Implementation of a theoretical pipeline for modeling navigated transcranial magnetic stimulation

Ali Mohammadi
Master’s Thesis
Master’s degree in medical physics programme
University of Eastern Finland
Department of Applied Physics
02.05.2018
Abstract:

Transcranial magnetic stimulation (TMS) is a non-invasive method where magnetic pulses are applied to the brain using an electromagnetic coil placed over the head. Consequently, an electric field (EF) is induced in the cortical neural tissue, which can excite and modulate the neural function. The ability of TMS to target, locate and map the motor areas has been improved by combining TMS with a neuronavigation system. The main applications of navigated TMS are planning of neurosurgery and radiotherapy, and focused TMS therapy.

Electric field (EF) calculations based on realistic head models and numerical methods are increasingly utilized in TMS research. However, the current cortical mapping methods apply a simplified geometric model due to the complexity of realistic head models. Hence, realistic geometries cannot presently be used in real-time. Using simplified spherical geometries for navigated TMS results in a unique maximum EF on the cortex, which is used for pinpointing the stimulation target. SimNIBS is a free software, which can be used for the calculation of the EF induced by TMS in a realistic brain geometry. Nevertheless, SimNIBS has some practical issues, such as a limited number of available coils and a lack of a proper pipeline to implement large numbers of stimuli for simulations, which complicate its usage on experimental data.

In this thesis, a practically applicable pipeline for an easy application of SimNIBS with experimentally gathered data and additional coils is introduced. The pipeline generates a realistic head model using structural magnetic resonance images (MRIs), converts the experimental stimulus locations with their coil configurations to a SimNIBS-compatible form, and performs the EF calculation by employing the SimNIBS package. To validate the pipeline with experimental data, two TMS measurements were conducted. The simulations performed by the pipeline showed multiple EF maxima, which remain undetected by the current online TMS software. The novel pipeline will make the use of SimNIBS more broadly available and the offline analysis of navigated TMS stimulus areas more accurate presumably representing better the activation site on the cortex. Hence, the pipeline also has potential to function as a post-experimental processing tool before surgery or radiotherapy.
## Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADM</td>
<td>Abductor digiti minimi</td>
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<td>APB</td>
<td>Abductor pollicis brevis</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>D-wave</td>
<td>Direct wave</td>
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<td>EF</td>
<td>Electric field</td>
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<td>EMG</td>
<td>Electromyography</td>
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<td>FDI</td>
<td>First dorsal interosseous</td>
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<td>FEM</td>
<td>Finite element method</td>
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<td>GM</td>
<td>Gray matter</td>
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<tr>
<td>GUI</td>
<td>Graphical user interface</td>
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<td>ISI</td>
<td>Inter-stimulus interval</td>
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<td>I-wave</td>
<td>Indirect wave</td>
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<td>MEP</td>
<td>Motor evoked potential</td>
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<td>MNE</td>
<td>Minimum-norm estimate</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance image</td>
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<tr>
<td>MT</td>
<td>Motor threshold</td>
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<tr>
<td>nTMS</td>
<td>Neuronavigated TMS</td>
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<tr>
<td>rMT</td>
<td>Resting motor threshold</td>
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<tr>
<td>rTMS</td>
<td>Repetitive TMS</td>
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<tr>
<td>TES</td>
<td>Transcranial electrical stimulation</td>
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<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
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<tr>
<td>WM</td>
<td>White matter</td>
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# Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
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<tbody>
<tr>
<td>$\vec{A}$</td>
<td>Vector potential</td>
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<tr>
<td>$\vec{E}$</td>
<td>Electric field</td>
</tr>
<tr>
<td>$\vec{H}$</td>
<td>Magnetic field</td>
</tr>
<tr>
<td>$\vec{B}$</td>
<td>Magnetic induction</td>
</tr>
<tr>
<td>$\vec{D}$</td>
<td>Electric induction</td>
</tr>
<tr>
<td>$I(t)$</td>
<td>Current in the coil in the time domain</td>
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<tr>
<td>$I(\omega)$</td>
<td>Current in the coil in the frequency domain</td>
</tr>
<tr>
<td>$\vec{J}_{\text{coil}}$</td>
<td>Current density in the coil</td>
</tr>
<tr>
<td>$N_x$</td>
<td>Number of voxels in x-direction</td>
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<tr>
<td>$N_y$</td>
<td>Number of voxels in y-direction</td>
</tr>
<tr>
<td>$N_z$</td>
<td>Number of voxels in z-direction</td>
</tr>
<tr>
<td>$P_{\text{dim}x}$</td>
<td>Voxel dimension in x-direction</td>
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<tr>
<td>$P_{\text{dim}y}$</td>
<td>Voxel dimension in y-direction</td>
</tr>
<tr>
<td>$P_{\text{dim}z}$</td>
<td>Voxel dimension in z-direction</td>
</tr>
<tr>
<td>$\vec{r}$</td>
<td>Position</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Frequency</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Scalar potential</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>Permeability of vacuum</td>
</tr>
<tr>
<td>$\vec{\tau}(\vec{r})$</td>
<td>Unit vector tangent at the point $\vec{r}$</td>
</tr>
<tr>
<td>$\varepsilon_0$</td>
<td>Permittivity of vacuum</td>
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Preface

