Role of Electrical Conductivity & Electrode Configurations in the Forward Model of High Definition Transcranial Direct Current Stimulation (Hd-tDCS)

Author

Ghina Zia

NUST201463184MSMME62314F

Supervisor

Dr. Muhammad Nabeel Anwar

DEPARTMENT OF BIOMEDICAL ENGINEERING

SCHOOL OF MECHANICAL & MANUFACTURING ENGINEERING

NATIONAL UNIVERSITY OF SCIENCES AND TECHNOLOGY

ISLAMABAD

MAY, 2017

Role of Electrical Conductivity & Electrode Configurations in the Forward Model of High Definition Transcranial Direct Current Stimulation (Hd-tDCS)

Author

GHINA ZIA

Registeration Number

NUST201463184MSMME62314F

A thesis submitted in partial fulfillment of the requirements for the degree of

MS Biomedical Engineering

Thesis Supervisor:

DR. MUHAMMAD NABEEL ANWAR

Thesis Supervisor's Signature: _____

DEPARTMENT OF BIOMEDICAL ENGINEERING

SCHOOL OF MECHANICAL & MANUFACTURING ENGINEERING

NATIONAL UNIVERSITY OF SCIENCES AND TECHNOLOGY,

ISLAMABAD

MAY, 2017

Declaration

I certify that this research work titled "***Role of Electrical Conductivity & Electrode Configuration in the Forward Model of High Definition Transcranial Direct Current Stimulation (HD-tDCS)***" is my own work. The work has not been presented elsewhere for assessment. The material that has been used from other sources it has been properly acknowledged / referred.

Signature of Student

Ghina Zia

NUST201463184MSMME62314F

Plagiarism Certificate (Turnitin Report)

This thesis has been checked for Plagiarism. Turnitin report endorsed by Supervisor is attached.

Signature of Student

Ghina Zia

NUST201463184MSMME62314F

Signature of Supervisor

Dr. Muhammad Nabeel Anwar

Copyright Statement

Acknowledgements

In the name of Allah, the Most Gracious, the Ever Merciful. All the praises are for Allah Almighty who is the best disposer of affairs. I am extremely thankful to my Mother Mrs. Azmat Zohra, Father Mr. Ziauddin Ahmed Khan, family and friends for their unconditional love, support and prayers.

I express my deepest gratitude to Dr. Nabeel Anwar, for his immense support. The way he puts confidence in his students to work independently is exceptional. Inculcating a sense of responsibility in the students without any unnecessary pressures from the supervisor increases their productivity. Dr. Nabeel has maintained the lab atmosphere friendly, harmonious and research oriented without any leg pulling between the students. Not only as a Supervisor and Head of Department but also as a Mentor he always motivated and inspired me through the thicks and thins of my tenure at NUST.

I am deeply indebted to my GEC members for their valuable guidance and suggestions especially Sir Umar Ansari for his timely recommendations and inputs in my project. A special thanks to Dr. Syed Salman Shahid, Dr. Zartasha Mustansar, Dr. Aamir Mubashir and Sir Aiman Rashid for their technical support.

I would like to thank whole Human Systems Lab in which my Seniors (Samran, Aqsa, Nayab, Hafsa, Waqar, Azeem) and my Juniors (Zaeem, Amna, Izzat, Sonia and Namra) were always willing to help and support me. My appreciation goes to my extraordinary friends and classmates Amnah, Kinza, Zaid, Ahmed, Atif, Saad and Quratulain for patiently listening to my problems and trying to resolve them to the best of their knowledge.

My deepest, heartiest and sincerest regards to Sidra and Rabia for supporting me in every aspect of my project may it be technical, emotional or practical. I have no words to express my feelings for you. Once again I am highly thankful to Allah Almighty to direct me to SMME because here I met the most precious people of my life.

Ghina Zia

Dedicated to my parents Mr. & Mrs. Ziauddin Ahmed Khan,

teachers, friends and family members.

Table of Contents

List of Figures

List of Tables

ABSTRACT

Background: High definition Transcranial Direct Current Stimulation (HD-tDCS) is one of the most recent developments in neuro-modulation which finds its applications in treatment and research of many neurological and psychiatric disorders. HD-tDCS employs arrays of small concentric scalp electrodes for targeted, safe and cost effective stimulation of brain. HD-tDCS is an emerging technology and in-depth apprehension of the biophysical interactions is needed. Since in-vivo observations are quite difficult during performance of the clinical trials, computational modeling has played a vital role in the understanding and optimizing stimulation therapies.

Objective: The aim of the study is to address the shortcomings of existing HD tDCS computational models by constructing realistic three dimensional models with more layers and different electrode placements.

Methodology: Finite Element (FE) models were developed from the averaged and subject specific radiological images (Magnetic Resonance Imaging (MRI)). Using Maxwell's, Laplace's and Gauss's equation the Electric field (E-field) distribution has been assessed. Under the influence of different electrode configurations (anode fixed at C3) and biological tissue conductivities in a multilayer (19 layers) brain model, the electric field maps have been examined.

Results: Most of the current was shunted in non-cortical areas due to the large impedance of the scalp. In addition, the peak value of the induced E-field was spotted beneath the anode and the current was mainly distributed underneath the circumference of stimulation montage. As the current density in a brain layer tends to stay constant, the inclusion of directional conductivity caused significant changes in E-field (Topological ~ 40% and Magnitude ~ 0.7) as compared to isotropic models. Variations in the radius and shape of the montage brought noticeable changes in the E-field maps. The intensity and the depth of penetration amplified when the radius was increased. However, the spreading of fields over larger area of Head lessened their focality. The fields became more uniform and hence the skewness decreased. The same trends were observed when the electrode configuration was given a 45^0 shift in the orientation as the area under electrodes has increased.

Conclusion: The accuracy of the predicted region of interest and the dosage parameters of stimulation can be controlled by using effective modeling and simulation approaches. Based on individual anatomy and pathological conditions, this study would be beneficial to the clinicians for planning customized HD-tDCS treatments of the patients.

Keywords: High Definition Transcranial Direct Current Stimulation (HD-tDCS), Neuro-modulation, Magnetic Resonance Imaging (MRI), Finite Element (FE) Model, Anisotropy, Montage, Electric Field Distribution.

CHAPTER 1

INTRODUCTION

CHAPTER 1: INTRODUCTION

Neural disorders are one of the largest health care problems of this era affecting millions of people every year. As compared to other diseases, Neural Disorders require more hospitalization and Treatment cost comes out to be in billions which many patients cannot afford hence affecting their quality of life. Transcranial Direct Current Stimulation provides us an ideal alternative as this is a cost effective technique which stimulates the neural tissues without any residual effects. Also, the Electromagnetic stimulation treatment schemes can provide encouraging results in case of drug resistant neurological disorders such as Schizophrenia and Depression.

Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuro-stimulation technique especially used for patients who have developed resistance to medication. It is also used as treatment for neurological and psychiatric disorders, clinical diagnostics and investigative tool in Cognitive Neuroscience [1]. Transcranial Direct Current Stimulation is a low amplitude (0-2mA) neuro modulation technique that applies current via electrodes placed on the scalp. Transcranial Direct Current Stimulation is used in both clinical therapy and neuroscience research. Conventional tDCS uses two relatively large pads (greater than 25 cm^2) whereas high-definition tDCS (HD-tDCS) uses arrays of smaller electrodes to deliver targeted dosage.

1.1 Significance of Study

HD-tDCS, developed in 2010, is one of the most popular investigational form of brain stimulation due to increased accuracy of current delivery to the brain, low cost, portability, usability, and safety. Although HD-tDCS has many advantages but there are certain limitations as well in terms of area, focality, orientation and depth of stimulation. To cater for the limitations, the Volume Conductor Models need to be optimized by adopting a more realistic modeling approach. The topic of this project has been selected to consider the effects of electrical stimulation on the brain considering non-uniform and directional model of Head.

This Project seeks to develop a realistic finite element based human head model to address the problems involved in the forward modeling (brain as a passive element) of HD-tDCS. The effects of introducing complexity in designing of model and assignment of anisotropic properties have been assessed. The head models were developed by combining the averaged and subject specific Magnetic Resonance Imaging (MRI) data. The Electric field sensitivity has been studied under the influence of different stimulation parameters, anatomical variations, tissue conductivities and electrode montages.

1.2 Objectives of Study

The objectives of this study can be summarized as follows.

- To develop a realistic finite element based human head model to address the problems involved in the forward modelling of HD-tDCS.
- To provide a better understanding on cortical stimulation under more realistic head layers representation.
- To be able to comment on the subject specific optimization of dosage and location of placing the HD-tDCS electrodes to have an effective stimulation.

1.3 Problem Statement

To determine whether the below mentioned parameters have any significant effects on the electric field distributions in 4x1 HD-tDCS.

- The inclusion of anisotropic conductivity in model.
- The increase in the radius of stimulation.
- The shift in the angle of stimulation of electrode configuration.

1.4 Overview of Thesis

The dissertation comprises of five chapters. Chapter 1 presents a preface of the research topic and discusses the significance, objectives and problem statement of the research. Chapter 2 provides an extensive literature review about anatomy and physiology of human head and brain, Neural disorders and treatments, tDCS and its implications on neural excitability, significance of HD-tDCS, use of Computational Modelling, Previous studies and their limitations.

Chapter 3 discusses the methodology adopted for the implementation of the research. The chapter sequentially elaborates the steps taken to build a 3D Model from MRI. The tissue segmentation, head model development, placement of electrodes at different positions, volume meshing, introduction of directional material properties, boundary conditions, setting of stimulation parameters and finally finite element analysis with an end goal to test the research hypothesis. The computational cost, time taken for the execution of simulation and modelling has also been elicited.

In Chapter 4, the results of the study have been presented and analyzed. The electric field has been discussed in terms of changes in intensity, direction, focality and penetration in four different models. Chapter 5 concludes the project and provides recommendations for the improvements in this study.

CHAPTER 2

LITERATURE REVIEW

CHAPTER 2: LITERATURE REVIEW

2.1 Background

Before getting into the details of the project, it is essential to discuss the anatomy and physiology of different layers of Human Head and Brain.

2.1.1 Anatomy of Human Head

Human Head is one of the most vital parts of Human Body. Head which forms the topmost section of the body can be classified into many layers. Scalp is the outermost covering of head which is composed of soft skin and connective tissues. The next layer of head is the Skull which provides integrity and protection to the face, head and brain due to its rigid bony structure. Going further inside the human head, there are layers of muscles, subcutaneous fats and eyes. In addition to that, there is a significant layer of transparent liquid which surrounds the human brain. This layer is called Cerebrospinal Fluid (CSF) which acts as a shock absorber, lubricant, pressure maintainer and transporter of nutrients and wastes.

2.1.2 Anatomy of Human Brain

Brain, the central processing unit of human systems, is one of the most sophisticated and complicated marvels of Mother Nature. From intelligence to the interpretation of senses and from initiation of body movements to behavioral control, all the human body functions are directly or indirectly under the control of Brain. A complete and comprehensive understanding of human brain has been a perplexing issue. However, developments in neurological and behavioral studies have started unraveling the secrets of the brain. To appreciate the functioning of any processor, it is imperative to get familiar with its architecture. The Architecture of the brain comprises of three basic divisions namely forebrain, midbrain and hindbrain. The description of the parts of brain with their functions has been summarized in the table 2-1.

Table 2-1: Physiology of the Parts of Human Brain.

Sr. No	Part	Description	Sub Parts	Functions
1.	Forebrain	Anterior most and largest part of brain	Cerebrum Thalamus Hypothalamus Limbic System	**Cerebrum:** "Seat of consciousness", responsible for thinking, reasoning, memory and cognitive functioning. . Cerebrum is composed of two hemispheres (Left & Right), each hemisphere is further divided into four lobes, namely Occipital, Temporal, Frontal and Parietal. **Thalamus:** Relay centre of impulses being sent to the specific brain areas, involved in movement and motivation. **Hypothalamus:** Balances different body systems, works with the endocrine system, Homeostasis, Regulates involuntary activities e.g body temperature, thirst, appetite and sexual drives and emotional behaviours. **Limbic System** Composed of Amygdala and Hippocampus. Amygdala: Processes emotions and distinguishes different objects. Hippocampus: Memory storage (main part: Fornix Crura)

2.	Midbrain	Smallest part of brain A bridge between hindbrain & forebrain	Tectum Tegmentum	Links sensory and motor pathways between the upper and lower parts of the nervous system. Visual & Auditory functions. A switchboard for receiving nerve impulses all over the body, sorting them and sends them to higher brain centres.
3.	Hindbrain	Located at the bottom of the cerebrum & the midbrain. Connected to the spinal cord	Pons Medulla Oblongata Cerebellum	**Pons:** Autonomic Control, Sleep, Arousal, Sensory Transmission between Cerebrum and Cerebellum. **Medulla Oblongata:** Involuntary movements, e.g. breathing, heartbeat, peristalsis. **Cerebellum:** Coordination of voluntary motor activities, Balance and Posture, Learning of habits and skills, Regulates tongue and jaw movements during speech.

The parts namely Hindbrain, Thalamus, Fornix Crura and Basal Ganglia (Putamen, Caudate Nucleus, Red Nucleus, Globus Pallidus) have been considered as sub cortical or deep brain regions. Basal Ganglia work with the cerebral cortex and the cerebellum for coordinating voluntary movements, forming habitual behaviours. The role of some of the aforementioned entities has been explained in Table 2-1. The functions of rest of the parts have been detailed in Table 2-2.

Table 2-2: Physiology of Sub Cortical Regions of Human Brain.

Sr. No.	Part	Function
1.	Caudate Nucleus	To call the frontal lobe for action. In obsessive compulsive disorder (OCD) caudate is overactive whereas an underactive caudate is involved in diseases like depression, lethargy, schizophrenia, loss of memory, lack of motivation and attention deficit disorder.
2.	Putamen	To coordinate automatic behaviours (like driving a car or riding a bicycle). Tourette's syndrome [133] arises when putamen becomes faulty.
3.	Globus Pallidus	To regulate voluntary movements. It becomes impaired in case of damage and causes movement disorders.
4.	Red Nucleus	Situated in the midbrain region it coordinates motor movements. Due to the high concentration of iron, it is red in color hence named red nucleus
5.	Fornix Crura	It is a C-shaped part which is the main component of hippocampus. In limbic system, Fornix is involved in memory formation and recalling events.

2.2 Human Brain Disorders

Keeping in mind the role of Brain in Human Life, Brain disorders are one of the most critical, mysterious and costly health problems. There are broadly four types of Brain Disorders which have been described in the Table 2-3.

Table 2-3: Major classifications of Brain Disorders.

Sr. No	Type Of Brain Disorder	Diseases
1.	Brain Injury & Neurodegenerative Disorder	ALS, Parkinson, Huntington, Traumatic brain injury, Alzheimer, Stroke, Epilepsy
2.	Psychiatric Disorders	Anxiety, Depression, Bipolar, Schizophrenia
3.	Developmental Disorders	Autism, Dyslexia
4.	Other Disorders	Sensory deficits, Vision Losses

2.3 Treatment of Brain Disorders

Depending upon the type of brain disorder and conditions of the patient, following treatments are presently available [68].

1. Pharmacological Treatments (Medications).
2. Neural Stimulations (Electrotherapy).
3. Surgical Treatments.
4. Physiotherapy.
5. Rehabilitation.

2.4 Neural Stimulation Techniques

Neural Stimulations are generally preferred over medications because they are more focused and targeted in nature. Also, the Electrical Nerve impulses travel faster than chemical synapses so they show immediate results. In addition, Non-Invasive Electro-stimulation therapies are particularly used for the treatment of medication resistant patients to avoid surgical procedures [63], [79], [123]. In combination with physiotherapy and rehabilitation devices, the electrical stimulations have a strong potential of giving long lasting and desired response in disease management.

Neural Stimulation is one of the most popular research areas of Bio-electomagnetism due to the widespread applications in the diagnosis, treatment of Neural, Psychiatric disorders as well as in the cognitive neurosciences. Electrotherapy presents complete temporal control by delivering desired dosage of current in the activation period leaving no electrical residue afterwards. Whereas spatial control is achieved depending upon the type of stimulation montage

used [18]. Using electromagnetic stimulations (invasive/non-invasive), the activity of neurons in the brain tissues is enhanced or suppressed. Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are among the most conspicuous Non invasive Brain stimulation therapies.

The abovementioned techniques can be differentiated on the basis of stimulation parameters and mode of delivery of Electric Current. In ECT commonly termed as Electroshock therapy, high current (~800mA) is used noninvasively as a last choice of treatment for the patients suffering from severe psychiatric/neural disorders. However, tDCS is a low amperage current (0-2mA) direct current stimulation. In contrast to ECT and tDCS, Magnetic Fields are used to induce electric fields inside the cortex in case of TMS [26-28],[51],[150],[152].

2.5 Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation abbreviated as tDCS is one of the most promising forms of brain stimulation. tDCS has been gaining substantial importance due to its implementation simplicity, safety [99], tolerance, portability and low maintenance overheads[9],[52], [94], 145].Although the neural stimulation techniques share same underlying fundamental principles in terms of brain function however they have major differences in the modes and parameters of stimulation. tDCS originally conceived for the treatment of brain injuries [104] has now been used on healthy adults for increasing cognitive abilities like coordination, language, mathematics, aptitude, alertness, memory, and problem solving skills. [25],[29],[32],[45],[53],[64],[72],[84],[103],[125],[129].Moreover,tDCS has also been employed for the treatment of Alzheimer, Anxiety, Chronic pain [101], Depression, Fibromyalgia, Multiple Sclerosis, Obesity, Parkinson's, Post Traumatic Stress Disorders , Schizophrenia, Sleep Disturbances, Stroke and Tinnitus [3],[12],[16],[20],[31],[33],[35-36],[40],[44],[74-75],[83], [89],[90],[138].

