Individualized Computational Modeling of Transcranial Direct Current Stimulation

Marko Mikkonen
Due to coronavirus pandemic the time of the defence has been postponed from 12 noon to 2:00 p.m.

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**Abstract**

Different psychiatric and neurologic illnesses are a great burden to our society. These kinds of disorders are often treated with pharmaceuticals, regardless of a wide variety of side-effects, poor suitability for many patients and high costs. During the recent decades, non-invasive brain stimulation (NIBS) has risen as a viable treatment alternative to the use of drugs. In NIBS, the state of the brain is affected via electric currents either induced by magnetic fields, or applied directly via electrodes on the scalp. One such method is called transcranial direct current stimulation (tDCS), where a small direct current is applied non-invasively to the brain via electrodes placed onto the scalp. This has, for instance, been shown to be a potential treatment for depression.

There is, however, a significant flaw with tDCS in terms of variable efficacy between different patients (inter-individual variability). This arises partially from the dosimetry of tDCS. The tDCS dose is commonly estimated based on the input current, which can be easily set to be the same for a group of subjects. However, multiple studies have pointed out that although the ingoing current is kept the same, the electric field experienced by the brain varies between subjects due to anatomic factors. As it is highly impractical to measure the electric fields in the brain during the stimulation in order to use them as a dose measure, computational modeling therefore remains the only viable way of studying them.

In this doctoral thesis comprising five peer-reviewed journal articles, the inter-individual variability of tDCS electric fields is studied using anatomically realistic head models in finite element analysis (FEA). The aim of this thesis is to shed light onto the causes of this variation, as well as to provide evidence to support the viability of using these predicted electric fields as a dosimetric parameter for tDCS.

Publication I presents an approach that lowers the computational costs of tDCS electric field predictions using the finite element method. In Publication II, we present a connection between transcranial magnetic stimulation (TMS) motor thresholds and the predicted tDCS electric fields, and in Publication V a connection between predicted electric field normal components and the outcome of tDCS. Publication III and Publication IV study the determinants of the inter-individual variability in tDCS electric fields, and show that body position affects the tDCS electric fields and the focality of the electric field montage used has an effect on the inter-individual variability of those tDCS electric fields.

These results provide new information on the causes of inter-individual variability and offer possible approaches to better take it into account with tDCS. Additionally, these results provide further links to connect the FEA-predicted electric fields into physiologically measurable quantities related to NIBS thus giving further support for the value of using these models in the study of tDCS.

**Keywords** non-invasive brain stimulation, transcranial direct current stimulation, interindividual variability, individualized models, finite element method

TDCS:ssä on kuitenkin huomattava ongelma, sillä sen tulokset vaihtelevat yksilöiden välillä. Tämä johtuu osittain tDCS:n dosimetristä; tDCS-annos arvioidaan yleisesti syytövirtaan perustuen, sillä se voidaan helposti asettaa samaksi yksilöiden välillä. Useat tutkimukset ovat kuitenkin huomauttaneet, että vaikka syytövirta pidetään samana, aivojen kokemat sähkökentät vaihtelevat yksilöiden välillä anatomisista tekijöistä johtuen. Koska sähkökentän mittaminen aivoissa stimulaation aikana sen käyttämiseksi annosmittana on lähes mahdotonta, mallintaminen on toteuttamiskelpoisin menetelminä päänsisäisten sähkökenttien tutkimiseksi.

Tässä viidestä vertaisarvioidusta lehtiartikkelista koostuvassa väitöskirjassa tutkitaan tDCS-sähkökenttien yksilöidenvälistä vaihtelua anatomisesti realistisia päämalleja ja elementimenetelmää (FEM) hyödyntäen. Väitöskirjani tavoitteena on sekä vaalista tDCS:n yksilöiden välisen vaihtelun syitä että tukea ennustettujen sähkökenttien käyttöä tDCS:n dosimetrisena parametrina.


Tämän väitöskirjan tulokset tarjoavat uutta tietoa tDCS:n yksilöidenvälistä vaihtelun syistä ja esittävät mahdollisia lähestymistapoja, jotta tämä vaihtelu voidaan huomioima paremmin. Lisäksi tulokset yhdistävät mallinmukaisten sähkökenttien ja fysiologisesti mitattavissa olevia kajaamattomia aivostimulataatioon liittyviä määrieitä, mikä tukee edelleen näiden mallien hyödyllisyyttä tDCS:n tutkimuksessa.

Avainsanat transskranialinen tasavirtastimulataatio, kajaamaton aivostimulataatio, yksilöllinen mallinnus, yksilöiden välinen vaihtelu, elementimenetelmä

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Preface

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Otaniemi, February 10, 2020,

Marko Mikkonen
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>1</td>
</tr>
<tr>
<td>Contents</td>
<td>3</td>
</tr>
<tr>
<td>List of Publications</td>
<td>5</td>
</tr>
<tr>
<td>Author's Contribution</td>
<td>7</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>9</td>
</tr>
<tr>
<td>Symbols</td>
<td>11</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>13</td>
</tr>
<tr>
<td>2. Background</td>
<td>15</td>
</tr>
<tr>
<td>2.1 Human Nervous System</td>
<td>15</td>
</tr>
<tr>
<td>2.1.1 Anatomy of the Brain</td>
<td>15</td>
</tr>
<tr>
<td>2.1.2 Neurons</td>
<td>16</td>
</tr>
<tr>
<td>2.2 Non-invasive Brain Stimulation</td>
<td>18</td>
</tr>
<tr>
<td>2.2.1 Transcranial Magnetic Stimulation</td>
<td>18</td>
</tr>
<tr>
<td>2.2.2 Transcranial Direct Current Stimulation</td>
<td>20</td>
</tr>
<tr>
<td>3. Materials and Methods</td>
<td>27</td>
</tr>
<tr>
<td>3.1 Magnetic Resonance Imaging</td>
<td>27</td>
</tr>
<tr>
<td>3.2 Volume Conductor Models</td>
<td>28</td>
</tr>
<tr>
<td>3.2.1 Tools Used in Segmentation</td>
<td>29</td>
</tr>
<tr>
<td>3.2.2 Segmentation Pipeline</td>
<td>32</td>
</tr>
<tr>
<td>3.2.3 Electric Properties of Tissues</td>
<td>36</td>
</tr>
<tr>
<td>3.3 Electrode Models</td>
<td>38</td>
</tr>
<tr>
<td>3.4 Finite Element Method</td>
<td>39</td>
</tr>
<tr>
<td>3.5 Statistical Methods</td>
<td>41</td>
</tr>
<tr>
<td>3.5.1 Partial Least Squares Regression</td>
<td>41</td>
</tr>
</tbody>
</table>
List of Publications

This thesis consists of an overview and of the following publications which are referred to in the text by their Roman numerals.


Author’s Contribution

Publication I: “Sub-voxel refinement method for tissue boundary conductivities in volume conductor models”

The author implemented the voxelization scheme, analyzed the results and wrote the manuscript.

Publication II: “TMS motor thresholds correlate with TDCS electric field strengths in hand motor area”

The author segmented the MR images, performed the modeling, analyzed the results and wrote the manuscript.

Publication III: “Effects of posture on electric fields of non-invasive brain stimulation”

The author contributed in planning the project and participated in acquisition of the MR images, segmented the MR images, performed the modeling, analyzed the results and wrote the manuscript.

Publication IV: “Cost of focality in TDCS: Interindividual variability in electric fields”

The author contributed in planning the project, segmented 33/77 subjects, did the modeling, analyzed the results and wrote the manuscript.
Author's Contribution

Publication V: “Can electric fields explain inter-individual variability in transcranial direct current stimulation of the motor cortex?”

The author segmented the subjects, modeled the electric fields and participated in writing the manuscript and making the figures.

Language check

The language of my dissertation has been checked by William Martin. I have personally examined and accepted/rejected the results of the language check one by one. This has not affected the scientific content of my dissertation.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APB</td>
<td>Abductor pollicis brevis</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>FEA</td>
<td>Finite element analysis</td>
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<tr>
<td>FEM</td>
<td>Finite element method</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<tr>
<td>HD</td>
<td>High definition</td>
</tr>
<tr>
<td>M1</td>
<td>Primary motor cortex</td>
</tr>
<tr>
<td>MEP</td>
<td>Motor evoked potential</td>
</tr>
<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NIBS</td>
<td>Non-invasive brain stimulation</td>
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<tr>
<td>nTMS</td>
<td>Neuronavigated transcranial magnetic stimulation</td>
</tr>
<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
</tr>
<tr>
<td>PLSR</td>
<td>Partial least squares regression</td>
</tr>
<tr>
<td>QCD</td>
<td>Quartile coefficient of dispersion</td>
</tr>
<tr>
<td>RF</td>
<td>Radio frequency</td>
</tr>
<tr>
<td>rMT</td>
<td>Resting motor threshold</td>
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<tr>
<td>rTMS</td>
<td>Repetitive transcranial magnetic stimulation</td>
</tr>
</tbody>
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Abbreviations

tDCS  Transcranial direct current stimulation
TES  Transcranial electric stimulation
TMS  Transcranial magnetic stimulation
VIP  Variable importance projection
VTK  The visual toolkit
### Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1$</td>
<td>Proportion of the cortical area, where $E &gt; 0.5E_{target}$, [%]</td>
<td></td>
</tr>
<tr>
<td>$E$</td>
<td>Electric field, [V/m]</td>
<td></td>
</tr>
<tr>
<td>$I$</td>
<td>Electric current, [A]</td>
<td></td>
</tr>
<tr>
<td>$i$</td>
<td>Electric current density, [A/m$^3$]</td>
<td></td>
</tr>
<tr>
<td>$K$</td>
<td>FEM system matrix</td>
<td></td>
</tr>
<tr>
<td>$N$</td>
<td>Basis function</td>
<td></td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Electric permittivity, [F/m]</td>
<td></td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Electric conductivity, [S/m]</td>
<td></td>
</tr>
<tr>
<td>$\phi$</td>
<td>Electric scalar potential, [V]</td>
<td></td>
</tr>
<tr>
<td>$\Psi$</td>
<td>Test function</td>
<td></td>
</tr>
<tr>
<td>$\Omega$</td>
<td>Domain of FEM calculations</td>
<td></td>
</tr>
<tr>
<td>$\partial \Omega$</td>
<td>Boundary of $\Omega$</td>
<td></td>
</tr>
<tr>
<td>$\nabla$</td>
<td>Differential operator</td>
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</tr>
</tbody>
</table>
1. Introduction

With more than one sixth of EU citizens suffering from mental health problems [1], mental illnesses are an enormous burden to both the individuals suffering from them and to the economy. In 2018, the Organization for Economic Co-operation and Development (OECD) estimated an annual cost of 600 billion ($10^9$) euros in the EU for these problems [1]. For Finland, the OECD estimated the direct and indirect costs from mental illnesses to add up to 5.3% of the gross domestic product [1](over 11 billion euros), which is the second highest in Europe.