The studies in this thesis were conducted in the Department of Clinical Neurophysiology, in the Department of Clinical Radiology, Kuopio University Hospital and in the Department of Applied Physics, University of Eastern Finland.

Sometimes you need to walk into new world to discover new interests. I had difficult but amazing moments during my Master thesis. The work was consisted of bunch of unanswered questions related to brain simulation. However, with great teacher, problems are solved easier. I would therefore like to express my sincere and special gratitude to my role-model supervisor Professor Petro Julkunen, who not only was my scientific supervisor but also was encouraging and inspirational teacher with his special “smile”. In addition, I deeply thank my second supervisor, Jusa Reijonen, M.Sc., who had the main role in the experimental part of this thesis and always tended to help me in theoretical part. I want to thank soon-to-be Dr. Minna Pitkänen and Professor Risto Ilmoniemi at Aalto University who helped me in this study.

My dear friend, Mohammad Hossein Ebrahimi, I warmly thank you, for being unique friend and scientific partner during last two years. Further, I wish to thank the NBS staff, Kuopio University Hospital, for their help to conduct TMS measurements.

I want to thank, Professor Rami Korhonen, who provided me the opportunity to join this great Master programme in UEF. Medical physicist Siru Kaartinen, thank you very much for your wonderful support during my Master studies. Last but not least, I would like to thank my friends, BBC students and professors.

This thesis is dedicated to my lovely and supportive family, my parents, and my brothers, Reza and Mohammad, who always supported and encouraged me to peruse my dreams.

Kuopio, April 2018
Ali Mohammadi
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1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique enabling painless modulation of neural activity in the human brain. TMS has versatile applications in clinical diagnostics, rehabilitation and treatment. It has been widely studied and tested as a tool for diagnosis and treatment of a wide range of neurological and psychiatric disorders [1,2]. TMS works by activating the cortex of the brain via a very strong and brief magnetic field, generated by a current flow through a coil held over the scalp [3]. The magnetic field induces an electric field (EF) in the brain, which can stimulate the cortical neurons and subsequently the connected neuronal networks. The EF, when sufficient and targeted to primary motor area, induces an action potential in the trajectory of the pyramidal axons, which results in motor activation eventually leading to a measurable physiological response. The motor activation can be measured using electromyography (EMG) and assessed by motor evoked potentials (MEPs). Accordingly, TMS is mainly suitable for targeting, locating and mapping the motor areas [4–7]. Therefore, neuronavigation system has been combined with TMS to accurately perform TMS based on individual anatomical images [4,8]. Neuronavigated TMS (nTMS), as a preoperative procedure, has been utilized widely to plan surgical operations. Several studies have validated nTMS against reference methods [5,9]. Although nTMS activates the neighboring area of stimulation point due to the extent of the EF, current cortical mapping methods apply a simplified geometric (spherical) model of nTMS producing a unique maximum EF point that is used for pinpointing the stimulation focus [10,11]. The more realistic geometric models are, however, often too complex for real-time applications.