2.6 Relationship of tDCS Dosage & Neural Excitability

The exploration about the mechanism of tDCS began in early 1960's. Lippold and Redfean applied weak direct current (<0.5A) on the frontal cortex and observed changes in motor activity and behaviour [135-136]. After many years of research and development in analysis techniques, it was verified that low amperage currents can lead to modification in Motor Evoked Potentials (MEP). In 2000, Nitshce and Paulus studied cortical excitability and polarity effects in direct current stimulations [85]. They found enhancement in MEP amplitude for anodal stimulation and decrease in motor cortex excitability for cathodal stimulation as depicted in Figure 2.2.

An important parameter in defining the threshold of stimulation is the intensity of induced electric field. High electric field strengths can trigger action potential at cellular level [98], [131]. This disturbs the membrane potential causing current to travel across the gradient which in turn modulates neural activities [23], [76], [122]. The threshold of Action Potential for cortical neurons is 22-275 A/m^2 [46]. Contrary to most of the brain stimulation therapies, weak electric fields of tDCS do not induce neuronal firing (supra-threshold depolarization of neuronal membrane) rather they produce electrotonic potentials (non-propagating) in neurons. Electrotonic potential modulate the spontaneous activity of neuronal networks and hence control the action potential by altering the threshold of membrane potential. [43], [85].

Although the knowledge about internal mechanisms of neural stimulations is still incomprehensible but it is generally believed that the change in polarization of neural membrane is the ultimate result of any electrical stimulation. Contrary to most of the brain stimulation therapies, low amperage direct currents do not induce neuronal firing (supra-threshold depolarization of neuronal membrane) rather they modulate the spontaneous activity of neuronal networks [2],[81], [86-88]. Considering the polarity dependent nature of tDCS [17],[71],[121], it can be divided into two types; Anodal and Cathodal tDCS.(Figure 2.1) Generally, Anodal tDCS amplifies and cathodal tDCS attenuates the neural activities by modifying resting potential threshold of neuronal membrane. The anodal stimulation [43][85] causes depolarization whereas the cathodal electric currents results in hyper-polarization [42],[48], [54], [127]. But in case of inhibitory inter-neurons the polarity effects are reversed i.e. anodal and cathodal stimulations correspond to inhibition and excitation respectively [98].

The sodium and calcium channels in the membrane are voltage dependent. The changes caused by induced electrical stimulation in the neuronal membrane potential overpower the effects of signalling pathways of neurons for the applied duration of stimulation. [2], [43], [106]. Therefore, it is generally asserted that the tDCS effects do not last after the stimulation procedure. However, by adjusting the timings of exposure, the after-effects of tDCS can last for a few hours [2], [49], [55], [78]. Apart from the local membrane potential changes, tDCS can also be used to modulate subcortical structures associated with the cortical area of stimulation [13], [50], [69].

Bikson discovered a linear relationship between the effect of an induced electric field on neurons and the intensity of electric field [98]. However, the morphology, size and length of neurons also add to the resulting stimulation. The orientation of soma, dendrites and axons with regard to the induced electric field also plays a vital role in stimulation. Radman carried out an in vitro study of rat cortical tissues [142-143]. Radman suggested that in a properly oriented sub-threshold field, the soma of pyramidal cells of layer 5 were most sensitive in terms of polarization. The study also reported that layer 5 and 6 neurons had the lowest action potential thresholds. Figure 2.2 depicts the cerebral cortex layered structure.

2.7 High Definition Transcranial Direct Current Stimulation

In terms of stimulation electrodes, tDCS can be classified into Conventional and High Definition tDCS. Rectangular patch electrodes have been employed in conventional tDCS that covers large surface area of brain. Most of the applied current in conventional tDCS is shunted in the scalp due to its high impedance and hence only a small amount of current reaches the brain. By shaping the induced electric field through change in electrode montages of tDCS, focal neural stimulation can be achieved. The advancements in tDCS research paved way for the development of comparatively more efficient montage in terms of focality [41], High Definition tDCS (HD-tDCS). [8],[11],[14],[24],[61],[73],[120].Small circular electrodes (6mm radius) are used in HD-tDCS. 4x1 HD-tDCS comprises of one central active electrode and four surrounding return electrodes. The considerations for operating an HD-tDCS device have been properly detailed in [102].

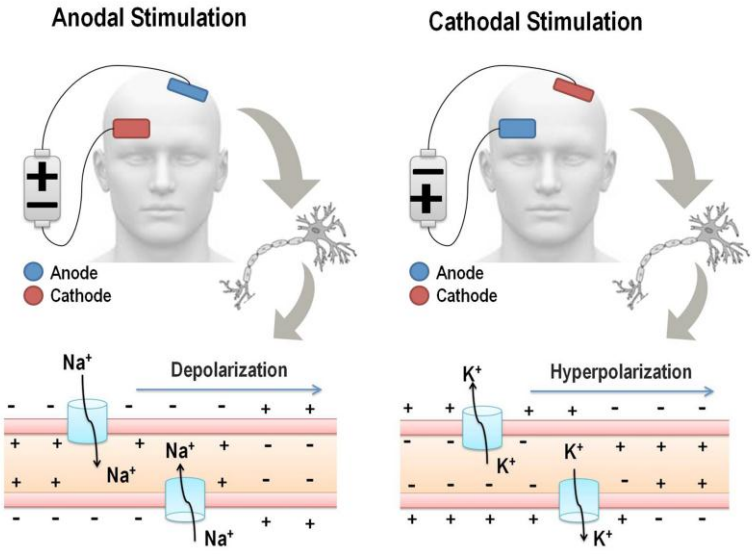


Figure 2.1 Effects of tDCS on Membrane Polarization. (Left) illustrates anodal whereas figure (Right) represents cathodal conventional stimulation of primary motor cortex (M1). The former causes depolarization of the neuronal membrane subsequently enhancing excitability. The later hyperpolarizes the membrane consequently diminishing M1 excitability. Source: Rozisky et al 2015.

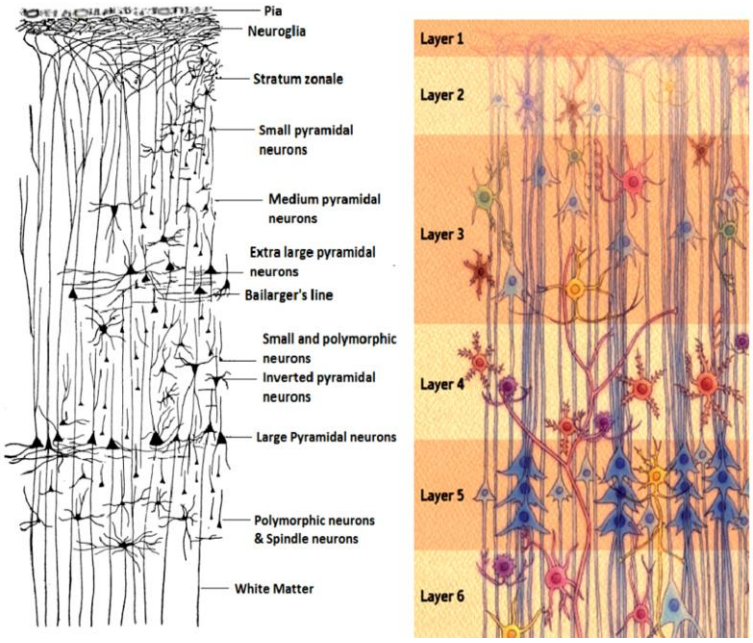


Figure 2.2 Layered Structures of Neurons in Cerebral Cortex. Source: http://chronopause.com.

2.8 Computational Modeling

Computational modeling has been recognized as a predictive tool for current flow in tDCS. Keeping in view the above discussion, it is necessary to determine the parameters controlling the modulatory effects of stimulation before starting any tDCS study [5-7], [19], [30], [37], [39], [56], [62], [65-67], [82], [92],[100], [105],[113],[119],[137], [141-147]. These parameters are as follows.

1. Inter and Intra individual variations.
2. Configuration of electrodes.
3. Cortical area targeted for stimulation.
4. Stimulation polarity (Anodal/Cathodal).
5. Stimulus Intensity.
6. Stimulation Dosage (Duration/No. of Sessions).
7. Reason of Stimulation (Type of Disorder/Pathological Condition of Patient/ Cognition).

Since in vivo measurements are not practically possible, therefore computational modeling serves as an important tool for clinicians to predict and determine the electric field generated for a specific setting and configuration of Neural Stimulation[3],[10],[139-140].Moreover, it helps in understanding and improvement of stimulation outcomes [95-96].

2.9 Gaps in Previous Research

When the computational modeling was started for tDCS, oversimplified models were developed. The role of anisotropy of tissues (cortical/non cortical) and the morphology of the brain region was underestimated in the assessment of induced field variables [7-8],[37-38], [115-117],[145]. With the passage of time, directional conductivity in white matter (WM) and skull was employed in field estimations [58],[130],[140]. However, few anatomical regions of head were used and the estimates were montage specific. Hence, it was not feasible to generalize the effects of tissue anisotropy on field variables. Some anatomically intricate and voxel based modeling studies were done on Virtual Family models with isotropic conductivities [107-109]. These models do not incorporate subject variations.

The ignorance in understanding of the underlying mechanisms of tDCS is a major impediment in the optimization of its use [112]. Recent studies have shown that in the case of Conventional tDCS modeling, the anatomical features [1],[21-22],[114],[153], and conductivity [57-59],[92],[148-149],[154] systematically shape the brain's electric field distribution [15],[60],[110-112],[126],[132]. Most of the research conducted in HD-tDCS has been based on empirical results [77],[80],[134]. Moreover, the modeling of HD-tDCS has considered a simplified homogenous conductivity profile [9],[12],[70],[91],[120],[124-125] for the human head layers in response to electrical stimulations of brain. Such assumptions can therefore lead to an inaccurate estimation of dosage delivery and other relevant parameters.

For 4x1 HD-tDCS, some studies have used plus configuration [134-135] in defining return electrodes while some has used multiply (with a 45 degree phase shift) configurations [47],[91],[60]. However, no proper reasoning for the selection of a particular angle in stimulation montage has been provided. The spatial distribution of induced E-field is highly sensitive to electrode configuration [93], [118] and dielectric properties of the tissues .This research will provide a solid ground to figure out the underlying bio-physical concepts [128]. Consequently, this will lead to better comprehension of neuro modulatory phenomena in HD-tDCS and hence improve its efficiency.

2.10 Chapter Summary

In this chapter, an in-depth review of literature has been presented. The Anatomy and Physiology of Human Head and Brain, the elements and activation sequences involved in Motor control mechanism of the Brain, Brain disorders and their treatments, Neural Stimulation Therapies with special consideration to different types of tDCS and the role of computational modeling have been elaborated. The chapter also discusses about the research gaps in previous work and how to mitigate them.

CHAPTER 3

METHODOLOGY

CHAPTER 3: METHODOLOGY

The research was conducted in two phases; Modeling and Simulation see figure 3.1. The modeling phase was further deconstructed into three divisions; Tissue Classification, Model and Mesh Generation. Whereas, the Simulation phase dealt with the application of Electrical Stimulations on the Head Models developed in first phase. Each phase and its sub-phases have been discussed in detail in the following text.

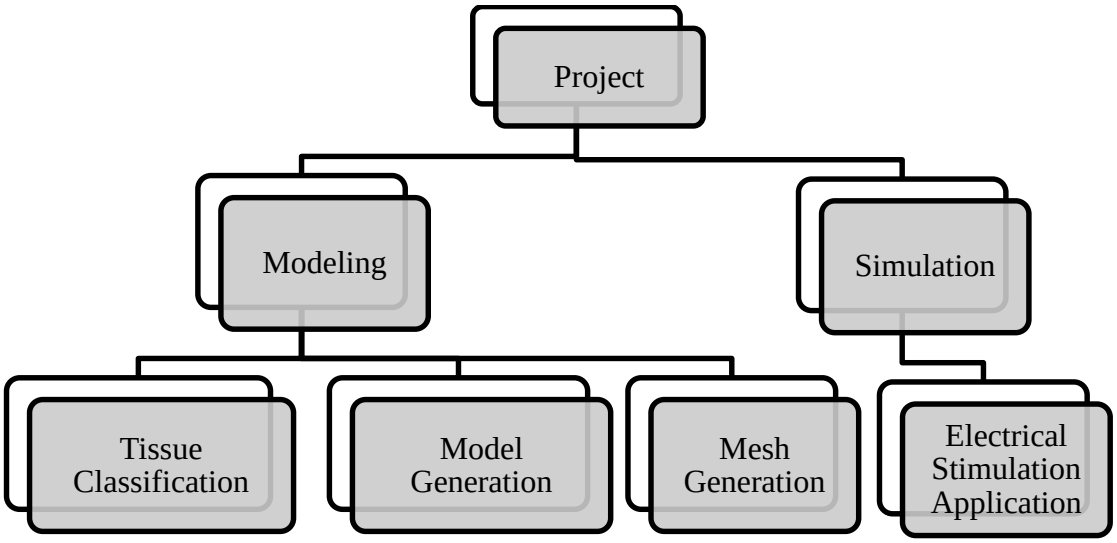


Figure 3.1 Phases of the Project.

3.1 Modeling Phase

In this phase, Volume conductor Head Model was developed. Following is the detailed description of the sub-classifications of modeling phase.

3.1.1 Tissue Classification

The first step in this phase was the collection of data. 3D Scalar MRI datasets (weighted T1, T2 and PD) were used in this study [34].Each modality consisted of 1x1x1 mm3 isotropic voxel resolution and 181 x 217 x 181 slices. The second step was the construction of head tissue masks. The software employed for tissue differentiation was Simpleware. In addition, Brain Atlas was used to further assist Tissue mask separation. Masking was done using the image

processing protocols described in [135-136]. The figure 3.2 shows the Simpleware environment in which tissue classification of 3D scalar images was carried out.

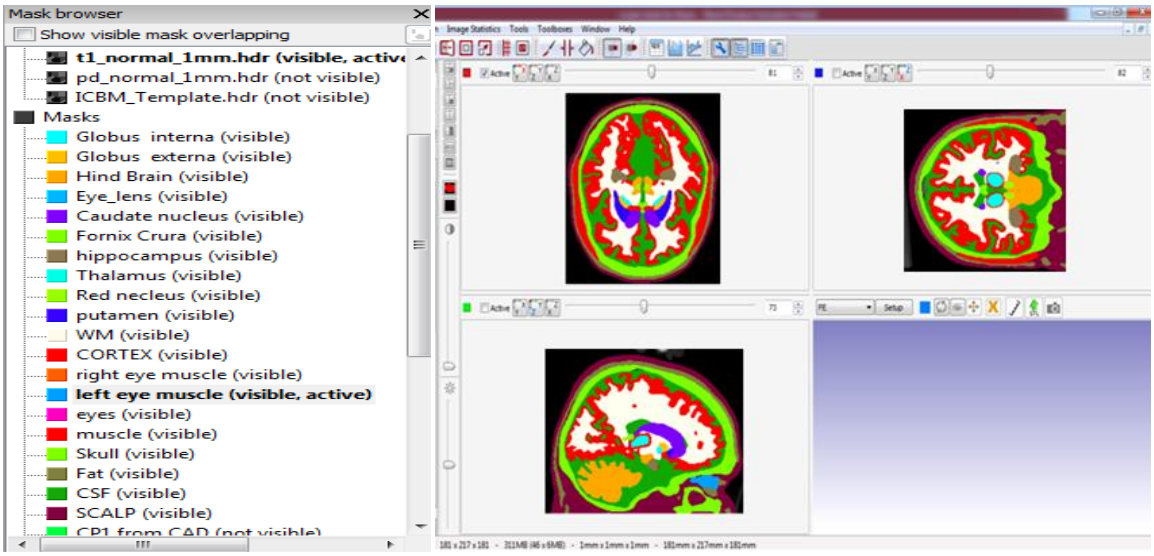


Figure 3.2 Tissue Classifications in Simpleware.

3.1.2 Model Generation

The development of three dimensional Head Models for the application of Transcranial Stimulations was carried out in two stages which are given as follows.

1. Generation of Realistic Head Model.
2. Placement of Electrodes over the Head Model.

3.1.2.1 Generation of Realistic Head Model

After the development of tissue masks as described in the previous section, these tissue masks were then transformed into 3D Head model layers in ScanIP (Simpleware Software). The Head Model (see figure 3.3) comprised of nineteen anatomical regions of head and brain which includes Scalp, Skull, Subcutaneous Fats, Muscles of Mastication, Eyes, Eye Muscles, Left and Right Eye Muscles, Cerebrospinal Fluid, Grey Matter, White Matter and Subcortical Regions (Hindbrain, Thalamus, Hippocampus, Fornix Crura, Caudate Nuclueus, Red Nucleus, Putamen, Globus Pallidus interna and externa). It is worth mentioning here that for ease of analysis the Brainstem, Cerebellum, Medulla and Pons were combined in Hindbrain Layer.