Medication can be used to treat these illnesses, although these medications possess some problems [2]. They are known to have various side-effects [3], their efficacy might be little better than a placebo treatment [4] and they are expensive. The OECD estimates pharmaceuticals to be the third largest expenditure in healthcare [1]. During the past decades, non-invasive brain stimulation (NIBS) has risen to be a viable alternative to the drug treatment of neurological and psychological disorders. Methods like transcranial magnetic and electric stimulation (TMS and TES, respectively) are widely studied and for some applications already used in treatment of mental and neurological disorders [5, 6]. For example, transcranial direct current stimulation (tDCS) offers a simple, well-tolerated and relatively cheap alternative to drug treatment of various mental health problems such as non-drug-resistant major depression [6].

Although being a promising method for the treatment of mental illnesses, tDCS has a significant problem of varying efficacy between individuals and having contradicting research results [7]. This partially arises from individual anatomic differences [8, 9, 10], differences in experimental setups [11, 12] and dosage [13, 14] as well as differences in the state of the brain at the time of stimulation [5]. Many of these issues can be addressed by computational modeling [15, 16]. By individually modeling the electric fields in the brain during tDCS, the dose can be normalized over subjects and sessions [16, 17]. This could help in achieving more consistent results with tDCS. With higher consistency, tDCS could offer a superior alternative to pharmaceutical treatment of various mental health problems and provide new insights into the functioning of the brain.
Introduction

In this thesis, I study tDCS using individualized anatomically accurate head models based on magnetic resonance (MR) images with a focus on the causes of the inter-individual variability and possible ways of addressing it. The work is mainly computational in nature, concentrating on studying the predicted electric fields in groups of subjects with finite element analysis (FEA). The experimental data used in Publications II and V of this thesis were measured by our collaborators in Japan.

This thesis comprises five peer-reviewed journal articles. Publication I studies the tissue surfaces in voxelated models used in the computation of tDCS electric fields and shows that by using a weighted average of the surrounding tissue conductivities on the surface voxels, the accuracy of the computations increase. Publication II shows a connection between individual sensitivity to TMS and the predicted tDCS electric fields. In Publication III, we study the effects of posture on brain conformation and show that the tDCS electric fields can differ between positions. Publication IV compares the inter-individual variability of tDCS montages with different electric field focalities and shows that the cost for focality is often added inter-individual variability. Lastly, Publication V shows for the first time a connection between the normal component of modeled tDCS electric fields and the outcome of tDCS.

Before detailing the results of this thesis in Chapter 4 and discussing them in Chapter 5, a brief background to the topic and the methods used in the research are presented in Chapters 2 and 3, respectively. Finally, the thesis is concluded in Chapter 6.
2. Background

2.1 Human Nervous System

The human nervous system controls bodily functions by detecting and processing sensory information, which may, for example, allow a person to both learn how to do a roundhouse kick and that it is not nice to be hit by such a kick. The nervous system can be divided into the central and peripheral nervous systems. The central nervous system comprises the brain and the spinal cord, and the peripheral nervous system contains the peripheral nerves and sensory receptors. This chapter gives a brief introduction to the brain and the neurons responsible for processing the information within the brain. Further details on the anatomy and function of the nervous system can be studied, for example, from chapters 12–16 of the comprehensive book on anatomy by Gerard Tortora and Bryan Derrickson [18], on which this chapter is based.

2.1.1 Anatomy of the Brain

Located beneath the scalp, adipose tissue and muscles of the head, the brain is enclosed within the skull and cranial meninges and embedded in the cerebrospinal fluid (CSF). The human brain can be divided into four main components: the cerebrum, cerebellum, diencephalon and the brain stem. The cerebrum is in charge of sensory and motor functions, memory and emotions. The cerebellum is involved in fine control of voluntary movements. The diencephalon controls body temperature and produces hormones. The brain stem regulates the heart beat and breathing. Together, these components stand behind the essence of every being, keeping up the homeostasis as well as the consciousness. Complications in the functions of the brain are often severe, be it an epileptic seizure due to a lesion or memory loss and tremors in Parkinson’s disease.

The main interest of this thesis lies in the cerebrum, which is the largest of the four components of the brain. The cerebrum is divided into two approximately symmetrical hemispheres, both of which control the functions and perceive
the information from the opposite sides of the body. For example, the visual information from the right eye is processed in the left hemisphere and vice versa. Different regions of the cerebrum have different functions, for example, the visual cortex is located at the occipital lobe and the sensory cortex at the postcentral gyrus. In addition to the regions of the cerebral cortex, there are nuclei of gray matter deep within the brain, such as the hippocampus which is important for memory [18]. In the publications of this thesis, the stimulation was targeted at the primary motor cortex (M1) located on the precentral gyrus, and more precisely to the hand area of M1, which usually lies on a pend of the precentral gyrus resembling a capital omega, $\Omega$. Figure 2.1A presents a simplified head anatomy with precentral gyrus and an estimated region containing the hand M1 highlighted on the cortex.

### 2.1.2 Neurons

The brain consists of approximately $10^{11}$ neural cells [18], or neurons, responsible for information processing in the brain and glial cells which support them. A neuron consists of three major compartments presented in Figure 2.1B: a soma, which is the cell body; extensions of the soma that propagate the incoming information from a synapse to the soma called dendrites; and an axon, which propagates the outgoing information from the soma to the synapses. A synapse is a connection between two neurons. Within the cerebrum, the soma and dendrites are mainly located at the cerebral cortex within a thin layer on the surface of the cerebrum also known as gray matter, whereas the axons comprise the content of the brain, called white matter.

The information from a neuron to another is transferred in a dual manner. Within the neuron, information propagates as an electric signal known as an
action potential. An action potential is generated at the axon, if the incoming signals from the dendrites to the soma exceed a threshold at the junction of the soma and the axon called an axon hillock. The soma can be considered to integrate the input from the dendrites, and produce an output in the form of an action potential when the input is strong enough. Between the neurons, information is transferred via a chemical signal in the synaptic cleft.

In more detail, the resting membrane potential of an axon is often -70 mV [18]. If this potential is depolarized to approximately -55 mV [18], voltage-gated sodium channels on the membrane open causing a rapid influx of sodium ions and rapidly depolarization of the membrane locally to approximately +30 mV [18]. This local depolarization drives nearby voltage-gated ion channels to exceed the threshold causing a chain reaction along the axon. The propagation of this depolarization is called the action potential. Shortly after opening, the sodium channels become inactivated and voltage-gated potassium channels open allowing potassium ions to flow into extracellular space which leads to a gradual hyperpolarization of the membrane potential. Before the cell membrane recovers the resting state there is a brief refractory period, when the membrane cannot create a new action potential due to the inactivation of the sodium channels. This prevents the backpropagation of the action potential.

When the action potential reaches a synapse to another neuron, the depolarization of the cell membrane opens voltage-gated calcium channels causing an influx of calcium ions, which leads to a release of neurotransmitters into the extracellular space within the synapse. As these released molecules drift to the post-synaptic neuron they bind to receptors, which then cause the post-synaptic cell membrane to either depolarize or hyperpolarize depending on the type of the receptor. This postsynaptic potential is carried to the soma, which sums up the inputs from all the neuron’s dendrites and gives rise to a new action potential if the threshold is exceeded at the axon hillock. There are about 100 known neurotransmitters [18], such as dopamine, serotonin and gamma-aminobutyric acid (GABA).

In addition to simply relaying signals from a neuron to another, the synapses play an important role in the capability of the brain to remember old things as well as to learn new things. One of the main mechanisms behind these abilities is the activity-dependent modification of the synapses called synaptic plasticity or Hebbian plasticity after Donald Hebb who first introduced the basic concept in the 1940s [20]. The principle of synaptic plasticity is that a synapse is either strengthened or weakened over time in respect to its activity, i.e. constantly active synapses become stronger and constantly inactive synapses weaker. These phenomena are commonly referred to as long-term potentiation and long-term depression, respectively.


2.2 Non-invasive Brain Stimulation

Non-invasive brain stimulation comprises a group of methods capable of altering the ongoing neural activity as well as the neural plasticity non-invasively, i.e. without the need for surgical procedures or penetrating the scalp. Hence, these methods provide an interesting approach for treating neurological and psychiatric diseases as well as for studying the brain function.

The concept of using electricity to treat disease is far from novel. One of the earliest reported experiments of using electricity as a treatment dates back to 1755, when Charles Le Roy elicited phosphenes to a blind subject using Leyden jars [21]. Since Galvani’s famous frog’s leg experiments [22] and Alessandro Volta’s tests on voltaic cell applied to his own ears [23] in the late 18th century, electricity has been sought as a treatment for various problems. For example, Galvani’s nephew Giovanni Aldini reported experiments on treating psychosis with electricity in 1804 [21], and there has been a trend of do-it-yourself electricity treatments at the turn of the 20th century using devices known as "medical batteries" with noticeable similarities to current tDCS devices [24].

Modern NIBS is widely considered to date back to 1980, when the capability to stimulate the human brain in a non-invasive manner locally with electric currents to evoke a behavioral response corresponding with the stimulation site was first demonstrated by Merton and Morton [25]. They used a brief pulse of 2 kV to cause twitch-like movements in a finger. However, the use of such strong electric pulses can be painful to subjects and is no longer widely used [5].

NIBS methods can be divided roughly into TMS and TES. Further, TES can be divided into transcranial alternating current, direct current, and random noise stimulation. TMS is the most popular of the NIBS methods, and tDCS is the most popular among different TES methods [5]. The main difference between TMS and TES methods is that TMS is capable of stimulating the brain to cause action potentials whereas the weak electric currents of TES merely modulate the cortical activity. TES should not be confused with electroconvulsive therapy, the traditional "electroshock therapy" first introduced in 1943 [26], that is used to for producing controlled seizures to treat psychiatric disorders.

Next, a brief overview of TMS used as an assistive/comparative method in the Publications II-V is given before concentrating on tDCS, the method of interest for this thesis.

2.2.1 Transcranial Magnetic Stimulation

TMS is the most established from the current NIBS methods, having been approved for the treatment of depression in multiple markets including the EU and USA for longer than ten years [27]. In TMS, an electric field is induced to the brain by a strong, brief and rapidly changing magnetic pulse generated with a coil placed over the scalp according to Faraday's law of induction. This induced
electric field can be strong enough to exceed the stimulation threshold for the neurons under the coil and cause them to fire action potentials.