In order to design new coils and to characterize the spatial EF patterns, the field calculation has been utilized from the early use of TMS [12]. The geometry of the induced EF plays a crucial role in determining the spatial extent of the neural effects of TMS. However, the exact calculation of EF is challenging, due to its dependency on tissue heterogeneity in the head [13]. This complexity in the calculation resulted in using simplified head models, e.g., half planes and spherical shells [14–16]. Although the simplified models provide the general shape of the induced EF which can be used in some applications (e.g., to relate the spatial extent of TMS effects to that of the stimulated cortical muscle representations), a more accurate head model is needed to obtain more detailed knowledge of the biophysical mechanisms of TMS and the induced EF. Furthermore, the recent studies demonstrated that there are significant deviations between results from simplified models and more realistic head models [13,17,18].
In the recent years, high-resolution volume conduction models based on magnetic resonance images (MRIs) have been developed to enable accurate simulation of the TMS-induced EF [19]. Accordingly, the recent studies focused on complex models of the head using numerical simulations based on the finite element method (FEM), the boundary element method and the finite difference method to calculate a more realistic estimation of the EF [13,18,20–22]. For instance, Miranda et al. [20] studied the effect of an infarct region on the field in the neighboring healthy tissue, and Thielscher et al. [13] examined the impact of the complex gyral folding on the focality and the target position of TMS in spherical and accurate head model using the FEM.

The realistic models provide the opportunity to enhance spatial targeting, to obtain a quantitative measure of the stimulation “dose” and to improve the reproducibility of TMS effects [12]. The use of these models is currently limited to the engineering and theoretical research that is conducted off-line. Thus, they are far from the ultimate goal of incorporating these calculations into neuronavigation systems working in real-time and acting as standard tools for the planning and analysis of TMS. One of the main reasons, which reduces the usability of the accurate head models, is the tools that are available for realistic head EF calculation. Indeed, the tools are in an early stage of their development and are still premature. There is no information or broad guidelines for these tools, and they are created for particular TMS devices.

The SimNIBS software [12] is a free software package for TMS simulation, created at the Max-Planck Institute for Biological Cybernetics (Tübingen, Germany) and the Danish Research Center for Magnetic Resonance (Copenhagen, Denmark). It allows the realistic calculation of the EF induced by TMS. SimNIBS consists of two main parts: a command line script for automatic generation of tetrahedral volume meshes of the head from MR images, and a Graphical User Interface (GUI) to set up the EF calculations. However, it has some practical issues, which should be taken into account before using it. For instance, only two commercial coils are available in this software.

This thesis aims to create a practically applicable pipeline for easy application of SimNIBS with experimentally gathered data and with added coils to enable broad use of SimNIBS with any gathered nTMS data. The thesis includes two main parts: experimental and theoretical part. In Chapter 2, the theoretical background of TMS and TMS simulation are explained. Moreover, a broad guideline regarding the SimNIBS software is presented. Chapter 3 describes the performed TMS measurement, the procedure of coil modeling in the software, and finally the designed pipeline in this study. Chapter 4 includes the result of the pipeline, comparison between the results of simulations and TMS measurements, and comparison between different coils. Chapter 5 consists of the explanation of results, future work and brief conclusion.

More specifically, this thesis aims to 1) extend the features offered by SimNIBS software to make the realistic EF calculations more broadly available with navigated TMS, 2) to demonstrate the difference
between the maximum EF in online nTMS (simple head model) and the realistic models applying the new pipeline and 3) to evaluate the relevance of the different coil geometries on the induced EF.

Ultimately, the benefit of this work will be emphasized in future studies by enabling realistic EF calculations, e.g., for more realistic mapping of stimulation foci for large sets of experimental and clinical nTMS data thereby adding accuracy for identifying stimulated cortical areas.
2. Background

2.1. Brain

The brain is the most complex organ in the human body. Together with the spinal cord, it forms the central nervous system (CNS).

2.1.1. Neuron

The CNS consists mainly of glial cells and neurons (nerve cells). The glial cells are supporter cells that provide energy and structural stabilization to the brain tissue. In contrast to the neurons, the glial cells are not involved directly in information processing. Indeed, neurons are different from other cells due to two main components: the excitable neural membrane and the synaptic connection between the neurons.

Neurons are nerve cells, which are able to process and transmit information by either electrical or chemical signals. Neurons can be found in different types, such as the motor neurons, which control the muscles, and the sensory neurons that transform sensory input into electrical signals. Neurons in the CNS typically are connected to thousands of other neurons, whereas the typical neuron in the peripheral nervous system is connected to one or a few other neurons [23].

Neurons are divided into three main parts: dendrites, soma and axons (Figure 2.1). Dendrites work as an input device and receive the input signal, which is called the synaptic potential, from other neurons via synapses, and transmit it to the soma. The soma acts as the central processing part of the neuron and processes the received signal. If the total input at the soma exceeds a certain threshold, an output signal to the axon is produced. The output signal, which is called the action potential, is carried by the axon to the axon terminals, which are connected to other neurons via synapses.