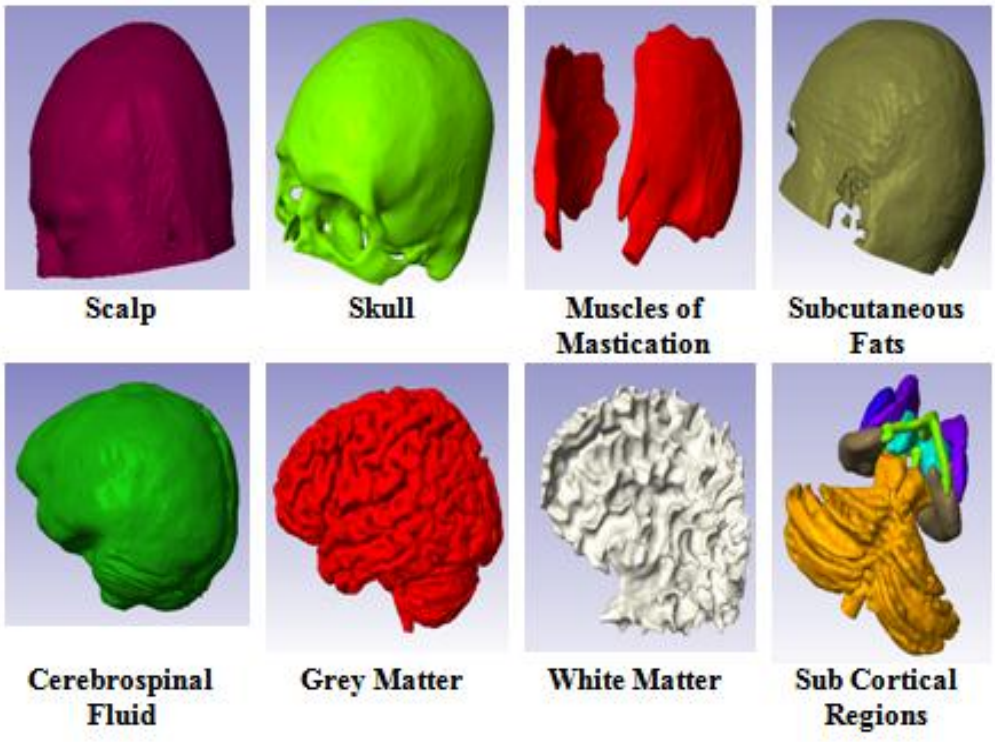
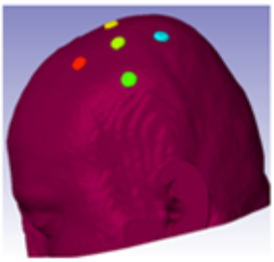
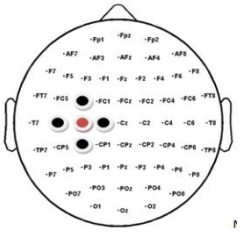
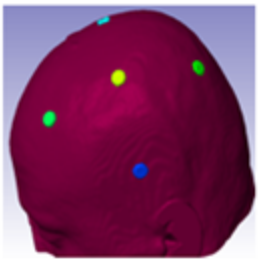
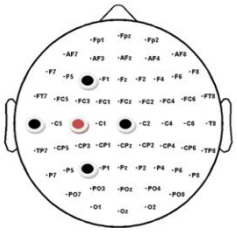
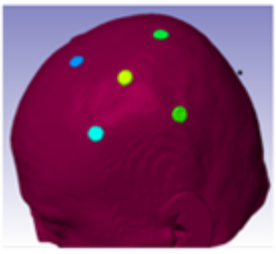
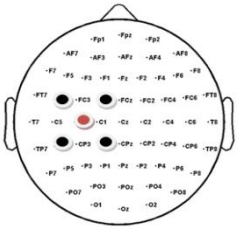
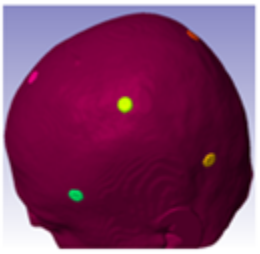
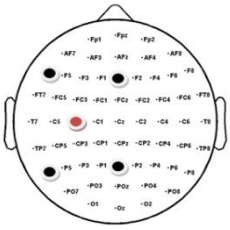


Figure 3.3 Different Layers of Head Model.

3.1.2.2 Placement of Electrodes over the Head Model.

In this stage, High definition electrodes were placed over the Head Model in ScanCAD (Simpleware Software). Electrode configurations were derived from Standard International 10–10 EEG Electrode system. The description of models is given in Table 3-1.

Table 3-1 Models with their respective electrode configuration.

Type	Details	Anode	Cathode	Electrode Placement	Electrode Position
Model 1	Small Radius Plus Configuration	C3	C1 FC3 C5 CP3	 Model 1	
Model 2	Large Radius Plus Configuration	C3	CZ F3 T7 P3	 Model 2	
Model 3	Small Radius Multiply (45 deg Shift) Configuration	C3	CP1 CP5 FC5 FC1	 Model 3	
Model 4	Large Radius Multiply (45 deg Shift) Configuration	C3	FZ F7 P7 PZ	 Model 4	

3.1.3 Mesh Generation

In this part, the four Models generated were prepared for the application of Stimulations on them. As the Transcranial Direct Current Stimulations are based on principle of Maxwell Equations, solving these equations on a highly non-uniform, irregular and convoluted structure of brain would be a cumbersome job. For such calculations, Finite Element Method (FEM) has been employed to estimate the solutions in the form of linear combination of basis functions (Piecewise linearity). FEM is a numerical technique which is used for the finding the solutions of Partial Differential Equations with Boundary Conditions.

Therefore, the whole model (Head and Electrodes) was discretized into 3D tetrahedral finite elements in ScanFE (Simpleware Software). The Final Volumetric Mesh Model contained 20 regions corresponding to 19 different segmented tissues & Electrode masks and consisted of around 2 million tetrahedral elements. To achieve better accuracy, the mesh generation algorithm was fine-tuned making the regions of interest (Grey Matter, White Matter and Sub-cortical regions) densely meshed.

3.2 Simulation Phase

The main aim of the simulation phase was the application of Electrical Stimulations over the Head Models which was carried out in COMSOL Multiphysics software. COMSOL was used to perform FEM analysis for calculating Electric Field Induced as a result of Stimulation. The simulation phase was divided in the following three stages.

1. Layer-wise Assignment of Materials
2. Application of Boundary Conditions
3. Setting of Stimulation Parameters

3.2.1 Layer-wise Assignment of Materials

Quasi-static approximation is applicable on Maxwell's Equations for low frequency stimulations. [96-97]. The dominant dielectric behaviour in this case is Resistive in Nature and hence only electrical conductivity has to be assigned in material properties. The electric field induced in tDCS is normal to the cortical surface under the quasi static conditions.[23],[98]. Laplace's equation (1) and Ohm's Law (2) were used for calculating Electric Field and Current

Density respectively. Where E=Electric field intensity (V/m), ∇= Gradient, V= Potential Difference (V), J=Current Density (A/m2), σ= Electrical Conductivity of Layer (siemens/m)

$$E = -\nabla V \quad \textbf{(1)}$$

$$J = \sigma E \quad \textbf{(2)}$$

3.2.1.1 Inclusion of Isotropic Conductivity in Model

Each segmented region of the Model was given its respective isotropic values of electrical conductivity which are listed in Table 3-2

3.2.1.2 Inclusion of Anisotropy Conductivity in Model

Recalling the objectives of this research project, the inclusion of anisotropy has to be tested. In this study, Skull, Muscles of Mastication, Eye Muscles (Left and Right) and White Matter have been assigned anisotropic values. The anisotropy of Skull has been attributed due to the difference in electrical behavior of different layers of Skull i.e Compacta and Spongiosa. Human Skull has low conductivity in the radial direction (σ_R) as compared to tangential direction (σ_T) (eq. 4). Whereas in the Muscles (Mastication and Eye), the longitudinal conductivity (σ_L) is 5 times more than the transverse (σ_{Trans}) (eq. 5). However, the white matter relationship between the longitudinal and transverse conductivity of white matter has been depicted in eq. 6.

Anisotropic Conductivity Tensors (eq. 3) for Skull, Muscles and White matter were derived using the directional conductivity of these layers as described in [136]. To restrict the anisotropic conductivity of a layer to its isotropic magnitude, the Wang Constraint was applied (Wang, Haynor & Kim 2001). Wang's Volume Constraint states that the product of the components (tangential and radial) of conductivity must be constant and equal to the square of its isotropic value (eq. 7). The conductivity values obtained were in local coordinate system (eq. 9). To use these values in FEM models, they had to be converted into Cartesian coordinate system for all the anisotropic layers (eq. 10).

$$\sigma = \begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{xy} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{xz} & \sigma_{yz} & \sigma_{zz} \end{pmatrix} \quad \textbf{(3)}$$

$$\sigma_T = 10\sigma_R \quad \textbf{(4)}$$

$$\sigma_L = 5\sigma_{Trans} \quad \textbf{(5)}$$

$$\sigma_L = 10\sigma_{Trans} \quad \textbf{(6)}$$

$$\sigma_R \sigma_T = \sigma_{ISO}^2 \quad \textbf{(7)}$$

$$\frac{4}{3}\pi\sigma_R \, \sigma_T^2 = \frac{4}{3}\pi \, \sigma_{ISO}^3 \quad \textbf{(8)}$$

$$\sigma_{(local)} = \begin{pmatrix} \sigma_R & 0 & 0 \\ 0 & \sigma_T & 0 \\ 0 & 0 & \sigma_T \end{pmatrix} \quad \textbf{(9)}$$

$$\sigma_{(x,y,z)} = A\sigma_{local} \, A^T \quad \textbf{(10)}$$

The values of isotropic and anisotropic conductivities used in COMSOL for material properties assignment have been listed in Table 3-2.

Table 3-2 The Conductivity Assignments of Tissues.

Material	Isotropic Model (S/m)	Anisotropic Model (S/m)	Material	Isotropic Model (S/m)	Anisotropic Model (S/m)
Scalp	0.43	0.43	**Hind Brain**	0.25	0.25
CSF	1.79	1.79	**Thalamus**	0.32	0.32
Subcutaneous Fat	0.025	0.025	**Hippocampus**	0.32	0.32
Eye Muscles/ Muscles of Mastication	0.16	Anisotropic	**Fornix Crura**	0.32	0.32
Eye	0.5	0.5	**Caudate Nucleus**	0.32	0.32
Eye Lens	0.31	0.31	**Globus Externa/Interna**	0.32	0.32
Skull	0.015	Anisotropic	**Putamen**	0.32	0.32
Grey Matter	0.32	0.32	**Red Nucleus**	0.25	0.25
White Matter	0.15	Anisotropic	**Electrode Gel**	0.43	0.43

3.2.2 Application of Boundary Conditions

For the solving Maxwell's equation in a particular stimulation setting, it is necessary to define the boundary conditions at the interfaces of the electrode and different tissue layers accordingly. As the Conductivity of Electrode Gel is much higher than the Volume conductor, therefore Dirichlet boundary condition ($\boldsymbol{V = V_0}$) was used at the exposed surface of Electrode acting as Anode. Whereas the exposed surfaces of the cathodes have been assigned $\boldsymbol{V = 0}$. The

External boundaries of the head were electrically insulated ***(n.J = 0).*** For all the inner interfaces, the continuity of the normal component of J has been maintained by Neumann Boundary Condition($\boldsymbol{n.J_1 = n.J_2}$)**.** See figure 3.4.

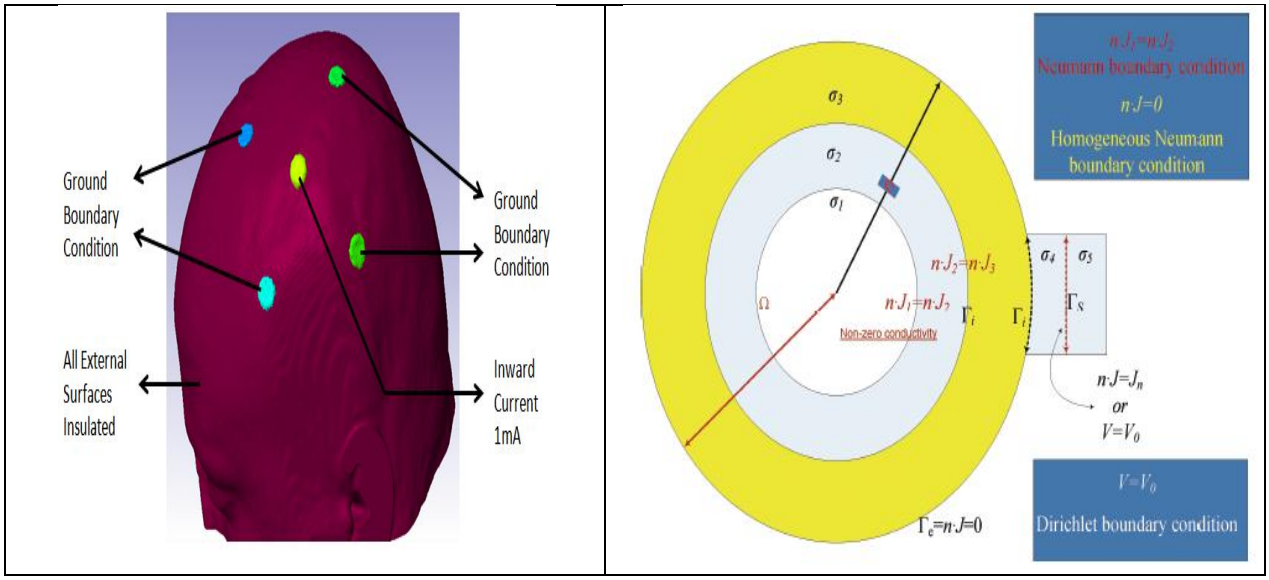


Figure 3.4 Application of Boundary Conditions. (Left) Outside View and (Right) Inside View where Γs= Exposed Surface, Γ_i= inner boundary, Γ_e= exposed boundary. Source (Right): Shahid et al 2013.

3.2.3 Setting of Stimulation Parameters

A constant current stimulating device (ranging from 0-2mA) has been used for Transcranial Direct Current Stimulation in clinical practice. Therefore, in all the eight test cases of this computational study, the stimulation current was set at 1mA current. The desired electric current injected through the Anode was achieved by readjustment of Voltage across anode surface. For this purpose, Gauss's Theorem was applied which states that the total current flowing outward across surface of Anode is equal to the Rate of change of charge in the Volume of the Head (eq. 11).

$$\oint_S \boldsymbol{J} \cdot \hat{\boldsymbol{n}}\, dS = -\frac{\partial}{\partial t}\int_V \rho\, dV, \qquad \textbf{(11)}$$

The Initial Voltage of 1V has been applied to find out the value of surface integral in COMSOL. Using this value, the Bulk Resistance of the model has been calculated. Thereafter, the value of Bulk Resistance has been used to calculate the new voltage for the application of desired current. This process has been performed for the simulation of all the eight models separately (figure 3.5). The corresponding values for each model have been mentioned in Table 3-3.

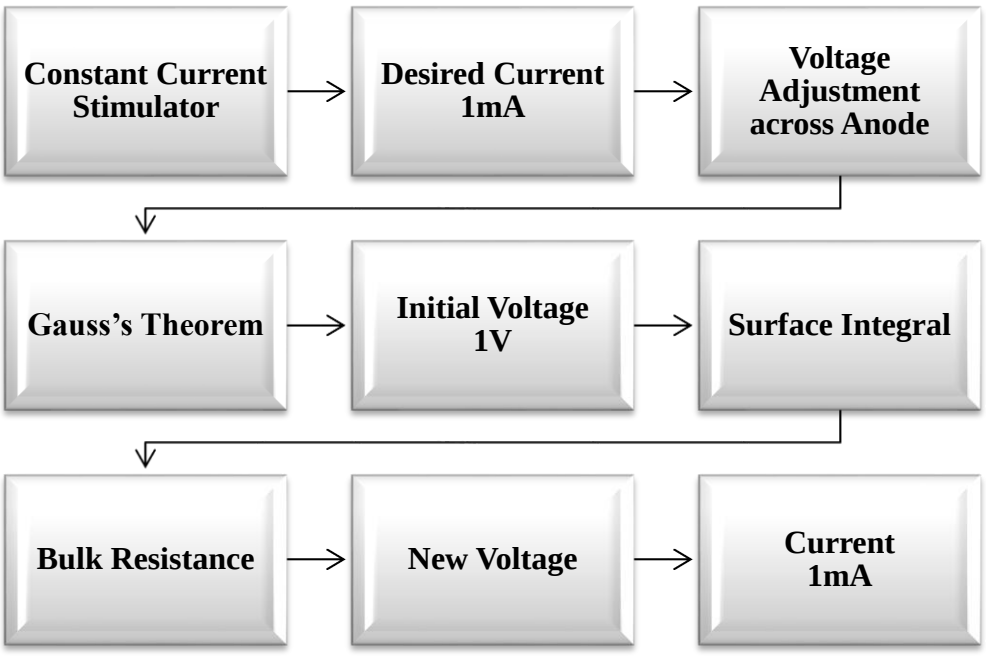


Figure 3.5 Workflow for the Setting of Stimulation Parameters.

Table 3-3 The Settings of Stimulation Parameters.

Sr. No	Model	Conductivity Profile	Bulk Resistance (Ω)	Voltage (mV)	Current (mA)
1.	Model 1	Isotropic	630.159	630.159	0.99997
2.	Model 1	Anisotropic	635.364	635.364	1
3.	Model 2	Isotropic	768.994	768.994	1
4.	Model 2	Anisotropic	787.154	787.154	1
5.	Model 3	Isotropic	702.642	702.642	1
6.	Model 3	Anisotropic	712.962	712.962	0.99997
7.	Model 4	Isotropic	816.726	816.726	1
8.	Model 4	Anisotropic	844.880	844.880	0.99998

3.3 Computational Resources

The tasks performed in Modeling and Simulation is quite expensive computationally. Therefore, it is worth mentioning here the resources, amount of time and software utilized in this project is given in Table 3-4 and Figure 3.6.

Table 3-4 Time and Computational Cost of Each Model.