TMS was developed in Sheffield (United Kingdom) in 1985 by Barker et al. [28]. In their pioneering work, electric current was raised to 4 kA in 110 μs within a flat single coil with an outer diameter of 100 mm to stimulate the motor cortex resulting in a movement of hand and leg. These days, TMS devices meant to stimulate the human brain often use currents of 4-8 kA and peak-to-peak change times of 100-200 μs [29]. The coil shapes have also evolved since the early days of TMS, with coils such as the figure-of-eight coil [30] and the H-coil [31] used alongside the traditional round coil. Different coil shapes differ in their strengths and weaknesses. For example the commonly used figure-of-eight coil is more focal than the round coil, as presented in Figure 2.2, but its penetration depth is lower [29].

There are two types of input-current pulse shapes that are used with TMS, namely monophasic and biphasic. Monophasic pulses are often used in single-pulse experiments, such as the ones in Publications II and V, whereas biphasic pulses are more common with repetitive TMS (rTMS) as they are more energy efficient [32]. In addition, there is a multitude of different pulse patterns for TMS: single pulses, which can for example be used to map the motor cortex [33], paired pulses, useful for studying inter-regional interactions between brain regions [29], and rTMS with either continuous [34] or patterned (such as the theta burst [35] and quadripulse stimulations [36]) pulse trains, which are capable of producing long lasting effects. Here, we concentrate only on the single-pulsed TMS as it is used in the Publications II and V.

In single-pulsed TMS, the interval of individual pulses is at least 4 s [29] to avoid summation of the effects of individual pulses. For this thesis, single-pulsed TMS has the benefit of being able to generate quantifiable motor evoked

Figure 2.2. Examples of A) round and B) figure-of-eight TMS coils and the electric fields induced by them.
potentials (MEPs) by stimulating the motor cortex and measuring the response at the target muscle. This allows TMS to be used in measurement of stimulation thresholds for different muscles. For example, the resting motor threshold (rMT) studied in Publication II is defined as the lowest stimulator output to produce 50 $\mu$V MEPs at the target muscle in five out of ten measurements [37].

The placement of the stimulating coil is crucial for the outcome of the stimulation. Not only should the coil be placed over the targeted cortical region, but it should also be placed tangential to the surface of the scalp and angled appropriately to ensure a perpendicular current direction to the cortical surface at the targeted region. To help with the proper placement and alignment of the coil, and to ensure the reproducibility of the stimulation, neuronavigated TMS (nTMS) is often used. In nTMS, the location of the head and the coil are tracked in space and visualized on a screen where the coil location and alignment are overlaid onto a model based on the individual MR image of the subject helping the estimation of the target location.

In general, TMS is considered to be a safe method for influencing the brain [38]. Yet, approximately one third of subjects [38] undergoing TMS suffer from adverse effects such as general discomfort, local pain beneath the coil and headaches. Additionally, there are a small number of experiments reporting TMS-induced seizures. These are, however, extremely rare.

### 2.2.2 Transcranial Direct Current Stimulation

After over a century [24] from the medical batteries were first devised, the concept of treating humans with direct current re-emerged in the new millennium when it was found to produce prolonged effects on the brain. The method became known as transcranial direct current stimulation. In their groundbreaking study, Nitsche and Paulus [39] used two small 35 cm$^2$ electrodes with a 1 mA current for 1 min, and found the effects lasted up to 5 minutes. Thereon, tDCS has largely accepted the use of two relatively large, 25–35 cm$^2$ electrodes, and small, 1–2 mA, input currents applied for 10–20 minutes as the default practice. However, also different amounts of electrodes (such as the 4 × 1 high definition (HD) montage [12]), different electric currents [40], electrode sizes (e.g. in bipolar HD-tDCS [41]) and stimulation durations [13] are used and studied. Figure 2.3 presents examples of tDCS montages that have been used.

To aid the placement of tDCS electrodes, the electroencephalography (EEG) electrode locations are often used. The most commonly used system for the placement of the electrodes is the EEG 10/20 system (Figure 2.1C), where the electrode placement is based on relative distances between cranial landmarks on the surface of the head allowing reproducible placement of the electrodes [42]. For example, C3 is a commonly used anode location [6].

The complete mechanisms of tDCS are not fully understood, however it is widely accepted that tDCS modulates the activity of the neurons. In its simplest form, tDCS is often considered to increase the excitability of the brain region
Fig. 2.3. Examples of different kinds of montages used with tDCS targeting to stimulate the motor cortex. The intended region of stimulation is pointed out with the arrows. A) Conventional M1 - contralateral forehead montage with $7 \times 5 \, \text{cm}^2$ electrodes, B) bipolar HD montage with 1 cm in radius electrodes, and C) a $4 \times 1 \, \text{HD}$ montage with 6 mm in radius electrodes. Anodes are shown in red, cathodes in blue.

beneath the anode (electrode where current enters the head) and decrease the excitability beneath the cathode (the electrode where current exits the head). Yet, this is not always the case [13, 43] and the dose-effect relationship of tDCS is likely to be more complex.

The effects of tDCS are dual: primary effects that happen during the stimulation and secondary effects explain the after-effects of tDCS [44]. The primary effects arise from the modulation of neurons’ membrane potential towards the potential of the stimulating electrode: anodal stimulation depolarizes the cellular membrane making it easier to excite and hyperpolarization by cathodal stimulation has an opposite effect. This effect was first shown with animal studies [45, 46, 47] and 40 years later in humans by Priori et al., and Nitsche and Paulus [48, 39]. Later studies showing that the effects of tDCS are removed by blocking the sodium or calcium channels of the cell membrane [49], and that the lack of sensitivity of tDCS effects during stimulation to blocking the GABAergic and glutamatergic synaptic activity [49, 50], further support that the primary effects are due to modulation of the membrane potential. The mechanisms of tDCS after-effects are not as well understood as the mechanisms of the primary effects, but they are likely linked with synaptic plasticity [51] as neurotransmitters important to synaptic plasticity such as glutamate [49, 52], GABA [50], noradrenaline [53], dopamine [54] and serotonin [55] have been associated with the after-effects of tDCS.

Since the pioneering work done in the turn of the millennium, much of the basic research with tDCS has involved stimulating the motor cortex and measuring the TMS-evoked MEPs as it makes it possible to obtain quantitative measures easily and reliably [7]. In motor cortical tDCS, TMS-induced MEPs are measured from the targeted muscle prior to and post tDCS keeping the TMS intensity the same. This allows the direct comparison of the values in order to find out whether tDCS had an effect on the excitability of the targeted brain region. Hence, MEPs were employed in Publications II and V of this dissertation. In addition, other measures such as short-interval cortical inhibition, event-related potentials, EEG, and functional MRI have been used to study tDCS with non-
Background

reliable results [7]. As these measures were not employed in this dissertation, they shall be omitted from further discussion.

In addition to basic research, various clinical applications of tDCS have been studied. As discussed earlier, tDCS after-effects are thought to affect the plasticity of the brain and hence tDCS could provide a treatment for various neurological and psychiatric disorders where the brain's plasticity is altered. During the last 20 years, tDCS has been studied as a potential treatment for e.g. Parkinson's disease [56], stroke [57], aphasia [58], multiple sclerosis [59], and epilepsy [60] with varying results. The strongest evidence for the efficacy of tDCS has been obtained with fibromyalgic pain, non-drug-resistant major depression and addiction/craving, all of which have gotten level B recommendation (probable efficacy) by a European panel of experts [6]. The same panel also found tDCS treatment to be probably ineffective (level B recommendation) for the treatment of tinnitus and drug-resistant major depression.

Notably, as tDCS influences the ongoing activity in the brain it may be possible to improve the results of tDCS by altering the state of the brain via medication [61] or tasks [62, 63]. For example, tDCS efficacy in cognitive training tasks has been found to depend on the task used [64], and tDCS combined with both cognitive behavioral therapy [65, 66] and medication [67] has been found to improve the response rate to treatment of depression.

In general, tDCS is considered a safe and well-tolerated method when applied with conventional parameters. Indeed, a recent review [68] found no serious adverse effects (i.e. irreversible damage of the brain, hospitalization/medical intervention or death due to tDCS) from a dataset of 33000 tDCS sessions with more than 1000 subjects with up to 40 min of stimulation and 4 mA input currents. The most common adverse effects of tDCS include skin irritation and tingling/itching sensations.

During the two decades of its existence, modern tDCS has gained popularity in neuroscience. In part, the popularity is based on its simplicity and cheapness compared to TMS. Recently, this simplicity and relative cheapness has widened the application of tDCS therapy to also include home-use scenarios. In home-use of tDCS, a physician sets up a tDCS device, which is then given to the patient to be used at home. This approach has the advantage in long-term treatment of patients who no longer have to visit the practice on daily basis for treatment but who can instead administer the preset dose at home [69].

More information on the basic principles of tDCS can be found from the first comprehensive book on tDCS published in the spring of 2019 [44].

Variability in tDCS

Regardless of its potential, there is a significant drawback with tDCS: the results are highly varying between individuals with up to half of the subjects undergoing tDCS not responding in an expected manner [40, 70, 71, 72, 73]. This has led to contradictory results [7] in studies making it more difficult to understand the foundation of tDCS albeit some of the findings have been promising.
Figure 2.4. Predicted electric fields on the right hemispheres of 77 subjects. For each subject, tDCS with a 5 cm in diameter anode on the right hand M1 and a $7 \times 5 \text{ cm}^2$ cathode on the contralateral forehead (Fp1 of EEG 10/20 system) was modeled with the input current of 1 mA. The inter-individual variability in the electric fields is clearly visible.

Partially this is an issue of tDCS dosage. As described earlier, the input current and stimulation duration are conventionally used to measure the tDCS dose. However, based on the electric fields predicted with the finite element method (FEM) in the publications of this thesis and also in previous modeling studies [8, 9, 10, 74], there is a high variability in the individual electric fields at the targeted brain region despite the input current being the same for each subject. This is also demonstrated in Figure 2.4. Multiple computational studies have suggested that with constant input current in all the subjects, the variability of the tDCS electric fields partially results from inter-individual differences in the anatomy of the head. Especially the variability in thicknesses of tissues such as fat [8], skull [9] and CSF [10] beneath the stimulating electrodes have had an effect on the predicted electric fields. Hence, the cortical electric fields of tDCS have been suggested as a better dose measure than the input current [16, 17].
Also the electrode montage affects the electric fields at the cortex. The conventional tDCS montages with large electrodes produce diffuse electric fields [75], which may stimulate different populations of neurons [76] in different individuals. Additionally, the cathode also stimulates the brain in these montages [11], which might have an effect on both the stimulation outcome and its variability, as it has been suggested that the stimulation results differ between this conventional montage type and a $4 \times 1$ HD-tDCS montage [12], which restricts the current flow to a small portion of the cerebral cortex. A third source of variation for the electric fields arises from the accuracy of the electrode placement: it has been suggested, that the electrode placement should be accurate to 1 cm between sessions to avoid variation [77]. Hence, it is possible that also small errors in the individual placement of tDCS electrodes could contribute to the inter-individual variability of tDCS.

