(DBS[d], GPi)

#Connect TMS to pop
#Uncomment this section to connect TMS to CTX
'''for d in range(0, TMSfreq):
    nest.Connect(TMS[d], pop[0])'''

#Make connections between populations

#Create synapse types
#Cortex to Striatum
nest.CopyModel("static_synapse", "CTX2STRe","weight":0.1, "delay":5.1)
#Substantia Nigra pars compacta to Striatum
nest.CopyModel("static_synapse", "SNc2STRe","weight":1.0, "delay":0.5)
nest.CopyModel("static_synapse", "SNc2STRi","weight":-5.0, "delay":0.5)
#Striatum to GPi
nest.CopyModel("static_synapse", "STR2GPii","weight":-2.0, "delay":4.0)
#Striatum to GPe
nest.CopyModel("static_synapse","STR2GPe","weight":-5.0, "delay":5.0)

#GPe to STN
nest.CopyModel("static_synapse","GPe2STNi","weight":-0.3, "delay":4.0)

#Subthalamic Nucleus to GPi
nest.CopyModel("static_synapse","STN2GPie","weight":1.2, "delay":1.5)

#CTX to STN
nest.CopyModel("static_synapse","CTX2STNe","weight":1.0, "delay":5.9)

#STN to GPe
nest.CopyModel("static_synapse","STN2GPee","weight":1.0, "delay":2.0)

#GPe to GPi
nest.CopyModel("static_synapse","GPe2GPie","weight":0.5, "delay":3.0)

#GPi to THL
nest.CopyModel("static_synapse","GPi2THLi","weight":-2.0, "delay":5.0)

#Direct Pathway
conn_CTX = {'rule': 'fixed_indegree', 'indegree': 800}
nest.Connect(CTX,STRD1,syn_spec = "CTX2STRe", conn_spec = conn_CTX) 
nest.Connect(CTX,STRD2,syn_spec = "CTX2STRe", conn_spec = conn_CTX)
nest.Connect(CTX,STN,syn_spec = "CTX2STNe", conn_spec = conn_CTX)

#Funneling from Striatum onward
conn_GPi = {'rule': 'fixed_indegree', 'indegree': 1000}
nest.Connect(STRD1,GPi,syn_spec = "STR2GPii", conn_spec = conn_GPi)

#Indirect Pathway
#for c in range(200):
#    conn_1 = {'rule': 'fixed_indegree', 'indegree': 800}
#    nest.Connect(GPe,STN,syn_spec = "GPe2STNi", conn_spec = conn_1)
#    nest.Connect(STN,GPi,syn_spec = "STN2GPie", conn_spec = conn_1)
#    nest.Connect(GPe,GPi,syn_spec = "GPe2GPie", conn_spec = conn_1)
#    nest.Connect(GPi,THL,syn_spec = "GPi2THLi", conn_spec = conn_1)

#Funneling from Striatum onward
conn_GPe = {'rule': 'fixed_indegree', 'indegree': 800}
nest.Connect(STRD2,GPe,syn_spec = "STR2GPei", conn_spec = conn_GPe)

#Dopaminergic Input to Striatum
"""conn_STR = {'rule': 'fixed_indegree', 'indegree': 1000}
nest.Connect(SNc,STRD1, syn_spec = "SNc2STRe", conn_spec = conn_STR)
conn_STRD2 = {'rule': 'fixed_indegree', 'indegree': 100}
nest.Connect(SNc,STRD2, syn_spec = "SNc2STRe", conn_spec = conn_STRD2)"

#connect readers to populations
for p in range(0,n):
    nest.Connect(multimeter[p], pop[p])
    nest.Connect(pop[p],spikedetector[p])
```python
#Simulate
nest.Simulate(simtime)

#Analysis
for p in range(0,n):
    #obtain list of dictionaries for one node (index 0)
    dmm[p] = nest.GetStatus(multimeter[p])
    #obtain data recorded for voltage and time
    Vms[p] = dmm[p]['events']['V_m']
    tss[p] = dmm[p]['events']['times']

    dSD[p] = nest.GetStatus(spikedetector[p], keys='events')[0]
    evs[p] = dSD[p]['senders']
    ts[p] = dSD[p]['times']

#Print average firing rate for each nucleus to the screen
print ''
print '*********************'
print ''
print 'SNc:',len(ts[3])/800
print 'CTX:',len(ts[0])/800
print 'STRD1:',len(ts[1])/800
print 'STRD2:',len(ts[2])/800
print 'GPi:',len(ts[4])/800
print 'GPe:',len(ts[5])/800
print 'STN:',len(ts[6])/800
print 'THL:',len(ts[7])/800

c = Counter(ts[4])
valuearray = c.values()
print 'Standard Deviation: ', np.std(valuearray)
print 'Mean: ', np.mean(valuearray)
print 'Max: ', max(valuearray)
print 'Min: ', min(valuearray)
totalsignals = sum(c.values())
print 'Total Signals: ', totalsignals
print 'Number of active timesteps: ', len(c)
print 'Total number of timesteps: ', len(tss[4])

print ''
print '*********************'
print ''
print ''
#show raster plot
nest.raster_plot.from_device(spikedetector[7], hist=False)
pylab.show()
```

nest.ResetKernel()
nest.ResetNetwork()