Sr. No	Tasks for Each Model	Time	Computational Resource
1.	Tissue segmentation	18 h	Dell T5500 workstation 24 GB RAM 2.0 GHz Xenon processor.
2.	3D head model & tetrahedral mesh generation	6 h	RCMS Supercomputer 24GB RAM node, 2.4 GHz processor.
3.	Resistance Calculation (COMSOL)	25.75 min	HSL SMME Dell Optiplex 9020 Intel-core i7, 16GB RAM, 3.6 GHz processor.
4.	Electric Field Simulation Runtime (COMSOL)	27.5 min	
5.	Scalar Analysis (COMSOL)	23 min	
6.	Statistical & Comparative Analysis (MATLAB)	20 min	

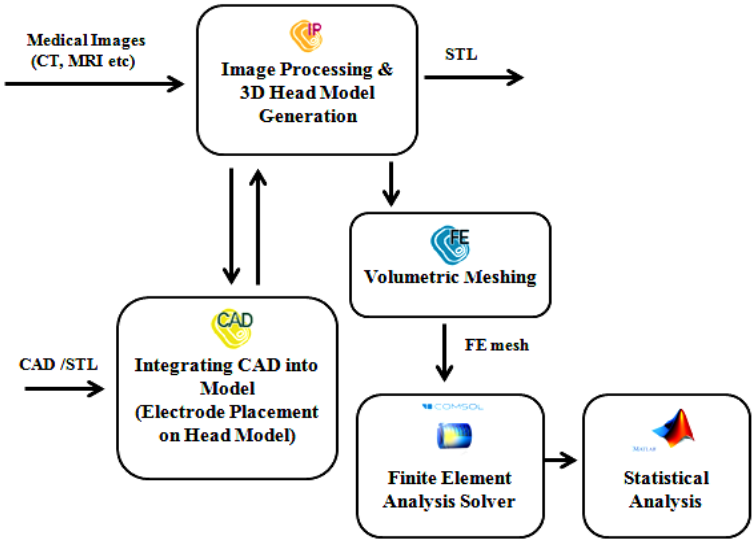


Figure 3.6 Workflow of the Software used.

3.4 Chapter Summary

In this chapter, the methodology for the implementation and designing of the project has been explained. A pictorial summary of this section has been presented in Figure 3.7.

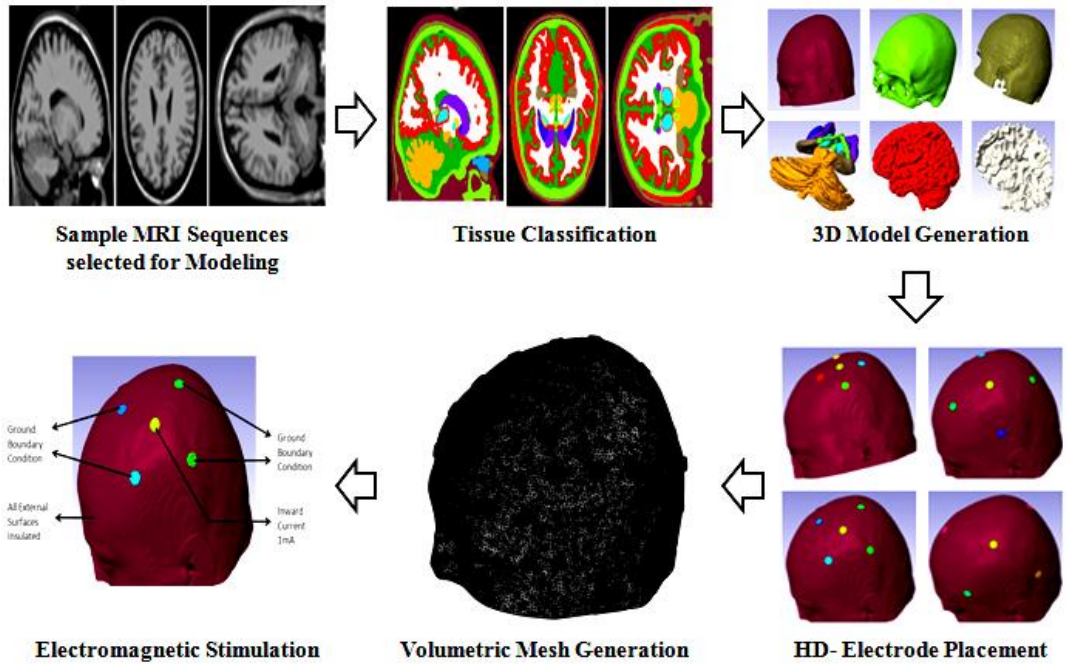


Figure 3.7 Summary of Methodology.

CHAPTER 4

RESULTS & DISCUSSION

CHAPTER 4: RESULTS & DISCUSSION

The main purpose of this study was to figure out the role of introducing anisotropy in the head models and investigate the effects of changing the radius and angle of stimulation of electrodes in electric field maps. For the former case, Residual Error (RE) and Relative Difference Measure (RDM) were used respectively for the magnitude and topographic comparisons (see Appendix A). Whereas, for the later two cases, variations in electric fields were quantified using Peak, Mean, Median, Skewness and Penetration plots. Apart from the statistical plots, the graphical plots are also presented for getting a better picture of the Electric field spread.

Before going into the observations of field maps inside the brain, it was imperative to check whether the models were working properly. For this purpose, the fields were plotted in the non-cortical areas and compared with the literature. It was found that most of the current was shunted in non-cortical areas due to the large impedance of the scalp. The peak value of induced E-field was spotted beneath the Anode. In addition, current was mainly distributed underneath the circumference of stimulation montage which is in concurrence with previous studies. For better visualization, the fields were shown in the form of threshold plots in which the maximum color range value of Electric field in all four models was set as 30V/m (see Figure 4.1).

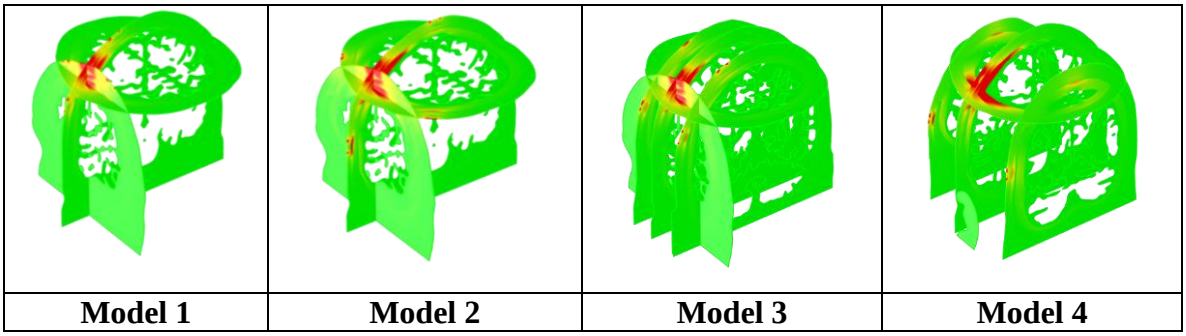


Figure 4.1 Electric Field Slice Threshold Plots (30V/m) showing Non cortical Regions.

The graphical plots obtained from COMSOL simulations give a comparison of the spread and the intensity of Electric Fields for the eight models (four isotropic and four anisotropic).

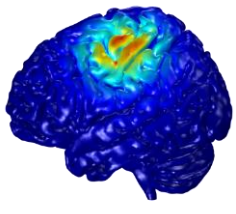
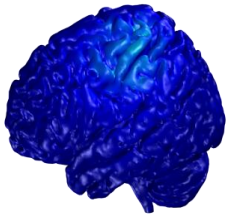
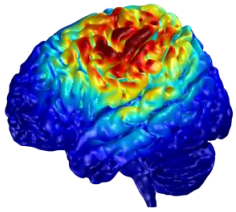
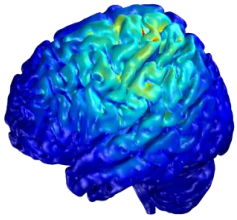
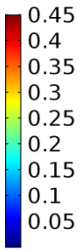
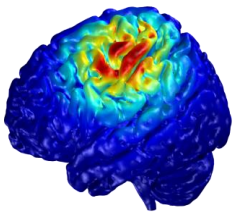
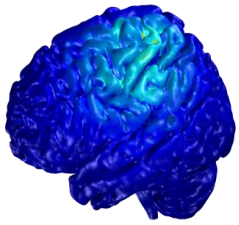
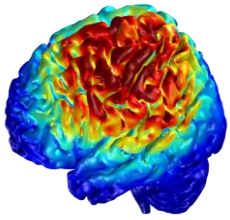
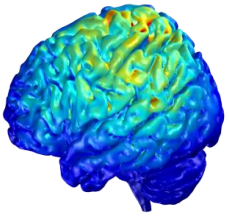
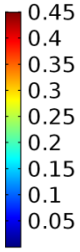
				
Max = 0.51 V/m	Max = 0.31 V/m	Max = 0.94 V/m	Max = 0.89 V/m	
Model 1 (Isotropic)	**Model 1 (Anisotropic)**	**Model 2 (Isotropic)**	**Model 2 (Anisotropic)**	**Plotting Range**
				
Max = 0.72 V/m	Max = 0.56 V/m	Max = 1.08 V/m	Max = 1.22 V/m	
Model 3 (Isotropic)	**Model 3 (Anisotropic)**	**Model 4 (Isotropic)**	**Model 4 (Anisotropic)**	**Plotting Range**

Figure 4.2 Volume Plots of Complete Brain showing differences in the Spread & Intensity of Electric Field (V/m) in Isotropic and Anisotropic Models.

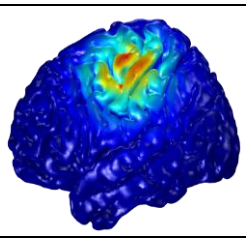
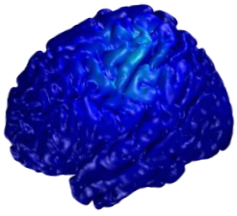
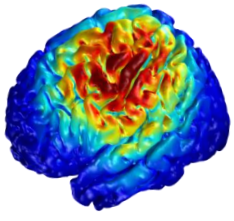
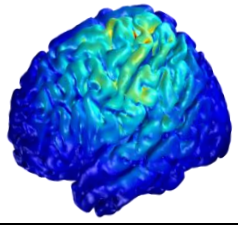
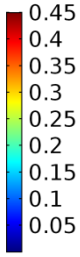
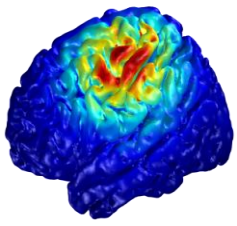
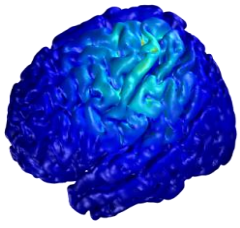
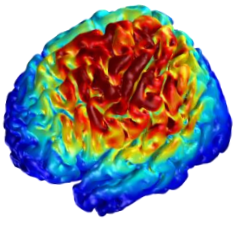
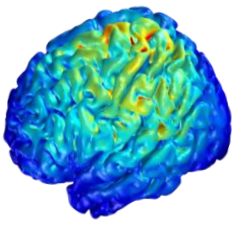
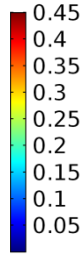
				
Max = 0.51 V/m	Max = 0.2 V/m	Max = 0.94 V/m	Max = 0.52 V/m	
Model 1 (Isotropic)	**Model 1 (Anisotropic)**	**Model 2 (Isotropic)**	**Model 2 (Anisotropic)**	**Plotting Range**
				
Max = 0.72 V/m	Max = 0.34 V/m	Max = 1.08 V/m	Max = 0.68 V/m	
Model 3 (Isotropic)	**Model 3 (Anisotropic)**	**Model 4 (Isotropic)**	**Model 4 (Anisotropic)**	**Plotting Range**

Figure 4.3 Volume Plots of Grey Matter showing differences in the Spread & Intensity of Electric Field (V/m) in Isotropic and Anisotropic Models.

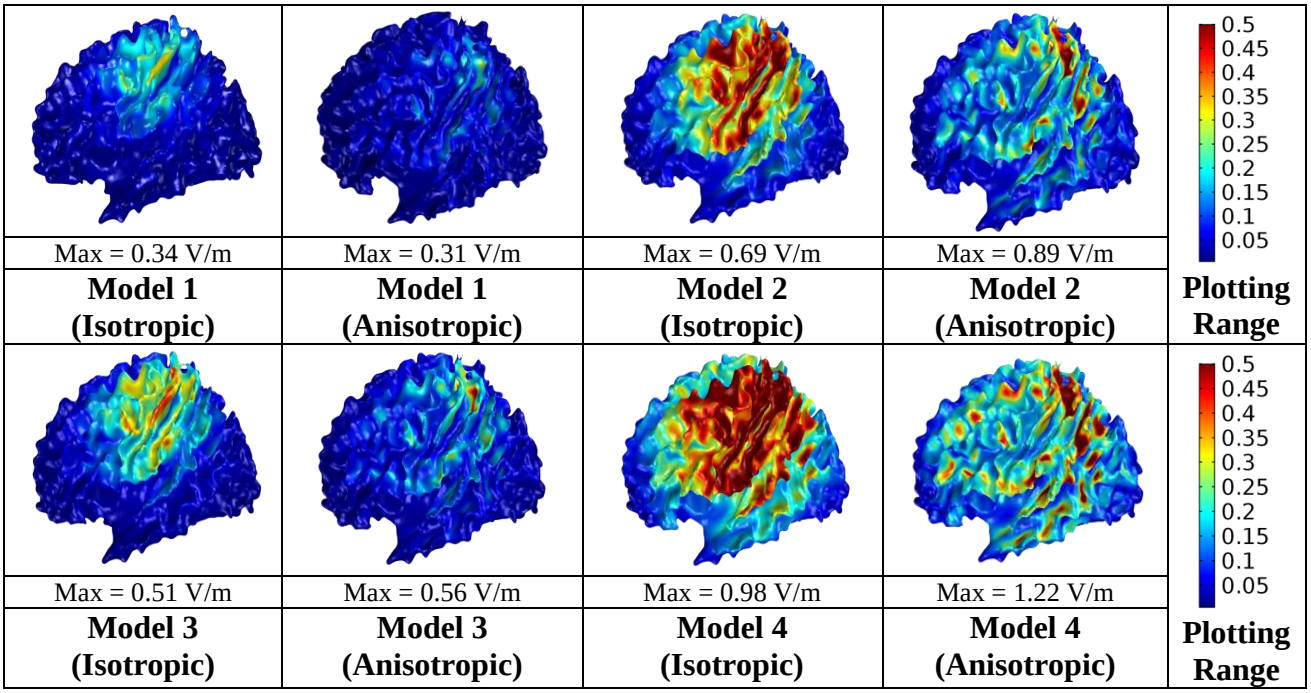


Figure 4.4: Volume Plots of White Matter showing differences in the Spread & Intensity of Electric Field (V/m) in Isotropic and Anisotropic Models.

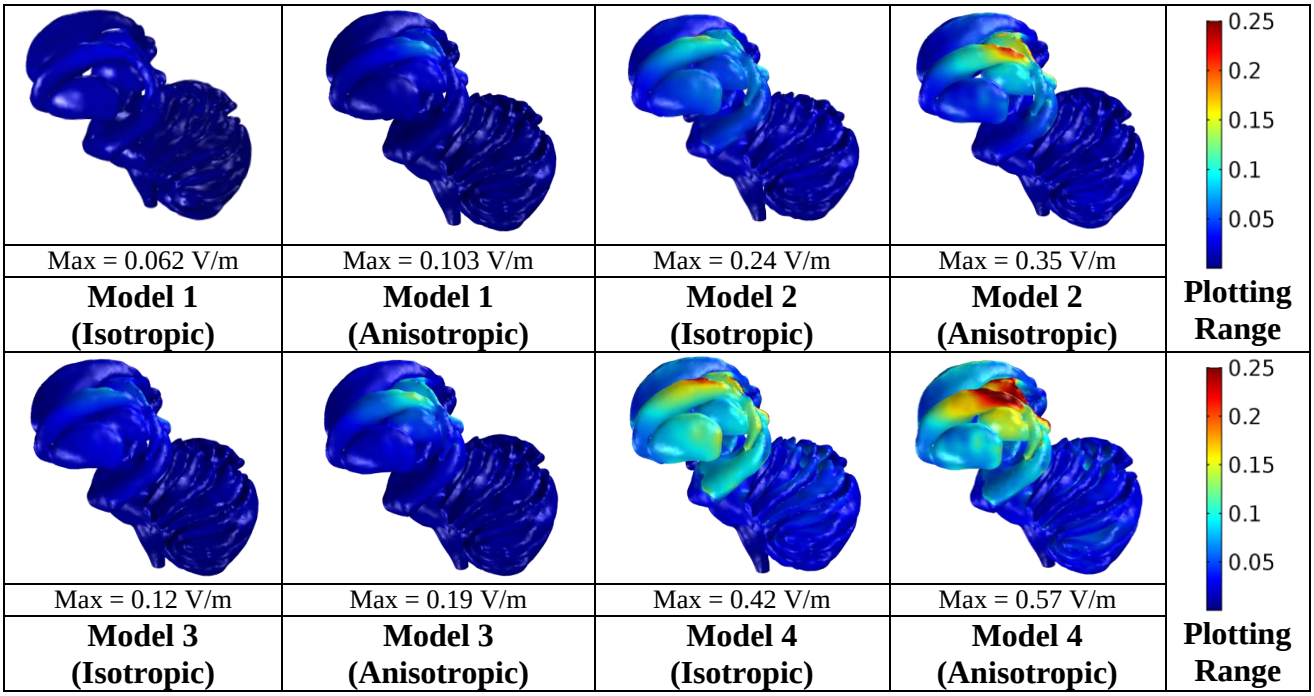
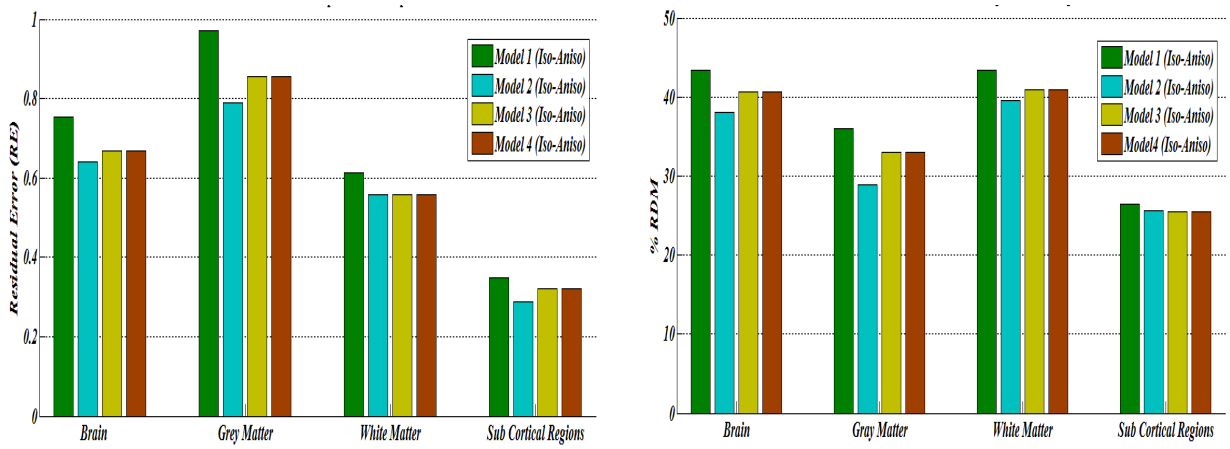


Figure 4.5: Volume Plots of Sub Cortical Regions showing differences in the Spread & Intensity of Electric Field (V/m) in Isotropic and Anisotropic Models.