In more recent studies also the direction of the electric fields in respect to cortical surface have been found to be important for the outcome [41, 78], with only electric fields normal to the cortical surface having had an effect in in-vitro experiments [79, 80]. Thus, it is possible that instead of the electric field magnitude at the targeted region, the direction of the electric fields with respect to cortical surface should be taken into account in the dosimetry of tDCS as differences in electric field direction could add the variation between individuals. Additionally, also the length of the stimulation has been shown to affect the outcome of tDCS, and thus should not be neglected in the dose estimation. For example, doubling the length of 1 mA stimulation from 13 to 26 minutes was found to reverse the outcome of stimulation [13].

In addition to the dosage, there are also a number of brain-intrinsic factors that can affect the outcome of tDCS, and NIBS in general. For example, these factors include the history of synaptic activity, the time of the day, attention and genetics [5, 81]. The state of the brain can also be altered using medication and tasks, all of which have their own effects on the outcome of tDCS [61, 64]. This suggests that not only the dosage, but also brain-intrinsic factors and possible stimulants affecting the state of the brain should be accounted for careful planning of tDCS experiments to minimize the sources of variability.

In good experimental planning practice, blinding is used to mitigate possible placebo effects. In tDCS, blinding is performed using sham stimulation as a comparison to active stimulation. Sham stimulation is achieved by ramping the current up in a way similar to the active stimulation, maintaining it for a brief period of time, and either ramping/dropping the current down to zero or to some small electric current value for the duration of the stimulation protocol. At the end of the stimulation session, the ramp-up and -down are repeated. This approach aims to imitate the cutaneous sensations of tDCS in order to blind the subject. However, the application of current during the sham stimulation may also affect the brain and the approach chosen to blind the trial may affect tDCS efficacy [82].
Computational Modeling of tDCS

It is difficult to study the electric fields experienced by the brain during tDCS because the procedure would be highly invasive. Hence, the primary approach in estimating these electric fields has been computational modeling. In the early modeling studies of tDCS, the head models used were coarse simplifications with the head modeled as a layered sphere [83], or as simplified geometry based on individual MR images [84]. As computational power has increased in the past decade, the head models used currently are anatomically realistic and based on individually segmented MR images. In segmentation, toolkits such as SPM [85](https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and FreeSurfer [86](http://surfer.nmr.mgh.harvard.edu/) are often used. The most common approach in solving the electric fields is the FEM used also in computations of this thesis and explained in detail in Section 3.4. Various open-source complete solutions such as SimNIBS [87] and ROAST [88] have also been developed to create the models and calculate the electric fields. In addition, there are commercial software for solving TES electric fields (Neurophet TES lab, Seoul, Rep. of Korea), some generic commercial FEM solvers such as Comsol Multiphysics (COMSOL Inc., Burlington, MA) and Abaqus (Simulia, Johnston, RI) have been employed in the study of tDCS [75, 89], and also tDCS hardware manufacturers such as Soterix Medical (New York, NY) and Neuroelectrics (Barcelona, Spain) have recently started to offer their own solutions for studying the electric fields produced by their stimulators. Here we focus on applications of FEM in the study of tDCS.

The main benefit of computational modeling for tDCS is the ability to predict the distribution and strength of electric fields, which has been in the core of most computational studies concerning tDCS. Individualized computational modeling has been used to study how the electric fields are distributed with different montages [15]. The electrode size has been shown to affect the electric fields with the electric fields becoming more focal [90] as the electrodes become smaller.

In addition, novel montages like the $4 \times 1$ [75] and bipolar [41, 91] HD-montages have been developed with the aid of computational modeling.

Individualized modeling can also be used to study the effects of different anomalies of the head on the distributions of electric fields. For example, the effects of holes or metallic plates [92] in the skull on the electric fields have been studied and found to concentrate the electric currents in the vicinity of the defect. Additionally, computational models have been used to study differences in cortical electric fields between pediatric [93] populations and healthy adults to ensure the safety of tDCS also for children.

Increasing computational capabilities have enabled studies with multiple subjects being modeled. This way, modeling studies are able to study the inter-individual variability between subjects, which is also the focus of this thesis. A recent study using models of 50 subjects [16] showed that it is possible to control the inter-individual variability of the electric fields by individually controlling the input current. Additionally, these multi-subject computational studies have
suggested that there is variability in the electric fields between subjects due to inter-individual anatomic differences [8, 9, 10]. Publications III and IV of this thesis study how the head position and electric field focality affect the inter-individual variability of tDCS electric fields.

Aside from cerebral stimulation, tDCS can also be used to stimulate the cerebellum. As cerebellar tDCS has gained interest as a therapeutic interventions [94, 95], computational modeling has been used to analyze the electric fields at the cerebellum during tDCS. For example, the electric field distribution and magnitude [96], and their inter-individual variability [97] has been studied.

An important aspect regarding the modeled electric fields is to establish how they relate to the outcome of tDCS. The direction of the electric fields has been shown to affect the stimulation outcome by modeling the electric fields created by the montage, and studying whether changing the direction has an effect on the stimulation outcome [41]. Publications II and V of this thesis relate the predicted electric fields to biological measures, namely resting motor threshold and MEP, respectively. Recently, multiple studies [77, 89, 98] have attempted to validate the tDCS electric fields predicted by Abaqus [89], SimNIBS [77] and ROAST [88] using electric potential measurements performed during surgical operations. These results suggest that the results obtained via modeling of tDCS are approximately valid. However, in general the modeled electric fields tend to be higher than those measured, which could be partially due to methodological issues in these validations: A recent publication by Puonti et al. [99] found that linear regression models used in [77, 89] may not be optimal for validating the models. Additionally, their results from Bayesian regression analysis suggest only a weak support for overestimation of the electric fields by the models.
3. Materials and Methods

This chapter describes the methodological background for studying the cortical electric fields of tDCS computationally. In order to create the models, one must first obtain MR images (Figure 3.1A) and segment them into tissues. Each tissue type is then assigned an electric conductivity value based on experimental data from the literature (Figure 3.1B). Finally, the electric fields are modeled using the finite element method (Figure 3.1C), and studied using statistical measures. Each of these steps are described next.

Figure 3.1. Modeling workflow: The MR images (A) are segmented into volume conductor models (B) and used for solving the distributions of electric currents within the head (solved electric current density, C).

3.1 Magnetic Resonance Imaging

MR imaging (MRI) is a tomographic imaging technique, capable of producing three-dimensional anatomic images non-invasively based on the principles of nuclear magnetic resonance. In this thesis, MR images of heads of healthy subjects are used to create the anatomically realistic models. Prior to advancing to the actual model formation it is necessary to describe the acquisition of the MR images. The description given here is brief, and for more in-depth information on MRI, the comprehensive books used as the basis for this chapter by Westerbrook, Roth and Talbot [100] and Liang and Lauterburg [101] are recommended.

In MRI, a static external magnetic field is used to affect the protons of the hydrogen nuclei in tissues. For example, the magnetic fields used in clinical
MRI devices are between 1.5 and 3 teslas. Application of the static magnetic field causes a longitudinal (parallel to the axis of the applied magnetic field) magnetization in the tissues. Once magnetized, a radio frequency (RF) pulse is used to excite the protons and to rotate the magnetization away from the axis of the external field. This is referred to as transverse magnetization. After the RF pulse, the magnetization is allowed to relax back to longitudinal direction and the signal emitted by the protons is measured. In order to spatially localize the origins of the signal to build the MR image, different kinds of magnetic pulses called gradients are used.

During this relaxation period, the longitudinal magnetization gradually recovers to the steady state. This is called T1 recovery. Meanwhile, the transverse magnetization decays gradually. This is called T2 decay. T1 relaxation and T2 decay are measured with T1 and T2 relaxation times, which are the times to recover or lose 63% of the longitudinal or transverse magnetization, respectively. These relaxation times differ between tissues due to different environments of the protons of the hydrogen nuclei. For example, water has a long T1 and T2 whereas fat has short T1 and T2.

These tissue-specific differences are employed to adjust the contrast of the final image by designing the imaging sequence in a way that it weights either T1 or T2 relaxation. In T1-weighted MRI, fatty tissues are bright and watery tissues like CSF dark. The gray matter is darker than the white matter. In T2-weighted MRI, these are the opposite. Figure 3.2 gives an example on the differences in contrasts of T1- and T2-weighted MRI on a slice of a MR image.

### 3.2 Volume Conductor Models

The anatomically realistic head models, such as the one in Figure 3.3 used in this thesis, were segmented from the structural T1- and T2-weighted MR images of individual subjects. Here, the semi-automatic segmentation pipeline used in this thesis will be briefly described alongside basic image processing methods and the open-source tools used within the pipeline.
3.2.1 Tools Used in Segmentation

**FreeSurfer**

The brain tissues are segmented using FreeSurfer, an open-source software freely available online (http://surfer.nmr.mgh.harvard.edu/). The segmentation process of FreeSurfer is summarized here, for more details see the publications cited.

FreeSurfer uses T1-weighted MR image for the segmentation. First, the MR image is normalized and the skull and extracortical structures are stripped from the MR image using a hybrid watershed and surface deformation approach [102]. Then, the brain is segmented by a two-step procedure including classification based on voxels intensities and individual adjustment of the labels of voxels that have ambiguous intensity, i.e. the voxels that have nearest neighbors with differing labels and a significant portion of the voxels on their plane of least intensity variation having a different label [86].

Tessellated white matter surfaces for both hemispheres are built by generating a single connected mass of white matter for both hemispheres that is then tessellated and refined. The white matter surface is then deformed outwards until the gray matter surface is reached [86]. Additional topology correction is
applied to minimize the amount of topological defects in the surfaces [103, 104]. FreeSurfer creates also volumetric segmentation of subcortical structures such as the hippocampus, amygdala, caudate, putamen, and ventricles using an automatic probabilistic method [105].

Additionally, FreeSurfer has multiple features useful for visualization, data analysis and cortical target estimation. FreeSurfer creates an inflated cortical surface [106] for visualization purposes, registers the brain with a spherical atlas [107] which is useful for mapping one brain to another for group-level analysis, and parcellates the cortical surface into gyri and sulci [108], e.g. pre and post central gyri, as well as into anatomical regions of interest [109], such as the Broca areas. This parcellation is useful in defining regions of interest for various purposes.

**MNI Template**
The Montreal Neurological Institute (MNI) ICBM2009a nonlinear asymmetric template [110, 111] (available at http://nist.mni.mcgill.ca/?p=904) is an average atlas of 152 adult human MRI scans, providing a high quality template without specific features from any single individual. This template is used as an initial guess in parts of the segmentation pipeline to improve the quality of the segmentation. In the description of the segmentation pipeline, the MNI template is referred to as *template*.

In addition, this template is used in group-level studies of tDCS and TMS electric fields. An individual subject’s brain is mapped to the MNI template brain via their registrations to the spherical atlas created by FreeSurfer. This way, the electric fields from multiple subjects can be studied statistically, and e.g. spatial average electric field hotspots can be found.

**BodyParts 3D Models**
An anatomic model of an adult male containing surface models of 382 individual anatomical concepts [112] is provided freely online by the BodyParts 3D repository (https://lifesciencedb.jp/bp3d/). Some of these model concepts are used as an initial guess in parts of the segmentation process to localize structures like the skull from the MR images. Additionally, the surfaces of models provided by BodyParts are used directly for visualization of the spine and the mandible.

In the description of the segmentation pipeline, the anatomical concepts from the BodyParts 3D repository are referred to as model ‘X’, where the ‘X’ is replaced with the name of the anatomic concept, e.g. model skull.

**3D Slicer**
3D Slicer is an open-source (https://www.slicer.org/) software for working with medical images. In addition, it provides a large collection of functions useful for handling medical imaging data. In the segmentation process, these functions are employed in registering one set of MR images to another and in bias correction of the MR images.
VTK
The Visual toolkit [113] (VTK, available at https://vtk.org/) is a platform agnostic software system for computer graphics and scientific visualization, including tools for image processing and volume rendering. Within the segmentation pipeline, VTK's smoother algorithm is used to built tessellations of the segmented tissues for visualization purposes.

Morphological Image Processing Methods
During the segmentation of the MR images, various binary masks are created and processed using common morphological methods described here briefly. Further details on morphological image processing can be found, for example, from a comprehensive book on digital image processing by Rafael Gonzales and Richard Woods [114].

Thresholding based on T1 and T2 image intensities is used to extract voxels with intensities of interest for creation of the masks. An example of creation of a binary mask by thresholding a noisy-gray scale image is presented in Figure 3.4, where A is thresholded by selecting the pixels with intensities higher than 0.3 to create the mask B.

Erosion and dilation of the masks and their combinations opening and closure are used commonly within the segmentation pipeline. In the erosion and dilation, the voxel layers are either removed from or added to the surface of the mask thus either shrinking or expanding it, respectively. In opening, the mask is first eroded and then dilated, and in closure vice versa; the mask is first dilated and then eroded. Opening is useful in removing small bridges between volumes, small horns on the surface of the mask and small artefacts, whereas closure fills small dents and connects narrow breaks between volumes. In addition, both opening and closure smooth the surface of the mask. Figure 3.4 C-F presents an example of each of these operations onto the binary mask presented in Figure 3.4 B.

Closed surfaces or possible holes within the mask are filled using a polynomial convex hull. This can be achieved by finding the voxels outside the surface/mask and taking their complement. Additionally, convex hulls are used in the segmentation pipeline. A convex hull is the smallest volume of voxels, that contains the binary mask and is convex, i.e. a line connecting any two voxels is contained in the domain. Examples of a polynomial convex hull and convex hull onto the binary mask are presented in Figure 3.4 G and H, respectively.

Region growing used in the pipeline is performed simply by recursively thresholding the voxels in the MR image neighboring the surface of the mask. If the voxel’s T1 and/or T2 intensity in this region exceeds the threshold, it is included in the mask.
3.2.2 Segmentation Pipeline

The segmentation pipeline consists of ten steps, where the T1- and T2-weighted MR images are first preprocessed and then segmented into 24 tissue types listed in Table 3.1. The original MR images are resampled to a 0.5x0.5x0.5 mm³ grid for the segmentation of each tissue to improve the segmentation quality. This is also the resolution of the final volume conductor model. Each of the ten steps are briefly described here.

Step 1: Reorient and Reslice the MR Image
First, the MR images are preprocessed. The MR images are transformed into NIfTI (neuroimaging informatics initiative) format and formatted into RAS (right anterior superior) coordinates. If there is rotation in the MR images, they are resliced in order to match the content of voxels throughout the dataset.

Step 2: Dura and Eye Masks
Then, the T1- and T2-weighted MR images are used to find the inner-skull surface to obtain a mask for the contents of the dura. First, the T1 images are registered to T2 images and then to the template using BRAINSFit-function of 3D Slicer. The template's inner-skull surface in combination with estimations of white matter in the individual MR images is used as an initial guess of the location of skull contents. Then, a mask covering the contents of dura matter (CSF and the brain) is built by thresholding the data within the region of the initial guess. Closure, the polynomial convex hull and the opening of the mask are used to fine tune the thresholded mask. The eyes are located similarly using the template eyes as an initial guess and as a seed for region growing.
Table 3.1. The 24 tissues segmented within the pipeline, the steps of the pipeline, where they are segmented in, and the electric conductivities ($\sigma$) used in most of the publications of this thesis.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Step</th>
<th>$\sigma$ (S/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone tissues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical bone</td>
<td>5,8,10</td>
<td>0.008</td>
</tr>
<tr>
<td>Cancellous bone</td>
<td>5,8,10</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Brain tissues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray Matter (GM)</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>White Matter (WM)</td>
<td>7</td>
<td>0.14</td>
</tr>
<tr>
<td>Cerebellar GM</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Cerebellar WM</td>
<td>7</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Fluids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>10</td>
<td>1.8 [115]</td>
</tr>
<tr>
<td>Blood</td>
<td>6,10</td>
<td>0.7 [116]</td>
</tr>
<tr>
<td><strong>Subcortical structures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>7</td>
<td>0.14</td>
</tr>
<tr>
<td>Thalamus</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Caudate</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Putamen</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Pallidum</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Amygdala</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Accumbens</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Ventral diencephalon</td>
<td>7</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye humor</td>
<td>5</td>
<td>1.5 [117]</td>
</tr>
<tr>
<td>Vestibule</td>
<td>9</td>
<td>0.904</td>
</tr>
<tr>
<td>Meninges</td>
<td>10</td>
<td>0.16</td>
</tr>
<tr>
<td>Muscle</td>
<td>10</td>
<td>0.16 [118]</td>
</tr>
<tr>
<td>Skin</td>
<td>10</td>
<td>0.08 [118]</td>
</tr>
<tr>
<td>Fat</td>
<td>10</td>
<td>0.08 [118]</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>10</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Materials and Methods

Step 3: Preprocess the MR Images
Next, any possible bias fields resulting from the imaging are corrected from the resliced images in two steps. First, the CSF is located based on a 2D histogram of T1 and T2 intensities, and the image brightness is adjusted in the vicinity of the CSF voxels so that the CSF brightness is approximately the same throughout the MR image. Next, the bias in the images is further corrected using the N4ITK bias correction algorithm of 3D Slicer. The second bias correction improves especially the artifacts in white matter. For both steps, only the regions of the MR images within the dura mask as obtained in previous steps are used.

Next, the bias-corrected MR images are normalized so that the white matter peak of T1 and T2 in a 2D histogram of the MR images data have intensity of 0.7 for the T1 and 0.35 for T2 images. The white matter peak is defined to be the one with the higher T1 of the two largest peaks with T1>0.1 and T2<0.8.

Step 4: Head Mask
A rough estimation of the head is segmented from the MR images by thresholding the Euclidean norm of T1- and T2-image intensities, with the $L_2$-norm higher than 0.2 considered to be head tissue. A sequence of closures and polynomial convex hulls are used to fill holes and dents in the mask. Region growing techniques and polynomial convex hulls are then employed to create holes for the nose and ear canals. Finally the head surface is smoothed.

Step 5: Skull Mask
The dura mask, a model skull and the T1- and T2-image intensities alongside an estimation that the skull should be at minimum 2 mm thick are used to find an approximate location of the outer skull surface. First, multiple weighted affine registrations are used to built a fuzzy cloud describing the model skull representing the regions of the MR images likely to contain skull. The outer skull surface location is estimated based on the expected thickness of the skull and the dura mask. This approximation is combined with the thresholded mask of the MR images. Opening, closure and the polynomial convex hull are used to tune the mask surface, which is then filled using a polynomial convex hull. Finally, possible holes, ridges and horns on the outer surface are removed using closures and openings, and the forehead is shaped using a convex hull.

In addition, the segmentation of the eyes in step 2 is finalized by slightly increasing their size and filling possible dents using a closure.

Step 6: Segment Venous Sinuses
The superior sagittal, lateral, sigmoid and straight sinuses are segmented once there is an estimate of the skull and contents of the dura. The template is used as a preliminary guess for the location of the sinuses and the two masks are used to ensure that the sinuses are at least 5 mm beneath the surface of the skull and not within the brain or the CSF. Thresholding is used to find possible blood at the estimated location for a given sinus. Then, islands of blood are smoothed and
the smallest ones removed as artifacts. Possible bridges are removed from these smoothed islands with an opening. Finally, region growing is used to connect the remaining large islands of blood.

**Step 7: Segment the Brain with FreeSurfer**
Prior to the segmentation of the brain with FreeSurfer, the dura mask is used to filter the T1 image to emphasize the separation of intracortical structures and the skull. With this approach, the accuracy of skullstripping performed by FreeSurfer can be improved substantially.

After running FreeSurfer on the pre-processed T1 images, the tesselated gray and white matter surfaces are voxelized by finding the voxels in the grid of MRI data that pass through the surfaces and setting them to enclose the gray or white matter. This voxelated brain is used in the final segmented head instead of the volumetric voxelization provided by FreeSurfer, as the tesselated surfaces provide a more accurate presentation of the brain from the two. After voxelization, the white-matter hemispheres are connected to each other at the corpus callosum, and the inter-hemispheric fissure is ensured between the hemispheres. The subcortical segmentation of FreeSurfer is post-processed with the morphological processes described earlier to improve the segmentation of the ventricles, brainstem, cerebellum and the nuclei.

**Step 8: Finalize the Skull Segmentation**
The inner-skull surface is further adjusted after the segmentation of intracortical tissues to ensure that they are all enclosed by the skull. This is accomplished by making a closure on a mask containing the previously segmented brain, sinuses and contents of the dura (to ensure that the CSF is contained by the skull), which is further tuned by thresholding. Possible horns or ridges on the inner surface of this mask are removed using an opening and a closure. Possible holes in the mask are filled using a polynomial convex hull. Finally, the model foramen magnum is used as a template to create the foramen magnum for the segmented skull.

**Step 9: Segment the Vestibules**
The vestibules are located in the petrous part of temporal bones. A preliminary segmentation of them is obtained using in-house model vestibules. This preliminary segmentation is then improved, by tuning the surface of the vestibule by thresholding the T1 and T2 intensities.

**Step 10: Build the Volume Conductor Model**
Finally, the individually segmented tissues are combined and labeled to create a volume conductor model of the subject with a voxel size of 0.5x0.5x0.5 mm³. In this process, the brain segmented by FreeSurfer is expanded using a 2D histogram segmentation to ensure its correct size. The background material within the skull, that hasn’t been segmented to be brain, is assigned to be either blood, CSF or ‘meninges’ based on their T2 intensity.
Materials and Methods

Muscle, including tendons and ligaments, fat, and scalp, including skin and other possible tissues, are segmented by thresholding. The fat threshold is estimated to be the 70th percentile of the white-matter T1 intensity, and the muscle threshold the 20th percentile. The scalp is segmented by finding the voxels close to the boundary of the head mask that are neither part of the skull nor the eyes.