Figure 4.2 illustrates the results on Whole Brain (Grey Matter, White Matter and Subcortical Regions combined), whereas figures 4.3, 4.4, 4.5 depict separate 3D plots of Grey Matter, White Matter and Sub Cortical Regions respectively. Although it is quite evident from these graphical depictions that there are marked differences in the distribution of Electric Field in all the models but for the quantification and explanation of these results, Statistical calculations were performed in MATLAB for answering the problem questions of this research.

4.1 Effects of Anisotropy

The comparison between the isotropic and anisotropic models for brain, grey matter, white matter and sub cortical regions has been shown in the figure 4.6. The RE/RDM values of brain in Model 1, Model 2, Model 3 and Model 4 are (0.75/43%), (0.65/38%), (0.68/41) and (0.68/41) respectively. The magnitude difference is almost 0.7 and the topological difference is almost 40% in overall electric field distribution of brain as compared to isotropic models which is quite significant. Also, the human brain is naturally anisotropic therefore, in the next simulations only anisotropic models were considered.

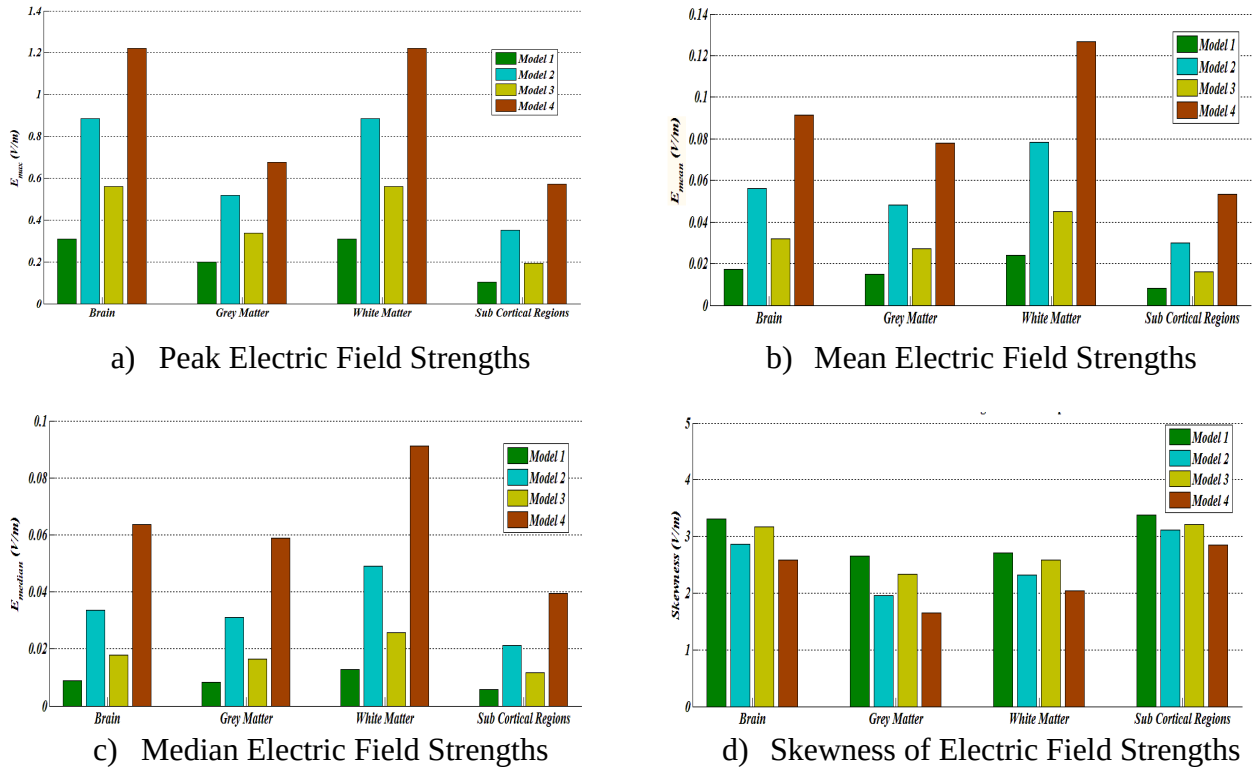


(a) (b)

Figure 4.6: (a) Residual Error and (b) Relative Difference Measure between Isotropic and Anisotropic Models in Electric Field Distribution.

4.2 Effects of Variation in Radius & Angle of Stimulation

The ($E_{max}/E_{mean}/E_{median}$) values of whole brain are (0.3/0.015/0.08), (0.9/0.058/0.035), (0.58/0.035/0.018) and (1.22/0.09/0.064) for Model 1, Model 2, Model 3 and Model 4 respectively. On increasing the radius of stimulation, the intensity (Peak) and the spread (Mean, Median) of E-field in all layers of brain increased whereas, the skewness decreased as the fields tend to become uniform. It is clearly evident from the plots that the same trends were followed by the electric fields when the angle of stimulation was shifted from 0^0 to 45^0 (See figure 4.7).



a) Peak Electric Field Strengths

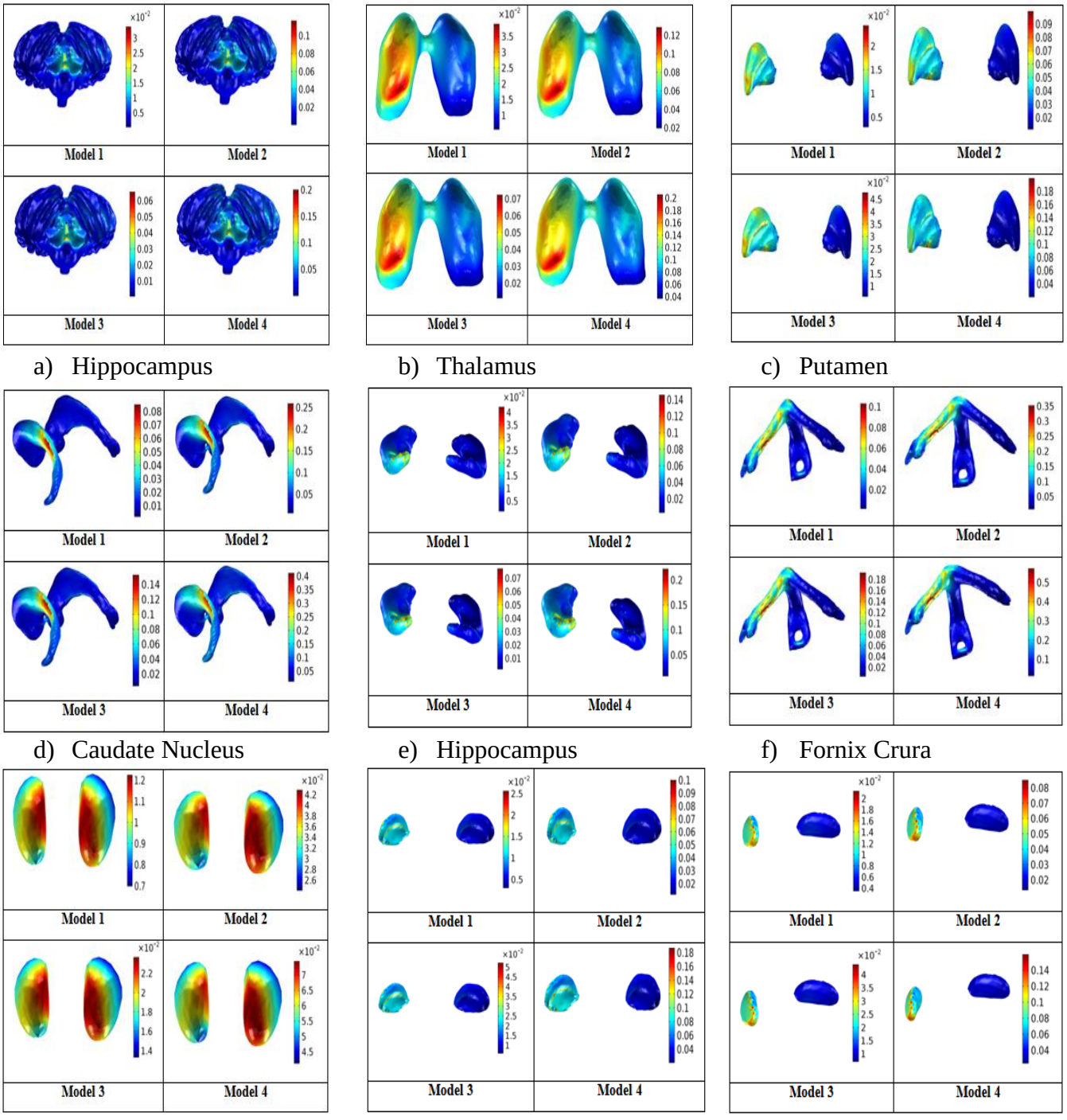
b) Mean Electric Field Strengths

c) Median Electric Field Strengths

d) Skewness of Electric Field Strengths

Figure 4.7: Electric Field Statistical Comparison Plots of Brain, Grey Matter, White Matter & Sub Cortical Regions (V/m) in Anisotropic Models.

For more elaborate explanation of the fields in sub cortical regions, they were separately plotted in figure 4.8 with their respective range of values.



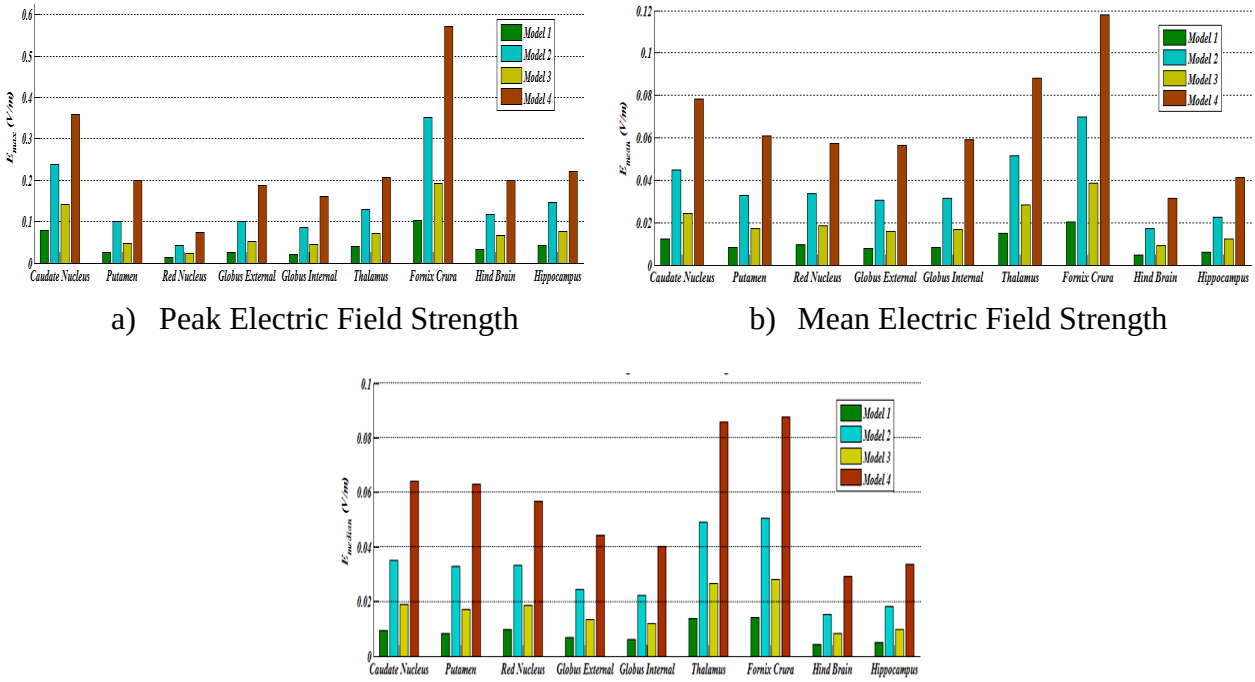
a) Hippocampus b) Thalamus c) Putamen

d) Caudate Nucleus e) Hippocampus f) Fornix Crura

g) Red Nucleus h) Globus Pallidus External i) Globus Pallidus Internal

Figure 4.8: Volume Comparison Plots of Sub Cortical Regions showing differences in the Spread & Intensity of Electric Field (V/m).

For the quantification of these results, statistical comparisons are provided in figure 4.9. The Peak, Mean and Median Plots illustrate that the Spread and Intensity increases in both cases (i.e. increase in radius and angle of stimulation).



a) Peak Electric Field Strength

b) Mean Electric Field Strength

c) Median Electric Field Strength

Figure 4.9 Statistical Comparison Plots of Sub Cortical Regions showing differences in the Spread and Intensity of Electric Field (V/m).

The penetration of fields inside the brain with respect to actual/threshold intensities and directions are shown in figure 4.10. It is quite obvious from the slice plots that the penetration intensity amplifies as the stimulation ring radius and angle increases. The coronal slice of brain has been taken to show the comparisons in dispersion of Electric field the labelling of which is shown in Figure 4.11.The third row of figure 4.10 shows the direction and intensity of Electric Field distribution in the form of Arrows. The density of arrows is more in the regions where the field is strong.

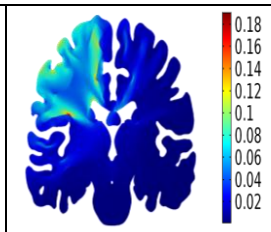
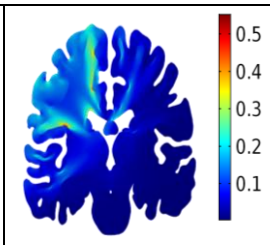
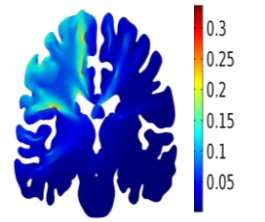
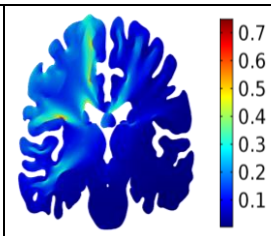
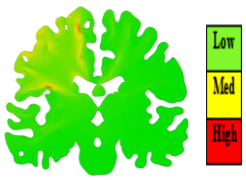
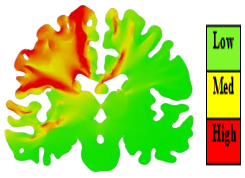
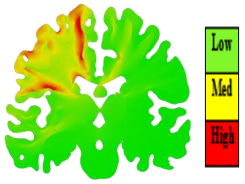
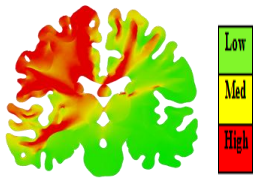
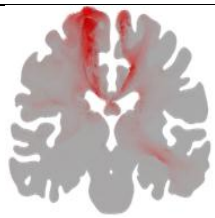
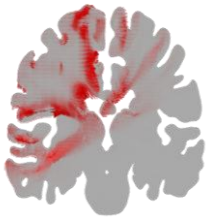
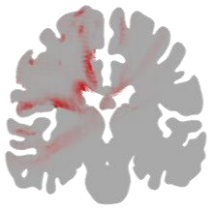
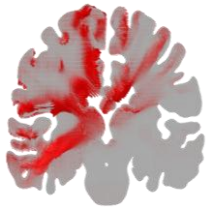
Actual Intensity Plots				
Threshold Intensity Plots (0.2V/m)				
Arrow Direction Plots				
Model	**Model 1**	**Model 2**	**Model 3**	**Model 4**

Figure 4.10 Coronal Slice Comparison Plots showing penetration (intensity and direction) of Electric Field in Cortical and Sub Cortical Regions of Brain (V/m).

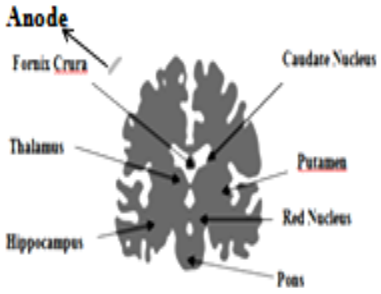


Figure 4.11 Coronal Slice of Brain

4.3 Discussion

In computational modeling, the validation of results is performed either by performing clinical trials or by consulting previous reported literature. The clinical trials also have their limitations. The recordings inside human brain cannot be performed in runtime stimulations. Therefore, till now the best way to validate the modeling study is to crosscheck the results with the literature in which researchers have themselves benchmarked their results with the experimental data on animal/human models.

It has been theorized by Radman [142-143] that the normal component of Electric field is optimally polarizes the cortical neurons along cortical columns (Layer 5 pyramidal neurons). Hence, this component of electric field is mainly responsible for the cortical stimulation. Therefore the Normal Electric Field component has been used for the analysis.