The segmented skull is divided into cortical and cancellous bone by thresholding the smoothed T2 data within a portion of the skull that is further than 3 voxels from the skull surfaces. The nose cavity is added to the skull using the model cavity as a template and is lined with mucous membrane by finding the voxels close to the boundary with T2 intensity 1.5 times higher that the threshold for cancellous bone.

Limitations

In segmentation, the resolution of the MRI limits the accuracy of the surfaces and renders the segmentation of thin structures impossible. Hence, for example, the minor blood vessels within the brain are not included in the models. Additionally, there are some limitations inherent to the segmentation pipeline: the continuity of the blood vessels is not ensured during the segmentation, hence they might have breaks in the final models, and the parameters for Step 2 of the pipeline need to be manually selected making the outcome accuracy dependent on the expertise of the person selecting the parameters.

In general, the quality of segmentation is critical for the accuracy of modeled electric fields. For example, using only T1-weighted MR-images may result up to 49% differences in the electric field predictions [99] due to differences in segmentation between methods. The segmentation can be improved using both T1 and T2 [119] weighted MR images as done also in our pipeline. This improves especially the segmentation of the skull and CSF. Additional morphological modifications to segmentations, such as ensuring minimum thicknesses for certain tissues, smoothing the surface and removing possible rogue voxels further reduce the segmentation errors.

3.2.3 Electric Properties of Tissues

In addition to the anatomical accuracy of the segmentation, the electric properties of biological tissues are of great importance for the accuracy of the simulation outcome. In general, biological tissues are dielectric materials, that both conduct electric currents and can be polarized. The electric conduction in biological tissues is carried by free ions in the tissues, whereas the polarization of biological tissues occurs in the cell membranes. The capability of a material for electric conductivity is defined by its electric conductivity, \( \sigma \) (unit Siemens per meter, S/m), and the polarizability is defined by electric permittivity, \( \epsilon \) (unit Farads per meter, F/m). As polarization requires alternating currents which are not involved in tDCS by definition, only the electric conductivity is discussed here.
The electrical conductivity values used in the publications are presented in Table 3.1 with the exception that Publication I used a simplified model and an average of cortical and cancellous bone conductivities, 0.0175 S/m, as the conductivity of the skull. The gray-matter conductivity used is an average from multiple literature values [116, 120, 121, 122, 123, 124], and accordingly the white-matter conductivity used was selected to be 70% of the gray-matter conductivity based on literature [116, 120, 121]. The electrical conductivity of the meninges is selected arbitrarily to be the same as that of the muscle, and the bone conductivities were increased by 30% from literature values [125] to compensate for the room temperature measurements according to differences in conductivity values measured between room and body temperature [121]. The electric conductivity of the mucous membrane is arbitrarily chosen to be slightly lower than that of the muscle, and the vestibule is set to have an average conductivity of the cortical bone and CSF. The skin is estimated to have the same conductivity as subcutaneous fat. The conductivity values used are of similar order of magnitude to other computational studies [15, 16, 41, 77, 97], aside from the skin which is lower in our models than the 0.465 S/m used in many computational studies [16, 41, 77].

All the electric conductivity values used in the models for this thesis are obtained from literature for practical reasons. The measurement of the electric conductivities of tissues at low frequencies in vivo is generally difficult, and is practically impossible to be done with healthy subjects due to the invasiveness of the measurement. Due to this restriction, there is a large variation in the reported electric conductivities between different studies as the measurements have been performed in vitro [115], on different animals [116, 120, 122], or patients during surgery [124] rather than on healthy subjects. However, the conductivities measured from bodily liquids are likely accurate as they are easy to extract for conductivity measurement. Additionally, in literature there are only a few DC-conductivity measurements. Hence, the conductivities used are often from low frequency measurements, which are prone to errors related to electrode polarization [126], thus adding the variability observed in the literature conductivity values.

The electric conductivities of the tissues used in the models of this thesis are assumed to be homogeneous, i.e. the same throughout the tissue, and isotropic, i.e. not dependent on the direction of the electric current. Neither of these actually holds for living biological tissue, nonetheless this approximation is sufficient given all the uncertainties in the actual measurement of these values and the modeling procedure. The spatial resolution (often 1 cubic millimeter) and contrast of MRI limits the segmentation accuracy, thus making it difficult to include small inhomogeneities of the tissues in the actual models. Additionally, the measurement of conductivity for such inhomogeneities is highly impractical. On the other hand, the microstructures and inhomogeneities of tissues contribute also to the anisotropy of the conductivities. The amount of anisotropy changes from one tissue to another, but assuming that deep brain structures are not
sensitive to cortical stimulation, inclusion of tissue anisotropy into modeling is necessary only with white matter when targeting deeper targets, which are not readily reached with tDCS [127]. In addition to the quality of segmentation, this variability in conductivity value is a major source of error in modeling of electric fields in biological tissues. Fortunately, the variability affects the electric field distribution and peak location only slightly on the group level with a larger effect on the electric field strength [10]. Although the strengths are more affected by the electric conductivity, the order of magnitude, approximately 1 V/m [10, 75, 128], of the modeled electric fields remains similar with recent in vivo measurements [77, 98, 89] suggesting that the models are not false. Hence, when reading the results from an electric field modeling study, the distribution of electric fields and the order of magnitude for them can be considered rather trustworthy, but the amplitudes should not be interpreted as being indicative of accurate values.

### 3.3 Electrode Models

The tDCS electrodes used in the models of this thesis are based on a realistic sponge electrode that is used commonly with tDCS. The models consist of a 6 mm-thick saline soaked sponge ($\sigma=1.6$ S/m), containing a 1 mm-thick rubber sheet ($\sigma=0.1$ S/m), which further envelopes a connector disk, which contains the uniformly distributed electric current sources or sinks, depending on whether an anode or a cathode is modeled. The size of the sponge is selected based on the electrode being modeled, and was most often a round electrode with a 5 cm diameter or a square electrode of...
Materials and Methods

5 × 5 cm² in the publications related to this thesis. The rubber sheet was always 2/3 of the size of the sponge, and the connector sheet was round with a diameter of 5 mm regardless of the shape and size of the sponge. Figure 3.5 presents a schematic of the electrode model, and a modeled electrode.

3.4 Finite Element Method

Based on Maxwell’s equations, the electric field $E \ (V/m)$ can be written as

$$\vec{E} = -\nabla \phi,$$  

where $\phi$ is the electric scalar potential, which was solved in this thesis using the FEM. The governing equation for the FEM can also be derived from Maxwell’s equations and reads:

$$\begin{cases} \nabla \cdot \sigma \nabla \phi = -i, & \text{in } \Omega \\
\frac{\partial \phi}{\partial n} = 0, & \text{on } \partial \Omega, \end{cases}$$

where $\sigma$ is the electric conductivity, and $\Omega$ is the domain of the solution, i.e. the head and the electrodes. The electric current density $i$ satisfies the following conditions:

$$\begin{cases} i \neq 0, & \text{in } \Omega_{CD} \\
i = 0, & \text{in } \Omega \setminus \Omega_{CD} \\
\int_{\Omega} i dV = 0 \\
\frac{1}{2} \int_{\Omega} |i| dV = I. \end{cases}$$  

$I$ refers to the input current of tDCS, and $\Omega_{CD}$ to the connector plates within the modeled electrodes.

However, in a complex geometry such as a human head, solving this equation analytically is not possible and hence numeric methods are required. In the FEM, this problem is solved by dividing the geometry into a finite number of elements that comprise nodes at which the equation is solved. The set of elements is called a mesh. An example of the discretization is given in Figure 3.6A. Conventionally, the elements used are tetrahedral for accurate representation of curved surfaces, but the creation of a tetrahedral mesh that is of adequate quality for a complex geometry is a tedious task. We bypass this problem, by using the cubical voxels in our volume conductor models as elements, and solving the potential at their vertices. Hence, no separate mesh creation is required simplifying the process drastically. Although this results in some error in the approximation of curved surfaces within the head, the modeled electric fields differ only little from electric fields predicted using models with tetrahedral meshes [129].

In order to solve the equation (3.2) at the nodes of the mesh, it also needs to be discretized. This is done by first using the weighted residual method to modify equation (3.2) into a weak form and then discretizing the weak form. The weak formulation is required for the discretization as equation (3.2) is a second-order
differential equation and would need twice-differentiable test functions to be discretized, whereas the weak form benefits of the requirement of only once-differentiable test functions. The weak form can be obtained by multiplying equation (3.2) with a test function \( \Psi \) and integrating over the domain \( \Omega \). With the application of a boundary condition of zero normal components of \( \phi \) on the surface of the domain, the weak formulation of equation (3.2) is

\[
\int_{\Omega} \sigma \nabla \phi \cdot \nabla \Psi \, dV = \int_{\Omega} \Psi \, i \, dV, \quad \text{for all } \Psi
\]

which can be further discretized using \( \phi \approx \sum_{j=1}^{n} \phi_j N_j \), where \( N_j \) are first order basis functions and \( n \) the number of nodes. Basis functions are piecewise trilinear functions that are one at a single node and zero at all other nodes. To discretize equation (3.4), we use the Galerkin-FEM, i.e. we use the basis functions also as the test functions. Thus the discretized weak form is

\[
\sum_{j}^{n} \int_{\Omega} \sigma \nabla N_j \cdot \nabla N_k \, dV \, \phi_j = \int_{\Omega} N_k \, i_k \, dV, \quad \text{for all } k
\]

where \( k \) span from 1 to the number of nodes \( n \). This can be modified to form a global system equation of the form

\[
K \vec{\phi} = \vec{i}.
\]

As our elements form a regular grid, the surroundings for each node are geometrically identical and the integrals in equation (3.5) can be solved analytically. For each row of equation (3.6), e.g. node in the mesh, the potential can be solved from

\[
\frac{1}{h^2} \left( \frac{8}{3} \sigma_{12345678} \phi_j - \frac{1}{6} (\sigma_{12} \phi_{12} + ... + \sigma_{78} \phi_{78}) - \frac{1}{12} (\sigma_1 \phi_1 + ... + \sigma_8 \phi_8) \right) = i_j
\]

where \( h \) is the side length of a voxel, \( j \) is the index of the node where the potential is being solved and the subindexed \( \phi \) refer to the potentials at the nodes of the eight elements the node \( j \) belongs to as shown in Figure 3.6B. The subscripts in \( \sigma \) refer to arithmetic averages of the conductivities over the specified voxels, e.g. \( \sigma_{12} \) is the average of \( \sigma_1 \) and \( \sigma_2 \).

Equation (3.6) is solved iteratively employing the geometric multigrid method. In the geometric multigrid method, multiple coarser-grid sizes are employed recursively to speed up the convergence to a solution. For a more detailed description of the geometric multigrid method see the original publication on the solver used in this dissertation [130] or the descriptions by Yavneh [131] and Hülesemann [132].

The FEM provides a discretized estimation of the accurate solution for the governing equation and hence contains always some error, which is dependent on the quality and resolution of the mesh. In addition, the iterative solution of Equation (3.6) results in some error, which is controlled by the relative residual norm. When this norm is less than \( 10^{-6} \), the resulting error in the electric field is less than 0.1% [130].
3.5 Statistical Methods

The statistical methods used in analyzing the results of this dissertation included mainly standard measures such as mean, median, standard deviation, interquartile range, linear regression, t-tests and false discovery rate. All these methods are standard and widely used, and hence are not discussed in detail here. More information can be found from any book covering the basics of statistics.

However in Publication V, we used partial least squares regression (PLSR) to study whether the measured MEPs could be explained by the modeled electric fields, and variable importance projection (VIP) to identify the brain regions important for prediction of the MEPs based on the important variables of PLSR. These two methods are not typically used in tDCS studies and are described here briefly. For more detailed information on PLSR and VIP, please refer to [133].

3.5.1 Partial Least Squares Regression

The modeled electric fields in the brain are not independent of each other on the nodes of the mesh. This is problematic when studying their connection to measured biological signals, such as the MEPs, because the collinearity of the electric fields renders conventional multivariate linear regression erroneous. However, PLSR, which is a generalization of multiple linear regression [133], has the advantage of being able to analyze this kind of strongly collinear data.

PLS assumes that a small amount of latent variables describe the studied system, and that both the predictors and responses are realizations of these variables. Simply, PLSR works by creating "PLSR components" to estimate the latent variables as linear combination of the original predictors, and uses these PLSR components as predictors of the responses. As PLSR assumes
the responses to be predicted with just a few latent variables, the predictive significance of each component needs to be tested. This is usually done with cross-validation.

PLSR has also the advantage of not needing a priori selection of a region of interest. Rather, the parameters of PLSR can be used to find cortical regions where electric fields have high predictive power using the VIP. VIP is a measure of the predictor variables importance for both modeling the predictor and the response. VIP is solved as a sum of squares of predictor weighs weighted by the amount of response-variance in PLSR components.
This thesis concentrated on the individualized modeling of tDCS aiming to study its inter-individual variability. Publication I studied an approach to lower the computational burden of solving tDCS electric fields with FEM. In Publications II and V, experimental data was linked to the predicted electric fields. Publications III and IV studied reasons contributing to the inter-individual variability of the predicted electric fields. This chapter summarizes briefly the main results of each of these publications, alongside their core methodology.

### 4.1 Towards Faster FE Solutions

Publication I used the T1- and T2-weighted MR images of a 36-year-old male freely available online (NAMIC: Brain Multimodality, subject case01025) in building the anatomically accurate model. Tesselated surfaces of the scalp, inner and outer skull, gray matter and white matter were used to build differently voxelized volume conductor models for the FEM. The voxelizations differed at the tissue surfaces, where the conductivity was either set to be the average of the surrounding tissues (unrefined, Figure 4.1A) or a more accurate refined value (Figure 4.1B). The refined conductivity was obtained by voxelizing the model with higher-than-intended resolution, finding how large the proportion of the fine voxels is within each tissue, downscaling the voxel size to the intended, and calculating its conductivity based on the proportions of the small voxels in both tissue types. A C3-Fp2 (EEG 10/20) tDCS montage with round electrodes of 25 cm² and input current of 1 mA was modeled and the results from the differently voxelized models were compared to the model with 0.2-mm unrefined voxels considered to be the most accurate model.

The results presented in Figure 4.1C demonstrate that refining the tissue boundary conductivity reduces the error in the modeled electric fields. For example, using 0.2-mm voxels during voxelization and downscaling the voxel size to 0.8 mm, i.e. refinement by a factor of 2, the boundary-layer voxel conductivities can be approximated better. Instead of using the average of the surrounding tissue conductivities, using a refinement by a factor of two, for example, could
Summary of the Results

Figure 4.1. A) and B) present the tissue boundaries between gray matter (red) and CSF (white) with refinement factors 0 and 2, respectively. C) Relative error calculated on the left hemisphere with different refinement factors. Refinement factor is the amount of increase in resolution during voxelization, i.e. 0 refers to the standard unrefined case, and 1 and 2 mean that each voxel is replaced with $2^{\text{Refinement factor}}$ smaller ones for voxelation. The figure is modified from Publication I.

mean that the voxel has a conductivity of $1/64$ of the conductivity of inner and $63/64$ of the conductivity of the outer tissue. This results in a relative error similar to using 0.4-mm unrefined voxels, but with an 82% decrease in computation time and an 87% decrease in degrees of freedom.

4.2 Sensitivity to TMS Can Predict tDCS Electric Fields

In Publication II, rMT was measured from 28 subjects from the left abductor pollicis brevis (APB) muscle using a Magstim 200 magnetic stimulator (Magstim Company, UK). T1- and T2-weighted MR images were obtained from each subject, and used to create anatomically realistic models used for solving the electric fields produced by hand M1-contralateral forehead tDCS montage, that uses $5 \times 5 \text{ cm}^2$ electrodes with 1 mA input current. In addition, TMS aimed at the same location as the tDCS anode was modeled for each subject.

Figure 4.2. Regression plots presenting the correlation between tDCS electric-field magnitude and A) resting motor threshold (rMT) and B) electric field magnitude of TMS. The gray cross in A) marks an outlier. The figure is modified from Publication II.
Results in Figure 4.2 present a negative correlation ($R^2=0.58$) between the TMS rMT of the APB muscle and the electric fields of tDCS at a region of interest with a diameter of 3 cm within the hand M1, but not outside it. In addition, the electric fields of both tDCS and TMS were found to have a positive correlation ($R^2=0.36$).

### 4.3 Differences in Posture Might Add Inter-individual Variability

Publication III studied the effects of the movement of the brain between postures on the electric fields of tDCS and TMS with 5 subjects in supine, prone and left lateral positions. T1- and T2-weighted MR images obtained in prone and left lateral positions were aligned to the MR images from the supine position for each subject. TDCS and TMS electric fields were solved using the FEM and models created from the aligned MR images. In FEA, the possible segmentation errors of extracortical tissues were mitigated by replacing the extracortical tissues with those of the supine position models for the models of prone and left lateral positions. Two tDCS montages and a TMS case were studied. In the tDCS models, 25 cm$^2$ round electrodes were placed at C3 and C4 or C3 and Fp2 of EEG 10/20 system. In both cases the input current was 1 mA.

The brain was found to move approximately 1 mm towards the pull of gravity as the subject moved from supine to prone or left lateral position. This shift in the brain was also found to affect the electric fields of tDCS and TMS: as a rule of thumb, the tDCS electric field magnitude increased approximately 10% and became more diffuse in comparison to the supine position for both prone and left lateral positions. For TMS, the trend was found to be similar, however the differences in electric field magnitude were only 2%. Figure 4.3 presents the

![Figure 4.3](image)  
Figure 4.3. The group average motion from supine to left lateral and prone as well as the electric fields in each position with C3-C4 tDCS montage, 1 mA input current and 25 cm$^2$ round sponge electrodes. The figure is modified from Publication III.
average brain motion between positions, and the average electric field for each position.

### 4.4 Trade-off Between Focality and Inter-individual Variability of Electric Fields

Publication IV studied the effects of tDCS focality on the inter-individual variability of tDCS using 77 subjects and 13 tDCS montages with the stimulating electrode located above the hand M1. Eight of the montages were conventional M1-contralateral forehead montages with different stimulating electrode sizes and a $7 \times 5 \text{ cm}^2$ reference electrode. In addition, we studied three $4 \times 1 \text{ HD}$ montages with different distances from the anode to the cathode, and two bipolar HD montages with anode-to-cathode distance of 7 cm and different orientation. The models used in this study were obtained from Publications II and III and previous research done by our group [10, 74].

Using conventional hand M1–contralateral forehead montages, the electric fields were found to become stronger, more focal and more varying between individuals with decreasing anode size as presented in Figure 4.4. The $4 \times 1 \text{ HD}$-tDCS montage was found to have the most focal and the most varying electric fields. Bipolar HD montages, where a small anode and cathode are placed symmetrically around the target, were found to provide electric fields with equal magnitudes to $4 \times 1 \text{ HD}$-tDCS with reasonable focality and low

![Figure 4.4](image-url)

**Figure 4.4.** A) Individual (gray) and median (black) electric fields at the target and the interquartile range (red) and quartile coefficient of error (QCD, blue) for each electrode montage studied. B) Individual (gray) and median (black) electric field focality, $A^2_1$, at the target and the interquartile range (red) and quartile coefficient of error (blue) for each electrode montage studied. The $A^2_1$ presents the proportion of cortical surface area, where the electric fields are higher than 50% of that at the target point. The figure is modified from Publication IV.
variability. However, the direction of the electric field produced by the bipolar montages differ from that of the conventional montages or $4 \times 1$ HD-tDCS.

### 4.5 Electric-field Normal Components are Related to tDCS Outcome

In Publication V, we studied tDCS experimentally with right hand M1 - contralateral forehead montage using a 1-mA input current, stimulation duration of 20 min and $5 \times 5 \text{ cm}^2$ electrodes. The experiment was sham controlled. Pre- and post-stimulation MEPs and rMT of the left APB muscle were measured from 28 subjects using a Magstim 200 magnetic stimulator (Magstim Company, UK). Additionally, the electric fields in the brain during tDCS were modeled for each subject to find out whether the predicted electric fields were related to the measured MEPs. The subjects and rMT data in this study were the same as in Publication II, so the same models were used in this study for FEA.

The results in Figure 4.5 show that the modeled electric fields are indeed related to the inter-individual differences in the subjects’ response to tDCS. The electric-field normal component was found to be important for the prediction of the tDCS effect within the hand area on the cerebral cortex. Especially the region between the primary motor cortex and pre-motor area in the vicinity of the TMS hotspot of the APB muscle was found to have high importance on the effects. The subjects with high electric field normal components within this region exhibited a larger decrease in MEPs compared to sham and baseline than the subjects with weak electric field normal components.

![Figure 4.5](image-url)  
**Figure 4.5.** A) The effect of the electric field normal component and time on normalized MEPs. Regression lines are shown in red/blue for sham/active stimulation, respectively, with filled lines differing significantly from the baseline. The gray area presents the 95% confidence intervals. B) Linear regression between the electric field normal component at MNI coordinate $[42,-13,66]$ and the grand mean of normalized MEPs. Disks present the individual data divided into quartiles by gray shades, the gray lines connect the data from individual subjects. The figure is modified from Publication V.
Recently, the validity of using the conventional input current as a dose metric for tDCS has started to be questioned, up to a point where the electric fields at the targeted brain site have been suggested as being a more appropriate dose measure for tDCS [16, 17, 134]. Although recent studies [77, 98, 89] have managed to measure tDCS electric fields in vivo from patients undergoing cranial surgeries, for healthy subjects and patients not requiring craniotomy, computer modeling remains the path of choice to estimate the electric fields within the skull during tDCS.