The normal electric fields were plotted in cortical and non cortical regions of the head. Anodal stimulation has been considered in this study therefore the electric field had its maximum value just below the anode and the distribution of current inside the brain is mostly constricted in the area hemmed in by the cathodes. Due to the large resistance of the non cortical areas especially the scalp region, most of the current was dispersed in this region. Beneath the anode, the induced E-field had its peak value. Current distribution was mainly focused under the ring formed by the stimulation montage. These observations are in concurrence with the previous studies (Datta et. al 2009).

The results were plotted in graphical form to get a comprehensive three dimensional perspective of the electric field distribution in human head (Figure 4.2, 4.3, 4.4, 4.5). But to have a statistical comparison of different models MATLAB analysis was run separately on each layer of the head for all the considered cases. For the case of studying anisotropy in the model, Relative Difference Measure has been used as topological measure whereas Residual Error has been used magnitude measure.

The inclusion of directional conductivity caused significant changes in overall brain's electric field (Topological ~ 40% and Magnitude ~ 0.7) as compared to isotropic models (Figure 4.6). As the current density remains constant in a layer, therefore the electric field strength

changes in order to compensate for the variations in conductivity. However, the intensity variation depends upon the extent of alignment between the induced current and the neurons. Hence, the layer in-homogeneity and anisotropy leads to high values of RE and RDM as deduced by Shahid [135].

When anisotropy is introduced, the white matter conductivity becomes lower in the direction of stimulating current which creates an enhancement in electric field intensity in the subcortical regions of the brain. Although there is a decrease in current density but as there is an inverse relationship between electric field and current density ($E = J/\sigma$) rapid changes in conductivity of tissues can cause discontinuities in current density. For this reason, a sharp increase in intensity of electric field is observed at the interacting surface of grey and white matter.

When stimulation ring radius was varied, our prognosis shows that as the distance between the ring electrodes (cathodes) and the center electrode (anode) increased the electric field intensity increased. This was validated across different subjects from the previous literature [91]. Though there were differences in the values of peak intensity of field reflecting changes in tissue conductivity, model's anatomical complexity and positioning of electrodes. Only a slight distribution of current was observed outside the cortical areas covered beneath the stimulation ring.

Many of the researchers used plus configuration [134-135] in setting the stimulation electrodes whereas some of them have used Multiply; a 45 degree shifted configuration [47],[91],[60]. But they have not explained the reason for the selection of a particular montage used in their studies. As the electrode configuration highly influences the spatial distribution of induced E-field [93], [118] and dielectric properties of the tissues. Hence, the third objective of this study was to compare the orientations of stimulation montage. In this study we have kept the anode fixed at C3 and changed the return electrodes. The other parameters such as stimulation current, radius of stimulation and the conductivity of tissues were maintained constant in each case of the study.

The variations in the shape (i.e. Plus and Multiply) of the montage brought noticeable changes in the spread; intensity and the depth of penetration. It was observed that the area that has been stimulated in shifted angle configuration was bigger than it was in the case of Plus configuration. Therefore, the bulk resistance and consequently the voltage required to maintain the desired current of 1mA increased by Ohm's Law. As a result, the electric field intensity amplified. (Figure

In both cases i.e. radius change and angle shift, the focality decreased and spread increased as the area covered by the stimulating electrodes increased (Figure 4.7 (a), (b), (c)). For the same reason, the skewness decreased as the fields tend to become uniform when the area increased (Figure 4.7 (d)).

The depth of penetration of current increased as a consequence of increasing the area covered by the stimulating montage (Figure 4.8, 4.9, 4.10). Although, the general perception is that the penetration should decrease as the spread is increasing. But the converse was observed i.e. the penetration increased. Alam [91] has explained the reason for this enhancement in terms of conservation of current density.

When our results were compared with the existing literature it was found that they are concurrent. The results showed that electric field distribution were following the same trends in all the cases considered in this study. Though there were differences in terms of maximum and minimum values. These differences were attributed to the anatomical variations, directional conductivity profiles and the orientation of stimulating electrodes.

These findings and the electric field maps in various cortical and sub cortical regions are essential in determining the type of polarization (Depolarization/Hyper polarization) occurring as a result of the externally induced electric field as described in the Chapter 2. This information will play a key role in deciding the configuration which should be employed in a particular pathological or learning task as explained in the Table 2-1 and Table 2-2.

4.4 Chapter Summary

In this chapter, the results have been presented. There is a noticeable change in electric field distribution when the complexity in conductivity of brain layers has been introduced. Also, the research hypothesis has been validated for the variations in stimulation montage. The electric field has been discussed in terms of changes in intensity, direction, focality and penetration in four different models. It has been concluded that the stimulation parameters depend predominantly on the intervention goals and practical considerations.

CHAPTER 5

CONCLUSION & FUTURE PROSPECTS

CHAPTER 5: CONCLUSIONS & FUTURE PROSPECTS

In this project, the complexity of computational analysis has been improved with the inclusion of in-homogeneity, more sub-cortical layers, stimulating radius and angle shift. Previously researchers have employed this approach in head models having 6-7 isotropic layers. However, in this study the effects of stimulation montage radius change have been observed in Anisotropic Models. In addition, the comparison between the Plus and Multiply (45^0 shift) configuration with the alteration of radius has not been presented before to the best of our knowledge.

It can be concluded from this project, that the appropriate stimulating configuration depends upon the interventional goals (target application, pathological condition and subject's anatomy) and device considerations. From applications perspective, this research can provide the following advantages.

1. As the stimulating ring's radius and shape can be modified to create a more intense electric field, it can be applied as an alternative method to adjust the input stimulator current when the applied current is restricted by the safety limits.
2. The accuracy of the predicted region of interest and the dosage parameters of stimulation can be controlled by using effective modeling and simulation approaches
3. Based on individual anatomy, pathological conditions (Parkinson's, Stroke, Depression etc) and/or learning and memory enhancements, this computational study would be beneficial to the clinicians for planning customized HD-tDCS treatments of the patients.
4. This investigative study can be useful for future research in cognitive neuroscience and Non Invasive Deep Brain Stimulation.
5. Transcranial Direct Current Stimulation Device has been introduced for the very first time in Pakistan for research purposes by the Human Systems Lab, SMME, NUST. As a proud member of Human Systems Lab, SMME, NUST, my study will serve as a forward matter for hospitals, neural rehabilitation centers, and research and development organizations in Pakistan in the field of Neuro-modulation.

5.1 Future Recommendations

Following are some of the way forwards of this research (see figure 5.1).

1. This research has been based on C3 Anodal Stimulation in 4x1 HD-tDCS. The models used in this study can be adapted for other HD-tDCS configurations, positions and targets.
2. By incorporating neuronal fiber details in these models, microscopic level analysis can be done.
3. The integration of structural models with the functional (e.g. functional Magnetic Resonance) imaging and signaling (e.g. Electroencephalography (EEG)) modalities can lead to better understanding of brain connectivity.
4. There is a dire need of standardizing conductivity values of head layers in tDCS modeling. This will provide consistency in the analysis of realistic head models.
5. The present study has been performed on static conditions. In future, time based analysis can also be employed in the same models.
6. Some other Transcranial stimulation techniques like alternate current and random noise stimulations (tACS, tRNS) [151] can also be done by the inclusion of frequency and dielectric material properties in the present models.
7. The Deep Brain Stimulation (DBS) which was once thought to be an invasive procedure can also be probed in with this simple and non invasive technique.
8. The cost of computation (time and resources) [135] remains a major challenge in computational modeling. The refinement in algorithms to reduce this cost is essential for making Image Guided Intervention a constructive tool for clinicians.

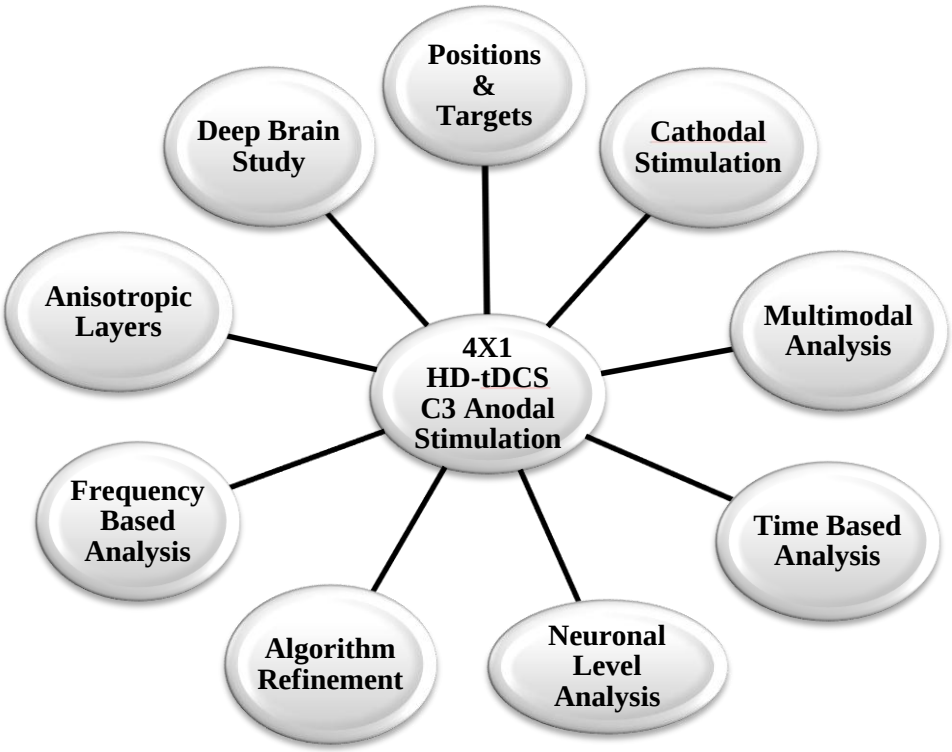


Figure 5.1 The Way Forward of Research.

REFERENCES

[1] A. Antal, R. Polania, C. Schmidt-Samoa, P. Dechent, and W. Paulus, "Transcranial direct current stimulation over the primary motor cortex during fMRI," *Neuroimage,* vol. 55, pp. 590-596, 2011.

[2] A. Antal, T. Z. Kincses, M. A. Nitsche, and W. Paulus, "Manipulation of phosphene thresholds by transcranial direct current stimulation in man," *Experimental brain research,* vol. 150, pp. 375-378, 2003.

[3] A. Brunoni, R. Ferrucci, M. Bortolomasi, M. Vergari, L. Tadini, P. Boggio, *et al.*, "Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder," *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* vol. 35, pp. 96-101, 2011.

[4] Antal, M. Bikson, A. Datta, B. Lafon, P. Dechent, L. C. Parra, *et al.*, "Imaging artifacts induced by electrical stimulation during conventional fMRI of the brain," *Neuroimage,* vol. 85, pp. 1040-1047, 2014.

[5] A. Datta, D. Truong, P. Minhas, L. C. Parra, and M. Bikson, "Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models," 2012.

[6] A. Datta, J. M. Baker, M. Bikson, and J. Fridriksson, "Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient," *Brain stimulation,* vol. 4, pp. 169-174, 2011.

[7] A. Datta, M. Bikson, and F. Fregni, "Transcranial direct current stimulation in patients with skull defects and skull plates: high-resolution computational FEM study of factors altering cortical current flow," *Neuroimage,* vol. 52, pp. 1268-1278, 2010.

[8] A. Datta, M. Elwassif, F. Battaglia, and M. Bikson, "Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis," *Journal of neural engineering,* vol. 5, p. 163, 2008.

[9] A. Datta, V. Bansal, J. Diaz, J. Patel, D. Reato, and M. Bikson, "Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad," *Brain stimulation,* vol. 2, pp. 201-207. e1, 2009.

[10] A. Datta, X. Zhou, Y. Su, L. C. Parra, and M. Bikson, "Validation of finite element model of transcranial electrical stimulation using scalp potentials: implications for clinical dose," *Journal of neural engineering,* vol. 10, p. 036018, 2013.

[11] A. F. DaSilva, D. Q. Truong, M. F. DosSantos, R. L. Toback, A. Datta, and M. Bikson, "State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control," *Frontiers in neuroanatomy,* vol. 9, p. 89, 2015.

[12] A. F. DaSilva, M. E. Mendonca, S. Zaghi, M. Lopes, M. F. DosSantos, E. L. Spierings, *et al.*, "tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine," *Headache: The Journal of Head and Face Pain,* vol. 52, pp. 1283-1295, 2012.

[13] A. F. DaSilva, M. S. Volz, M. Bikson, and F. Fregni, "Electrode positioning and montage in transcranial direct current stimulation," *JoVE (Journal of Visualized Experiments)*, pp. e2744-e2744, 2011.

[14] A. Flood, G. Waddington, and S. Cathcart, "High-definition transcranial direct current stimulation enhances conditioned pain modulation in healthy volunteers: a randomized trial," *The Journal of Pain*, vol. 17, pp. 600-605, 2016.

[15] A. Indahlastari, M. Chauhan, B. Schwartz, and R. J. Sadleir, "Changing head model extent affects finite element predictions of transcranial direct current stimulation distributions," *Journal of Neural Engineering*, vol. 13, p. 066006, 2016.

[16] A. J. Fagerlund, O. A. Hansen, and P. M. Aslaksen, "Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial," *Pain*, vol. 156, pp. 62-71, 2015.

[17] A. Ladeira, F. Fregni, C. Campanhã, C. A. Valasek, D. De Ridder, A. R. Brunoni, *et al.*, "Polarity-dependent transcranial direct current stimulation effects on central auditory processing," *PLoS One*, vol. 6, p. e25399, 2011.

[18] A. Opitz, A. Falchier, C.-G. Yan, E. M. Yeagle, G. S. Linn, P. Megevand, *et al.*, "Spatiotemporal structure of intracranial electric fields induced by transcranial electric stimulation in humans and nonhuman primates," *Scientific Reports*, vol. 6, 2016.

[19] A. Opitz, W. Paulus, S. Will, A. Antunes, and A. Thielscher, "Determinants of the electric field during transcranial direct current stimulation," *Neuroimage*, vol. 109, pp. 140-150, 2015.

[20] A. R. Brunoni, C. T. Teng, C. Correa, M. Imamura, J. P. Brasil-Neto, R. Boechat, *et al.*, "Neuromodulation approaches for the treatment of major depression: challenges and recommendations from a working group meeting," *Arquivos de neuro-psiquiatria*, vol. 68, pp. 433-451, 2010.

[21] A. R. Brunoni, J. Amadera, B. Berbel, M. S. Volz, B. G. Rizzerio, and F. Fregni, "A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation," *International Journal of Neuropsychopharmacology*, vol. 14, pp. 1133-1145, 2011.

[22] A. R. Brunoni, M. A. Nitsche, N. Bolognini, M. Bikson, T. Wagner, L. Merabet, *et al.*, "Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions," *Brain stimulation*, vol. 5, pp. 175-195, 2012.

[23] A. Rahman, D. Reato, M. Arlotti, F. Gasca, A. Datta, L. C. Parra, *et al.*, "Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects," *The Journal of physiology*, vol. 591, pp. 2563-2578, 2013.

[24] A. Roy, B. Baxter, and B. He, "High-definition transcranial direct current stimulation induces both acute and persistent changes in broadband cortical synchronization: A simultaneous tDCS–EEG study," *IEEE Transactions on Biomedical Engineering*, vol. 61, pp. 1967-1978, 2014.

[25] A. T. Hill, P. B. Fitzgerald, and K. E. Hoy, "Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations," *Brain stimulation*, vol. 9, pp. 197-208, 2016.

[26] A. V. Peterchev, T. A. Wagner, P. C. Miranda, M. A. Nitsche, W. Paulus, S. H. Lisanby, *et al.*, "Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices," *Brain Stimulation*, vol. 5, pp. 435-453, 2012.

[27] A. Woods, A. Antal, M. Bikson, P. Boggio, A. Brunoni, P. Celnik, *et al.*, "A technical guide to tDCS, and related non-invasive brain stimulation tools," *Clinical neurophysiology*, vol. 127, pp. 1031-1048, 2016.

[28] Alonzo, J. Brassil, J. L. Taylor, D. Martin, and C. K. Loo, "Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation," *Brain stimulation*, vol. 5, pp. 208-213, 2012.

[29] B. Elsner, J. Kugler, M. Pohl, and J. Mehrholz, "Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke," *The Cochrane Library*, 2016.

[30] B. Forogh, Z. Mirshaki, G. R. Raissi, A. Shirazi, K. Mansoori, and T. Ahadi, "Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: a pilot randomized controlled trial," *Neurological Sciences*, vol. 37, pp. 253-259, 2016.

[31] B. R. Webster, P. A. Celnik, and L. G. Cohen, "Noninvasive brain stimulation in stroke rehabilitation," *NeuroRx*, vol. 3, pp. 474-481, 2006.

[32] B. W. Vines, C. Cerruti, and G. Schlaug, "Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation," *BMC neuroscience*, vol. 9, p. 103, 2008.

[33] B. W. Vines, D. G. Nair, and G. Schlaug, "Contralateral and ipsilateral motor effects after transcranial direct current stimulation," *Neuroreport*, vol. 17, pp. 671-674, 2006.

[34] C. A. Cocosco, V. Kollokian, R. K.-S. Kwan, G. B. Pike, and A. C. Evans, "Brainweb: Online interface to a 3D MRI simulated brain database," in *NeuroImage*, 1997.

[35] C. J. Stagg and H. Johansen-Berg, "Studying the effects of transcranial direct-current stimulation in stroke recovery using magnetic resonance imaging," *Frontiers in human neuroscience*, vol. 7, p. 857, 2013.

[36] C. Saiote, T. Goldschmidt, C. Timäus, M. D. Steenwijk, A. Opitz, A. Antal, *et al.*, "Impact of transcranial direct current stimulation on fatigue in multiple sclerosis," *Restorative neurology and neuroscience*, vol. 32, pp. 423-436, 2014.

[37] C.-H. Im, H.-H. Jung, J.-D. Choi, S. Y. Lee, and K.-Y. Jung, "Determination of optimal electrode positions for transcranial direct current stimulation (tDCS)," *Physics in medicine and biology*, vol. 53, p. N219, 2008.

[38] C.-H. Im, J.-H. Park, M. Shim, W. H. Chang, and Y.-H. Kim, "Evaluation of local electric fields generated by transcranial direct current stimulation with an extracephalic reference electrode based on realistic 3D body modeling," *Physics in medicine and biology*, vol. 57, p. 2137, 2012.

[39] D. C. Klooster, A. J. de Louw, A. Aldenkamp, R. Besseling, R. Mestrom, S. Carrette, *et al.*, "Technical aspects of neurostimulation: focus on equipment, electric field modeling, and stimulation protocols," *Neuroscience & Biobehavioral Reviews,* vol. 65, pp. 113-141, 2016.

[40] D. Doruk, Z. Gray, G. L. Bravo, A. Pascual-Leone, and F. Fregni, "Effects of tDCS on executive function in Parkinson's disease," *Neuroscience letters,* vol. 582, pp. 27-31, 2014.

[41] D. Edwards, M. Cortes, A. Datta, P. Minhas, E. M. Wassermann, and M. Bikson, "Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS," *Neuroimage,* vol. 74, pp. 266-275, 2013.

[42] D. Mielke, A. Wrede, W. Schulz-Schaeffer, A. Taghizadeh-Waghefi, M. A. Nitsche, V. Rohde, *et al.*, "Cathodal transcranial direct current stimulation induces regional, long-lasting reductions of cortical blood flow in rats," *Neurological research,* vol. 35, pp. 1029-1037, 2013.

[43] D. P. Purpura and J. G. McMurtry, "Intracellular activities and evoked potential changes during polarization of motor cortex," *Journal of neurophysiology,* vol. 28, pp. 166-185, 1965.

[44] D. Q. Truong, G. Magerowski, G. L. Blackburn, M. Bikson, and M. Alonso-Alonso, "Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines," *NeuroImage: Clinical,* vol. 2, pp. 759-766, 2013.

[45] E. F. Chua, R. Ahmed, and S. M. Garcia, "Effects of HD-tDCS on memory and metamemory for general knowledge questions that vary by difficulty," *Brain Stimulation,* vol. 10, pp. 231-241, 2017.

[46] E. J. Tehovnik, "Electrical stimulation of neural tissue to evoke behavioral responses," *Journal of neuroscience methods,* vol. 65, pp. 1-17, 1996.

[47] E. M. Caparelli-Daquer, T. J. Zimmermann, E. Mooshagian, L. C. Parra, J. K. Rice, A. Datta, *et al.*, "A pilot study on effects of 4× 1 high-definition tDCS on motor cortex excitability," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*, 2012, pp. 735-738.

[48] F. Bolzoni and E. Jankowska, "Presynaptic and postsynaptic effects of local cathodal DC polarization within the spinal cord in anaesthetized animal preparations," *The Journal of physiology,* vol. 593, pp. 947-966, 2015.

[49] F. Bolzoni, L. G. Pettersson, and E. Jankowska, "Evidence for long-lasting subcortical facilitation by transcranial direct current stimulation in the cat," *The Journal of physiology,* vol. 591, pp. 3381-3399, 2013.

[50] F. Bolzoni, M. Bączyk, and E. Jankowska, "Subcortical effects of transcranial direct current stimulation in the rat," *The Journal of physiology,* vol. 591, pp. 4027-4042, 2013.

[51] F. Fregni and A. Pascual-Leone, "Technology insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS," *Nature clinical practice Neurology,* vol. 3, pp. 383-393, 2007.

[52] F. Fregni, M. Nitsche, C. Loo, A. Brunoni, P. Marangolo, J. Leite, *et al.*, "Regulatory considerations for the clinical and research use of transcranial direct current stimulation

(tDCS): review and recommendations from an expert panel," *Clinical research and regulatory affairs*, vol. 32, pp. 22-35, 2015.

[53] F. Fregni, P. S. Boggio, M. Nitsche, F. Bermpohl, A. Antal, E. Feredoes, *et al.*, "Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory," *Experimental brain research*, vol. 166, pp. 23-30, 2005.

[54] G. A. Zito, T. Senti, D. Cazzoli, R. M. Müri, U. P. Mosimann, T. Nyffeler, *et al.*, "Cathodal HD-tDCS on the right V5 improves motion perception in humans," *Frontiers in behavioral neuroscience*, vol. 9, p. 257, 2015

[55] G. Laste, W. Caumo, L. N. S. Adachi, J. R. Rozisky, I. C. de Macedo, P. R. Marques Filho, *et al.*, "After-effects of consecutive sessions of transcranial direct current stimulation (tDCS) in a rat model of chronic inflammation," *Experimental brain research*, vol. 221, pp. 75-83, 2012.

[56] G. S. Shekhawat, F. Sundram, M. Bikson, D. Truong, D. De Ridder, C. M. Stinear, *et al.*, "Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief," *Neurorehabilitation and neural repair*, vol. 30, pp. 349-359, 2016.

[57] H. Hallez, S. Staelens, and I. Lemahieu, "Dipole estimation errors due to not incorporating anisotropic conductivities in realistic head models for EEG source analysis," *Physics in medicine and biology*, vol. 54, p. 6079, 2009.

[58] H. S. Suh, S. H. Kim, W. H. Lee, and T.-S. Kim, "Realistic simulation of transcranial direct current stimulation via 3-D high-resolution finite element analysis: effect of tissue anisotropy," in *Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE*, 2009, pp. 638-641.

[59] H. S. Suh, W. H. Lee, and T.-S. Kim, "Influence of anisotropic conductivity in the skull and white matter on transcranial direct current stimulation via an anatomically realistic finite element head model," *Physics in medicine and biology*, vol. 57, p. 6961, 2012.

[60] H. Seo, D. Kim, and S. C. Jun, "Effect of Anatomically Realistic Full-Head Model on Activation of Cortical Neurons in Subdural Cortical Stimulation—A Computational Study," *Scientific reports*, vol. 6, 2016.

[61] H.-I. Kuo, M. Bikson, A. Datta, P. Minhas, W. Paulus, M.-F. Kuo, *et al.*, "Comparing cortical plasticity induced by conventional and high-definition 4× 1 ring tDCS: a neurophysiological study," *Brain stimulation*, vol. 6, pp. 644-648, 2013.

[62] I. Laakso, S. Tanaka, S. Koyama, V. De Santis, and A. Hirata, "Inter-subject variability in electric fields of motor cortical tDCS," *Brain stimulation*, vol. 8, pp. 906-913, 2015.

[63] J. A. Williams, M. Imamura, and F. Fregni, "Updates on the use of non-invasive brain stimulation in physical and rehabilitation medicine," *Journal of rehabilitation medicine*, vol. 41, pp. 305-311, 2009.

[64] J. Au, C. Karsten, M. Buschkuehl, and S. M. Jaeggi, "Optimizing transcranial direct current stimulation protocols to promote long-term learning," *Journal of Cognitive Enhancement*, vol. 1, pp. 65-72, 2017.

[65] J. C. Horvath, O. Carter, and J. D. Forte, "Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be)," *Frontiers in systems neuroscience,* vol. 8, p. 2, 2014.

[66] J. C. Horvath, S. J. Vogrin, O. Carter, M. J. Cook, and J. D. Forte, "Effects of a common transcranial direct current stimulation (tDCS) protocol on motor evoked potentials found to be highly variable within individuals over 9 testing sessions," *Experimental brain research,* vol. 234, pp. 2629-2642, 2016.

[67] J. D. Richardson, P. Fillmore, A. Datta, D. Truong, M. Bikson, and J. Fridriksson, "Toward development of sham protocols for high-definition transcranial direct current stimulation (HD-tDCS)," *NeuroRegulation,* vol. 1, p. 62, 2014.

[68] J. G. Rohan, K. A. Carhuatanta, S. M. McInturf, M. K. Miklasevich, and R. Jankord, "Modulating hippocampal plasticity with in vivo brain stimulation," *Journal of Neuroscience,* vol. 35, pp. 12824-12832, 2015.

[69] J. Giordano, M. Bikson, E. S. Kappenman, V. P. Clark, H. B. Coslett, M. R. Hamblin, *et al.*, "Mechanisms and Effects of Transcranial Direct Current Stimulation," *Dose-Response,* vol. 15, p. 1559325816685467, 2017.

[70] J. J. Borckardt, M. Bikson, H. Frohman, S. T. Reeves, A. Datta, V. Bansal, *et al.*, "A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception," *The Journal of Pain,* vol. 13, pp. 112-120, 2012.

[71] J. M. Galea, G. Jayaram, L. Ajagbe, and P. Celnik, "Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation," *Journal of Neuroscience,* vol. 29, pp. 9115-9122, 2009.

[72] J. M. Jo, Y.-H. Kim, M.-H. Ko, S. H. Ohn, B. Joen, and K. H. Lee, "Enhancing the working memory of stroke patients using tDCS," *American Journal of Physical Medicine & Rehabilitation,* vol. 88, pp. 404-409, 2009.

[73] J. P. Dmochowski, A. Datta, M. Bikson, Y. Su, and L. C. Parra, "Optimized multi-electrode stimulation increases focality and intensity at target," *Journal of neural engineering,* vol. 8, p. 046011, 2011.

[74] J. P. Dmochowski, A. Datta, Y. Huang, J. D. Richardson, M. Bikson, J. Fridriksson, *et al.*, "Targeted transcranial direct current stimulation for rehabilitation after stroke," *Neuroimage,* vol. 75, pp. 12-19, 2013.

[75] J. S. Gomes, P. Shiozawa, Á. M. Dias, D. D. Valverde, H. Akiba, A. P. Trevizol, *et al.*, "Left Dorsolateral Prefrontal Cortex Anodal tDCS Effects on Negative Symptoms in Schizophrenia," *Brain stimulation,* vol. 8, p. 989, 2015.

[76] K. Funke, "Quite simple at first glance–complex at a second: modulating neuronal activity by tDCS," *The Journal of physiology,* vol. 591, pp. 3809-3809, 2013.

[77] K. Heimrath, C. Breitling, K. Krauel, H. J. Heinze, and T. Zaehle, "Modulation of pre-attentive spectro-temporal feature processing in the human auditory system by HD-tDCS," *European Journal of Neuroscience,* vol. 41, pp. 1580-1586, 2015.

[78] K. J. Yoon, B.-M. Oh, and D.-Y. Kim, "Functional improvement and neuroplastic effects of anodal transcranial direct current stimulation (tDCS) delivered 1day vs. 1week after cerebral ischemia in rats," *Brain research,* vol. 1452, pp. 61-72, 2012.

[79] K. S. Al-Harbi and N. A. Qureshi, "Neuromodulation therapies and treatment-resistant depression," *Med Devices (Auckl),* vol. 5, pp. 53-65, 2012.

[80] L. Castillo-Saavedra, N. Gebodh, M. Bikson, C. Diaz-Cruz, R. Brandao, L. Coutinho, *et al.*, "Clinically effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: phase II open-label dose optimization," *The Journal of Pain,* vol. 17, pp. 14-26, 2016.

[81] L. J. R. Lauro, M. Rosanova, G. Mattavelli, S. Convento, A. Pisoni, A. Opitz, *et al.*, "TDCS increases cortical excitability: Direct evidence from TMS–EEG," *Cortex,* vol. 58, pp. 99-111, 2014.

[82] L. M. Li, K. Uehara, and T. Hanakawa, "The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies," *Frontiers in cellular neuroscience,* vol. 9, p. 181, 2015.

[83] L. N. S. Adachi, W. Caumo, G. Laste, L. F. Medeiros, J. R. Rozisky, A. de Souza, *et al.*, "Reversal of chronic stress-induced pain by transcranial direct current stimulation (tDCS) in an animal model," *Brain research,* vol. 1489, pp. 17-26, 2012.

[84] L. Tadini, R. El-Nazer, A. R. Brunoni, J. Williams, M. Carvas, P. Boggio, *et al.*, "Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents," *The journal of ECT,* vol. 27, pp. 134-140, 2011.

[85] M. A. Nitsche and W. Paulus, "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation," *The Journal of physiology,* vol. 527, pp. 633-639, 2000.

[86] M. A. Nitsche and W. Paulus, "Transcranial direct current stimulation–update 2011," *Restorative neurology and neuroscience,* vol. 29, pp. 463-492, 2011.

[87] M. A. Nitsche, D. Liebetanz, A. Antal, N. Lang, F. Tergau, and W. Paulus, "Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects," *Supplements to Clinical neurophysiology,* vol. 56, pp. 255-276, 2003.

[88] M. A. Nitsche, L. G. Cohen, E. M. Wassermann, A. Priori, N. Lang, A. Antal, *et al.*, "Transcranial direct current stimulation: state of the art 2008," *Brain stimulation,* vol. 1, pp. 206-223, 2008.

[89] M. A. Nitsche, P. S. Boggio, F. Fregni, and A. Pascual-Leone, "Treatment of depression with transcranial direct current stimulation (tDCS): a review," *Experimental neurology,* vol. 219, pp. 14-19, 2009.

[90] M. Acler, T. Bocci, D. Valenti, M. Turri, A. Priori, and L. Bertolasi, "Transcranial direct current stimulation (tDCS) for sleep disturbances and fatigue in patients with post-polio syndrome," *Restorative neurology and neuroscience,* vol. 31, pp. 661-668, 2013.

[91] M. Alam, D. Q. Truong, N. Khadka, and M. Bikson, "Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS)," *Physics in medicine and biology*, vol. 61, p. 4506, 2016.

[92] M. Bikson and A. Rahman, "Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms," *Frontiers in human neuroscience*, vol. 7, p. 688, 2013.

[93] M. Bikson, A. Datta, A. Rahman, and J. Scaturro, "Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size," *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, vol. 121, p. 1976, 2010.

[94] M. Bikson, A. Rahman, A. Datta, F. Fregni, and L. Merabet,"High-Resolution Modeling Assisted Design of Customized and Individualized Transcranial Direct Current Stimulation Protocols,"*Neuromodulation Technol. Neural Interface*, vol. 15, no. 4, pp.306–315, Jul. 2012.

[95] M. Bikson, A. Rahman, and A. Datta, "Computational models of transcranial direct current stimulation," *Clinical EEG and Neuroscience*, vol. 43, pp. 176-183, 2012.

[96] M. Bikson, D. Q. Truong, A. P. Mourdoukoutas, M. Aboseria, N. Khadka, D. Adair, *et al.*, "Modeling sequence and quasi-uniform assumption in computational neurostimulation," *Progress in brain research*, vol. 222, pp. 1-23, 2015.

[97] M. Bikson, J. Dmochowski, and A. Rahman, "The "quasi-uniform" assumption in animal and computational models of non-invasive electrical stimulation," *Brain stimulation*, vol. 6, p. 704, 2013.

[98] M. Bikson, M. Inoue, H. Akiyama, J. K. Deans, J. E. Fox, H. Miyakawa, *et al.*, "Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro," *The Journal of physiology*, vol. 557, pp. 175-190, 2004.

[99] M. Bikson, P. Grossman, C. Thomas, A. L. Zannou, J. Jiang, T. Adnan, *et al.*, "Safety of transcranial direct current stimulation: evidence based update 2016," *Brain Stimulation*, vol. 9, pp. 641-661, 2016.

[100] M. C. Chang, D. Y. Kim, and D. H. Park, "Enhancement of cortical excitability and lower limb motor function in patients with stroke by transcranial direct current stimulation," *Brain stimulation*, vol. 8, pp. 561-566, 2015.

[101] M. F. DosSantos, T. M. Love, I. K. Martikainen, T. D. Nascimento, F. Fregni, C. Cummiford, *et al.*, "Immediate effects of tDCS on the μ-opioid system of a chronic pain patient," *Frontiers in psychiatry*, vol. 3, 2012.

[102] M. F. Villamar, M. S. Volz, M. Bikson, A. Datta, A. F. DaSilva, and F. Fregni, "Technique and considerations in the use of 4x1 ring high-definition transcranial direct current stimulation (HD-tDCS)," *JoVE (Journal of Visualized Experiments)*, pp. e50309-e50309, 2013.

[103] M. Kekic, J. McClelland, I. Campbell, S. Nestler, K. Rubia, A. S. David, *et al.*, "The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and

temporal discounting in women with frequent food cravings," *Appetite*, vol. 78, pp. 55-62, 2014.

[104] M. L. Garcia, "The efficacy of use of transcranial direct current stimulation in the treatment of neurological disease & defect," Boston University, 2013.

[105] M. Lee, Y.-H. Kim, C.-H. Im, J.-H. Kim, C.-h. Park, W. H. Chang, *et al.*, "What is the optimal anodal electrode position for inducing corticomotor excitability changes in transcranial direct current stimulation?," *Neuroscience letters*, vol. 584, pp. 347-350, 2015.

[106] M. Nitsche, K. Fricke, U. Henschke, A. Schlitterlau, D. Liebetanz, N. Lang, *et al.*, "Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans," *The Journal of physiology*, vol. 553, pp. 293-301, 2003.

[107] M. Parazzini, E. Rossi, R. Ferrucci, I. Liorni, A. Priori, and P. Ravazzani, "Modelling the electric field and the current density generated by cerebellar transcranial DC stimulation in humans," *Clinical Neurophysiology*, vol. 125, pp. 577-584, 2014.

[108] M. Parazzini, S. Fiocchi, and P. Ravazzani, "Electric field and current density distribution in an anatomical head model during transcranial direct current stimulation for tinnitus treatment," *Bioelectromagnetics*, vol. 33, pp. 476-487, 2012.

[109] M. Parazzini, S. Fiocchi, E. Rossi, A. Paglialonga, and P. Ravazzani, "Transcranial direct current stimulation: estimation of the electric field and of the current density in an anatomical human head model," *IEEE Transactions on Biomedical Engineering*, vol. 58, pp. 1773-1780, 2011.