However, computational modeling is a demanding task, which is time consuming, requires expertise to perform, and may hence be beyond the reach of clinical practice. In recent years, there has been improvements in accessibility to electric field modeling with various commercial and open-source solutions for model creation and electric field computation as discussed earlier in Chapter 2.2.2. Conventionally, these approaches use tetrahedral meshes for FEM, which are sensitive for errors if the mesh quality is poor [119]. As an option to tetrahedral meshes, the voxels of the segmented model can be used directly as the mesh for FEM, as done in our in-house solver. This approach eliminates the laborsome steps of mesh generation and refinement, which are required with conventional tetrahedral meshes, and streamlines the modeling workflow. Although the cubical elements model curved surfaces worse than tetrahedral elements, the overall difference in the final predicted electric fields is small [129]. Additionally, the regular mesh allows some equations to be solved analytically and an easy application of the multigrid method, making the solver faster compared to one using tetrahedral elements [129]. Publication I presented a method to lower the computational costs of electric field modeling further with only a minor penalty in the accuracy of the results. On the other hand, this approach also enables to increase the accuracy of the model without increasing the computational costs thus diminishing the error from misestimation of surfaces.

On the other hand, TMS MEPs are an easily measured and quantifiable measure of tDCS efficacy, and they are considered to be the most reliable measure for tDCS efficacy [7]. In Publication II we found that the predicted tDCS electric fields in the vicinity of hand M1 correlate with TMS rMT suggesting that indi-
individuals sensitive to TMS are also sensitive to tDCS. This result is also supported by other studies: TMS coil orientation has been shown to affect the after-effects of bipolar HD-tDCS [41], and rMT was found to be positively correlated with tDCS efficacy [135]. This finding suggests that a portion of the inter-individual variability in motor cortical tDCS efficacy may arise from individual differences in sensitivity to tDCS, i.e. in differences of the electric fields at the target site.

In addition, this raises questions whether using individual sensitivity to TMS as a measure of subjects’ sensitivity to tDCS could enable bypassing the need for computational modeling in order to adjust the electric field dose individually in motor cortical tDCS. However, further research is still required to find out whether this hypothesis is viable. Lastly, it should be noted, that as rMT can by definition be measured only by stimulating the motor cortex representing the targeted muscle, these results cannot be generalized outside the motor cortex.

Publications III and IV concentrated on determinants of the inter-individual variability in tDCS. In Publication III, the effect of body position on the electric fields was studied as the deformation of the brain might affect the electric field distribution on the brain during tDCS. Indeed, the focality and magnitude of tDCS electric fields were affected by the body position. This suggests that it might be necessary to ensure that the subjects receive tDCS in the same position both between different subjects, and between stimulation sessions to reduce possible sources of variability. Especially with the rising interest in home-based treatment with repeated sessions of tDCS [69] administered by the patients themselves, it could be worth informing the patient to receive the treatment in the same position to mitigate possible variation in the electric fields in the brain. Unfortunately, this study did not include an upright position, which is commonly used in tDCS treatments, and its effects on the cortical electric fields remain unknown. However, a viable hypothesis based on these results would be, that from the supine to upright position the brain moves downwards toward the gravitational pull hence increasing the CSF thickness superior to the brain, which would result in lower and more diffuse electric fields at the motor cortex. As this study concentrated solely on computational modeling of electric fields, the possible differences in the outcomes of tDCS received in different positions remains an unanswered question.

As an approach to increase control of tDCS, ways to increase the focality of the tDCS electric fields have been studied [11, 136]. Yet, the possible effects of the increasing focality on inter-individual variability have been neglected. Publication IV revealed the connection between the electric field focality and electric field variability with montages producing more focal electric fields resulting also in higher electric field variation between subjects. Hence, it is paramount to acknowledge the effects of increased focality on the inter-individual variability of tDCS electric fields. This could be done, for example, by using individualized modeling to normalize the electric fields over a group of subjects. Of course, the electric field variability at the target is not the only factor affecting the variability of tDCS outcome as already discussed in Chapter 2, and the exact
effects of electric field focality on the tDCS outcome remains unknown, which provides an interesting research question for the future.

An additional finding of Publication IV was that bipolar HD-tDCS did not behave in a similar manner to the other montage types studied, but rather provided moderate focality electric fields with low inter-individual variability. As this montage type offers a possibility to control the direction of the current flow [41, 78], it could provide a useful tool for future tDCS studies.

The determinants of interindividual variability of tDCS electric fields established in Publications III and IV are relatively small, possibly smaller than the effect of expected modeling inaccuracies. However, this should not be interpreted to mean they are of no importance. In both publications, the findings were consistent over groups of subjects, suggesting that the effects are real and hence may contribute to inter-individual variability of tDCS electric fields.

Computational models provide only predictions on what may be happening in the modeled situation, and require experimental evidence to support them. In Publication V, we showed a connection between the predicted electric fields and efficacy of tDCS in terms of measured MEPs, and hence provide further proof that the electric fields are better suited as the dose measure for tDCS as opposed to the input current. In addition, and as suggested by multiple other publications [41, 78], it was the direction of electric fields that was important for the outcome of tDCS. In particular, the normal component of the electric fields in the vicinity of the TMS hotspot was found to be important for predicting the stimulation outcome. Noteworthy in this result was that the strong predicted electric fields, more than the weak, lowered the excitability although anodal stimulation was used. This is in accordance with earlier results [13, 14, 43] suggesting that the dose-effect relationship of tDCS may be non-linear. Of course this is but one combination of stimulation parameters and repetitions using different input currents or electric field values, stimulation durations and electrode montages are required for more thorough understanding of the connection between tDCS electric fields and stimulation outcomes.

There are some general limitations to computational studies common to all five publications of this thesis. As described earlier in Chapter 3, uncertainties in the segmentation and the tissue conductivities have a large impact on the simulation outcome. Especially, the in vivo electric conductivities of tissues are not well known at DC. Despite recent attempts in validating computational models used to study tDCS electric fields [77, 88, 98, 89], we still lack a reliable way to define the ground-truth to which the computational models could be compared to for validation [99], rendering the estimation of the exact amount of modeling error difficult. However, based on the validation attempts [98, 89], the order of magnitude of the predicted electric field is correct, yet the predicted amplitudes vary with conductivities [10]. Additionally, the electric field distributions were similar between measurements and models [77, 89], and varying the model conductivities [10] have been shown to have only a minor effect on the electric field distribution, hence their distribution can be expected to be realistic.
Additionally, there are some considerations regarding the generalizability of these results. Only one set of conductivity values were used in Publication I, so there may be differences in the results with differing conductivity values. Publications III and IV were both purely computational in nature and require further experimental validation to be used in predicting stimulation outcomes. Extrapolating findings for other stimulation parameters for Publications II and V should be done cautiously, as only one parameter set was used in these studies.

Future directions
In general, the results of this thesis agree with the hypotheses that individual electric field modeling is necessary for dose estimation [16, 17], and that the direction of electric fields [41, 78] affects the outcome of tDCS, with the normal component being the component of interested [79, 80]. In particular, if the results of Publication V can be confirmed in future, differences in the electric fields could prove to be a major contributor to inter-individual variability of tDCS. One potential approach for getting further support for the two hypotheses, would be to combine neuronavigation to bipolar HD-tDCS, which was found to provide a compromise between electric field focality and variability in Publication IV, in addition to having the capability of controlling the direction of current [41]. In combination with neuronavigation commonly used with TMS and individual electric field modeling, bipolar HD-tDCS electric field dosage in terms of the normal component at the target could be normalized individually over subjects and applied replicably. By studying multiple muscles, multiple electric field strengths and stimulation durations one could obtain comprehensive information on motor cortical tDCS.

Additionally, the effect of tDCS is easily lost due to the inter-individual variability if studied merely on group level. This was the case, for example, in Publication V, where some subjects increased the response, whereas others experienced a decreased response. Also earlier tDCS studies have been able to divide the subjects into responders and non-responders [40, 70, 71, 72, 73]. Hence, it would be interesting to shift the focus from studying results of tDCS at a group level and showing that some respond and others do not, to focusing on the reasons why the responders respond to tDCS, and non-responders do not. Publication V found that the normal component of the electric fields in the vicinity of the target site differs between the two, but there could be other differences as well. This would provide valuable information on the reasons behind the inter-individual variability, and possibly improve the patient selection for clinical purposes by giving insight on who would likely benefit from the treatment.

Finally, the models we use should be validated to establish their accuracy. However, by-date we lack a reliable way to determine the ground-truth for validation. In future, this may be achieved by intracranial potential recordings once the limitations of the methods are addressed [99] or by MRI-based approaches such as magnetic resonance current density imaging (MRCDI). [137]
6. Conclusions

TDCS has proven to be a valuable option for the treatment of various psychiatric and neurological disorders over the past two decades, and yet it still lacks a solid enough foundation to unleash its full potential for the treatment of these illnesses. One important aspect in enabling the full potential of tDCS, is a better understanding of the reasons behind its inter-individual variability, which was the focus of this thesis.

In this thesis, the adjustment of the conductivities on the tissue boundaries was found to reduce the computational costs of solving anatomically accurate models with the FEM. Combining the fast and light solver employing the segmented MR-image voxels as mesh has potential in providing a robust way to determine tDCS dose in terms of electric fields. On the other hand, our results also suggested a possibility of using a simple TMS sensitivity measure for defining the individual sensitivity to tDCS, and thus bypassing the need for modeling in normalization of tDCS dose within the motor cortex. In addition, the results suggest that both the subject posture and the focality of the electric fields are factors affecting the inter-individual variability of tDCS electric fields, and hence may be required to be considered in planning tDCS experiments. Lastly, and perhaps most importantly, we were able to show a connection between the normal components of the modeled electric fields in the vicinity of the TMS hotspot and the stimulation outcome further supporting the use of electric fields as a dose-measure for tDCS.

Nevertheless, these results only scratch the surface of the complexity behind the inter-individual variability of tDCS, and the computational predictions still require experimental validation. More rigorous research is still required to obtain a better understanding of tDCS, both in terms of its basic mechanisms as well as the reasons causing the inter-individual variability. Once the variability can be mitigated, the full power of tDCS may be revealed.
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Errata

Publication III

The tDCS conductivity for fat and skin reported on page 3 should be 0.08 S/m instead of 0.8 S/m.
Individualized Computational Modeling of Transcranial Direct Current Stimulation

Marko Mikkonen