[110] M. Parazzini, S. Fiocchi, I. Liorni, A. Priori, and P. Ravazzani, "Computational modeling of transcranial direct current stimulation in the child brain: implications for the treatment of refractory childhood focal epilepsy," *International journal of neural systems*, vol. 24, p. 1430006, 2014.

[111] M. Windhoff, A. Opitz, and A. Thielscher, "Electric field calculations in brain stimulation based on finite elements: an optimized processing pipeline for the generation and usage of accurate individual head models," *Human brain mapping*, vol. 34, pp. 923-935, 2013.

[112] N. Khadka, A. Rahman, C. Sarantos, D. Q. Truong, and M. Bikson, "Methods for specific electrode resistance measurement during transcranial direct current stimulation," *Brain stimulation*, vol. 8, pp. 150-159, 2015.

[113] N. M. Senço, Y. Huang, G. D'Urso, L. C. Parra, M. Bikson, A. Mantovani, *et al.*, "Transcranial direct current stimulation in obsessive–compulsive disorder: emerging clinical evidence and considerations for optimal montage of electrodes," *Expert review of medical devices*, vol. 12, pp. 381-391, 2015.

[114] P. C. Miranda, A. Mekonnen, R. Salvador, and G. Ruffini, "The electric field in the cortex during transcranial current stimulation," *Neuroimage*, vol. 70, pp. 48-58, 2013.

[115] P. C. Miranda, M. Lomarev, and M. Hallett, "Modeling the current distribution during transcranial direct current stimulation," *Clinical neurophysiology*, vol. 117, pp. 1623-1629, 2006.

[116] P. C. Miranda, P. Faria, and M. Hallett, "What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS?," *Clinical Neurophysiology,* vol. 120, pp. 1183-1187, 2009.

[117] P. Faria, A. Leal, and P. C. Miranda, "Comparing different electrode configurations using the 10-10 international system in tDCS: a finite element model analysis," in *Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE*, 2009, pp. 1596-1599.

[118] P. Faria, M. Hallett, and P. C. Miranda, "A finite element analysis of the effect of electrode area and inter-electrode distance on the spatial distribution of the current density in tDCS," *Journal of neural engineering,* vol. 8, p. 066017, 2011.

[119] P. Minhas, A. Datta, and M. Bikson, "Cutaneous perception during tDCS: role of electrode shape and sponge salinity," *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology,* vol. 122, p. 637, 2011.

[120] P. Minhas, V. Bansal, J. Patel, J. S. Ho, J. Diaz, A. Datta, *et al.*, "Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS," *Journal of neuroscience methods,* vol. 190, pp. 188-197, 2010.

[121] P. S. Boggio, S. Zaghi, and F. Fregni, "Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS)," *Neuropsychologia,* vol. 47, pp. 212-217, 2009.

[122] R. Coben and J. R. Evans, *Neurofeedback and neuromodulation techniques and applications*: Academic Press, 2010.

[123] R. Ferrucci, M. Bortolomasi, M. Vergari, L. Tadini, B. Salvoro, M. Giacopuzzi, *et al.*, "Transcranial direct current stimulation in severe, drug-resistant major depression," *Journal of affective disorders,* vol. 118, pp. 215-219, 2009.

[124] R. J. Sadleir, T. D. Vannorsdall, D. J. Schretlen, and B. Gordon, "Transcranial direct current stimulation (tDCS) in a realistic head model," *Neuroimage,* vol. 51, pp. 1310-1318, 2010.

[125] R. L. Goldman, J. J. Borckardt, H. A. Frohman, P. M. O'Neil, A. Madan, L. K. Campbell, *et al.*, "Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving," *Appetite,* vol. 56, pp. 741-746, 2011.

[126] R. Puri, M. R. Hinder, A. J. Canty, and J. J. Summers, "Facilitatory non-invasive brain stimulation in older adults: the effect of stimulation type and duration on the induction of motor cortex plasticity," *Experimental brain research,* vol. 234, pp. 3411-3423, 2016.

[127] R. Puri, M. R. Hinder, H. Fujiyama, R. Gomez, R. G. Carson, and J. J. Summers, "Duration-dependent effects of the BDNF Val66Met polymorphism on anodal tDCS induced motor cortex plasticity in older adults: a group and individual perspective," *Frontiers in aging neuroscience,* vol. 7, p. 107, 2015.

[128] S. Bestmann and N. Ward, "Are current flow models for transcranial electrical stimulation fit for purpose?," *Brain Stimulation,* 2017.

[129] S. H. Jang, S. H. Ahn, W. M. Byun, C. S. Kim, M. Y. Lee, and Y. H. Kwon, "The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study," *Neuroscience letters,* vol. 460, pp. 117-120, 2009.

[130] S. Hyun Sang, L. Won Hee, C. Young Sun, K. Ji-Hwan, and K. Tae-Seong, "Reduced spatial focality of electrical field in tDCS with ring electrodes due to tissue anisotropy EMBC'10: Annu," in *Int. Conf. of the IEEE Engineering in Medicine and Biology Society*, 2010, pp. 2053-6.

[131] S. J. Pelletier and F. Cicchetti, "Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models," *International Journal of Neuropsychopharmacology,* vol. 18, p. pyu047, 2015.

[132] S. M. Rampersad, A. M. Janssen, F. Lucka, U. Aydin, B. Lanfer, S. Lew, *et al.*, "Simulating transcranial direct current stimulation with a detailed anisotropic human head model," *IEEE Transactions on Neural Systems and Rehabilitation Engineering,* vol. 22, pp. 441-452, 2014.

[133] S. Mrakic-Sposta, S. Marceglia, F. Mameli, R. Dilena, L. Tadini, and A. Priori, "Transcranial direct current stimulation in two patients with Tourette syndrome," *Movement Disorders,* vol. 23, pp. 2259-2261, 2008.

[134] S. Nikolin, C. K. Loo, S. Bai, S. Dokos, and D. M. Martin, "Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning," *Neuroimage,* vol. 117, pp. 11-19, 2015.

[135] S. S. Shahid, M. Bikson, H. Salman, P. Wen, and T. Ahfock, "The value and cost of complexity in predictive modelling: role of tissue anisotropic conductivity and fibre tracts in neuromodulation," *Journal of neural engineering,* vol. 11, p. 036002, 2014.

[136] S. Shahid, P. Wen, and T. Ahfock, "Numerical investigation of white matter anisotropic conductivity in defining current distribution under tDCS," *Computer methods and programs in biomedicine,* vol. 109, pp. 48-64, 2013.

[137] S. Tremblay, F. Larochelle-Brunet, L. P. Lafleur, S. El Mouderrib, J. F. Lepage, and H. Théoret, "Systematic assessment of duration and intensity of anodal transcranial direct current stimulation on primary motor cortex excitability," *European Journal of Neuroscience,* vol. 44, pp. 2184-2190, 2016.

[138] S. Vanneste, M. Plazier, J. Ost, E. van der Loo, P. Van de Heyning, and D. De Ridder, "Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study," *Experimental brain research,* vol. 202, pp. 779-785, 2010.

[139] S. Wagner, S. Rampersad, Ü. Aydin, J. Vorwerk, T. Oostendorp, T. Neuling, *et al.*, "Investigation of tDCS volume conduction effects in a highly realistic head model," *Journal of neural engineering,* vol. 11, p. 016002, 2013.

[140] T. F. Oostendorp, Y. A. Hengeveld, C. H. Wolters, J. Stinstra, G. van Elswijk, and D. F. Stegeman, "Modeling transcranial DC stimulation," in *Engineering in Medicine and Biology Society, 2008. EMBS 2008. 30th Annual International Conference of the IEEE,* 2008, pp. 4226-4229.

[141] T. Powell, T. Boonstra, D. Martin, C. Loo, M. Breakspear, and A. Antal, "Modulation of Cortical Activity by Transcranial Direct Current Stimulation in Patients," 2014.

[142] T. Radman, A. Datta, R. L. Ramos, J. C. Brumberg, and M. Bikson, "One-dimensional representation of a neuron in a uniform electric field," in *Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE*, 2009, pp. 6481-6484.

[143] T. Radman, R. L. Ramos, J. C. Brumberg, and M. Bikson, "Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro," *Brain stimulation,* vol. 2, pp. 215-228. e3, 2009.

[144] T. T. Brunyé, J. Cantelon, A. Holmes, H. A. Taylor, and C. R. Mahoney, "Mitigating cutaneous sensation differences during tDCS: comparing sham versus low intensity control conditions," *Brain stimulation,* vol. 7, pp. 832-835, 2014.

[145] T. Wagner, F. Fregni, S. Fecteau, A. Grodzinsky, M. Zahn, and A. Pascual-Leone, "Transcranial direct current stimulation: a computer-based human model study," *Neuroimage,* vol. 35, pp. 1113-1124, 2007.

[146] V. F. Bueno, A. R. Brunoni, P. S. Boggio, I. M. Bensenor, and F. Fregni, "Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression," *Neurocase,* vol. 17, pp. 318-322, 2011.

[147] V. López-Alonso, M. Fernández-del-Olmo, A. Costantini, J. J. Gonzalez-Henriquez, and B. Cheeran, "Intra-individual variability in the response to anodal transcranial direct current stimulation," *Clinical Neurophysiology,* vol. 126, pp. 2342-2347, 2015.

[148] W. H. Lee, Z.-D. Deng, A. F. Laine, S. H. Lisanby, and A. V. Peterchev, "Influence of white matter conductivity anisotropy on electric field strength induced by electroconvulsive therapy," in *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE*, 2011, pp. 5473-5476.

[149] W. H. Lee, Z.-D. Deng, T.-S. Kim, A. F. Laine, S. H. Lisanby, and A. V. Peterchev, "Regional electric field induced by electroconvulsive therapy in a realistic finite element head model: influence of white matter anisotropic conductivity," *Neuroimage,* vol. 59, pp. 2110-2123, 2012.

[150] W. Paulus, "Transcranial direct current stimulation (tDCS)," *Supplements to Clinical neurophysiology,* vol. 56, pp. 249-254, 2003.

[151] W. Paulus, "Transcranial electrical stimulation (tES–tDCS; tRNS, tACS) methods," *Neuropsychological rehabilitation,* vol. 21, pp. 602-617, 2011.

[152] W. Paulus, A. V. Peterchev, and M. Ridding, "Transcranial electric and magnetic stimulation: technique and paradigms," *Handb Clin Neurol,* vol. 116, pp. 329-342, 2013.

[153] Y. Huang, A. A. Liu, B. Lafon, D. Friedman, M. Dayan, X. Wang, *et al.*, "Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation," *Elife,* vol. 6, p. e18834, 2017.

[154] Y. Wang, D. R. Haynor, and Y. Kim, "An investigation of the importance of myocardial anisotropy in finite-element modeling of the heart: methodology and application to the

estimation of defibrillation efficacy," *IEEE transactions on biomedical engineering*, vol. 48, pp. 1377-1389, 2001.

[155] J.R. Rozisky, "Trancranial Direct Current Stimulation and Neuroplasticity," *Transcranial Direct Current Stimulation (tDCS): Emerging Uses, Safety and, Neurobiological Effects, 2015.*

APPENDIX A

Relative Difference Measure (RDM)

A measure of topographic variation. The minimum error corresponds to 0 and the maximum error corresponds to an RDM of 1.

$$RDM = \sqrt{\sum_{i=1}^{n}\left(\frac{X_i^{BASELINE}}{\sqrt{\sum_{i=1}^{n}\left(X_i^{BASELINE}\right)^2}} - \frac{X_i^{VAR}}{\sqrt{\sum_{i=1}^{n}\left(X_i^{VAR}\right)^2}}\right)^2}$$

Residual error (RE):

$$RE = \sqrt{\frac{\sum_{i=1}^{n}\left(X_i^{BASELINE} - X_i^{VAR}\right)^2}{\sum_{i=1}^{n}\left(X_i^{VAR}\right)^2}}$$

Where $\mathbf{E_{BASELINEi}}$ = Baseline parameter (electric field of isotropic head models)

$\mathbf{E_{VARi}}$ = the same field parameter (electric field of anisotropic head models) of different head models considered in the comparison. 'i' represents the total number of data points (elements of a particular sub domain or Region of Interest).

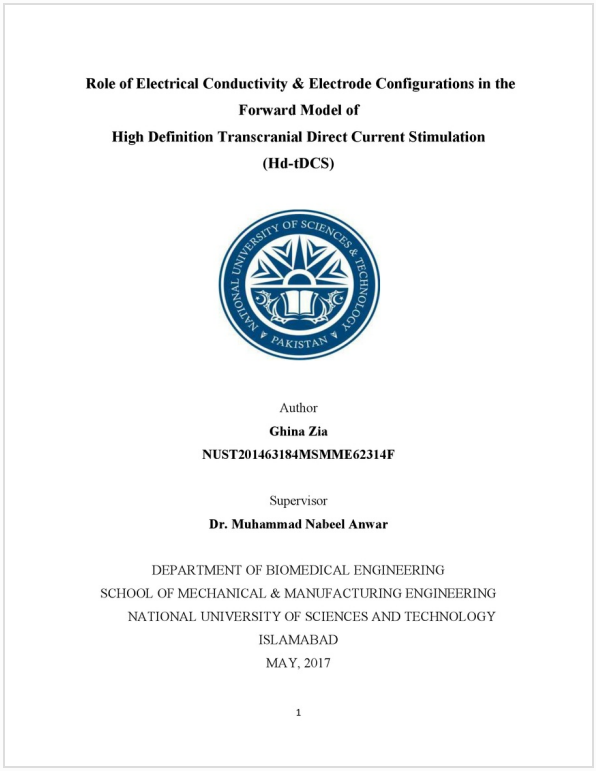
Skewness: The Skewness of Electric Field was calculated as a measure of how far in the positive or negative direction the distribution tail extends.

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Ghina Zia
Assignment title:	Plagiarism Detection Part 1 (Moodl…
Submission title:	Ghina Zia
File name:	76919_Ghina_Zia_Ghina_Zia_322…
File size:	13.27M
Page count:	49
Word count:	8,126
Character count:	48,863
Submission date:	19-May-2017 04:52AM
Submission ID:	813527521



Role of Electrical Conductivity & Electrode Configurations in the Forward Model of High Definition Transcranial Direct Current Stimulation (Hd-tDCS)

Author
Ghina Zia
NUST201463184MSMME62314F

Supervisor
Dr. Muhammad Nabeel Anwar

DEPARTMENT OF BIOMEDICAL ENGINEERING
SCHOOL OF MECHANICAL & MANUFACTURING ENGINEERING
NATIONAL UNIVERSITY OF SCIENCES AND TECHNOLOGY
ISLAMABAD
MAY, 2017

1

Ghina Zia

ORIGINALITY REPORT

8%	4%	6%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Shahid, Syed Salman, Marom Bikson, Humaira Salman, Peng Wen, and Tony Ahfock. "The value and cost of complexity in predictive modelling: role of tissue anisotropic conductivity and fibre tracts in neuromodulation", Journal of Neural Engineering, 2014. Publication	1%
2	Gajšek, Peter, Paolo Ravazzani, Joe Wiart, James Grellier, Theodoros Samaras, and György Thuróczy. "Electromagnetic field exposure assessment in Europe radiofrequency fields (10 MHz–6 GHz)", Journal of Exposure Science & Environmental Epidemiology, 2013. Publication	1%
3	www.tdcsnews.com Internet Source	1%
4	eprints.usq.edu.au Internet Source	1%

5	neuralengr.com Internet Source	1%
6	www.jpier.org Internet Source	1%
7	Alam, Mahtab, Dennis Q Truong, Niranjan Khadka, and Marom Bikson. "Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS)", Physics in Medicine and Biology, 2016. Publication	<1%
8	Miranda, Pedro Cavaleiro, Abeye Mekonnen, Ricardo Salvador, and Giulio Ruffini. "The electric field in the cortex during transcranial current stimulation", NeuroImage, 2013. Publication	<1%
9	dspace.lib.cranfield.ac.uk Internet Source	<1%
10	Textbook of Neuromodulation, 2015. Publication	<1%
11	espace.curtin.edu.au Internet Source	<1%
12	www.jove.com Internet Source	<1%
13	Kim, Sang-Hyung, and Chang-Hyun Cho. "Design of gravity compensators using the	<1%

Stephenson and Watt mechanisms", Mechanism and Machine Theory, 2016.
Publication

14	Electromagnetic Brain Imaging, 2015. Publication	<1%
15	Wen, Peng, Bo Song, Humaira Salman, Syed Salman Shahid, and Marilia Menezes de Oliveira. "Use of electric field orientation as an index for estimating the contribution of model complexity in transcranial direct current stimulation forward head model development", IET Science Measurement & Technology, 2015. Publication	<1%
16	mro.massey.ac.nz Internet Source	<1%
17	Submitted to The Open Polytechnic of New Zealand Student Paper	<1%
18	doaj.org Internet Source	<1%
19	Thom F. Oostendorp. "Modeling transcranial DC stimulation", 2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 08/2008 Publication	<1%
20	etd.lsu.edu	

	Internet Source	<1%
21	ijrsm.com Internet Source	<1%
22	docs.roguewave.com Internet Source	<1%
23	f1000.com Internet Source	<1%
24	etheses.whiterose.ac.uk Internet Source	<1%
25	Borckardt, J.J.. "A Pilot Study of the Tolerability and Effects of High-Definition Transcranial Direct Current Stimulation (HD-tDCS) on Pain Perception", Journal of Pain, 201202 Publication	<1%
26	researchonline.jcu.edu.au Internet Source	<1%
27	FANG, Jianfeng, Xiaomin WU, Hao DUAN, Chao LI, and Zhongquan GAO. "Effects of electrode configurations on the combustion characteristics of premixed methane-air flames", Journal of Thermal Science and Technology, 2015. Publication	<1%