The length of the axon can be from a few millimetres to one meter. The Schwann cells wrap around the axons and form a sheath of myelin, which provides electrical insulation by minimizing the “cross-talk” between neighboring neurons. This leads to a rapid transmission of the signal.

Neurons and muscle cells transmit the information using synapses. Synapses are cellular junctions for fast transmission of signals between the neurons. There are two types of the synapses in the brain: electrical and chemical. Most of the synapses in the brain are chemical synapses.
The neural membrane, which is formed by the lipid bilayer and ion channels, handles the input processing in addition to signal propagation. The neural membrane separates the intracellular fluid and extracellular fluid, which have different concentrations of ions. The concentration of ions that is controlled by automatic ion pumps maintains a negative resting membrane potential around $-70\text{mV}$.

Changing the permeability of the membrane to specific ions can lead to a change in the membrane potential. Depolarization is defined as an increase in the membrane potential, while hyperpolarization decreases the membrane potential. In 1952, Hodgkin and Huxley [24] showed by changing the membrane potential of a squid giant axon that a sufficient depolarization leads to a propagating action potential in the neuron. Their model shows the voltage- and time-dependent ion conductivities: the rapidly changing sodium conductivity and the slowly varying potassium conductivity. However, the neurons in the human brain are now known to be much more complex with more than ten ion channels, which results in a variety of action potentials.

![Schematic figure of a neuron. Figure modified from [25].](image)

2.1.2. Anatomy and function

The human brain consists of four principal sections: the brain stem, the diencephalon, the cerebellum and the cerebrum. The brain stem consists of the medulla, the oblongata, the pons, and the midbrain. It
connects the brain to the spinal cord and provides the main motor and sensory innervation to the face and neck. It also controls the regulation of cardiac and respiratory function, regulates the CNS, maintains consciousness, and regulates the sleep cycle. The diencephalon includes thalamus, which processes sensory information and relays it, and hypothalamus, which links the nervous system to the endocrine system via the pituitary gland (hypophysis). The cerebellum has role in learning and executing motor programs. It is attached to the bottom of the brain and fulfills an important role in motor control in addition to being involved in several cognitive functions.

The cerebrum is the largest part of the brain and the outer layer of it, the cerebral cortex, has approximately 2000 cm² area, 2–4 mm thickness and 20 billion neurons, which are connected to each other by 200 trillion synapses [26,27]. The heavily folded cerebrum consists of two hemispheres, right and left, which are separated by the medial longitudinal fissure. The left hemisphere takes control of the right side of the body and vice versa. The cerebral cortex is divided into two cortices. The smaller folds in each cortex are called sulci, with the bulges in between called gyri. The larger folds are called fissures, which separate the brain into different lobes, as can be seen in Figure 2.3. Each cortex consists of four lobes: the frontal, parietal, temporal and occipital lobe. The frontal lobe is related to short-term memory, controlling the movements and planning the future actions. The parietal lobe is related to somatic sensation, forming a body image and relating this image to extra personal space. Memory and emotion are associated with the temporal lobe. The main function of the occipital lobe is related to vision and hearing.

The brain tissue is made of three parts: the white matter, the gray matter, and the cerebrospinal fluid (CSF). The white matter consists mostly of bundles of myelinated axons; the myelin sheets that are wrapped around the axons produce the white color. The white matter handles the signal transmission between neurons and ensures the integrity of different parts of the brain. On the other hand, the gray matter, which includes the cell bodies of the neurons, performs the thinking and calculating functions. Skull with three meninges, namely the dura matter, the arachnoid, and the pia mater, protects the brain against injuries. The CSF located between the pia mater and the arachnoid, supplies nutrients to the brain, and removes the waste in addition to acting as a protective cushion for the cortex (Figure 2.2).
Figure 2.2: Schematic representation of the structural anatomy of the brain. Figure modified from [28].
Figure 2.3: The brain lobes.
2.2. Transcranial magnetic stimulation (TMS)

2.2.1. Background

Merton and Morton demonstrated three decades ago the possibility of stimulating the brain motor areas electrically through transcranial electrical stimulation (TES). They used a short, high-voltage electric shock to stimulate the motor cortex; however, it was painful due to the activation of pain fibers in the scalp [29]. Barker and colleagues in 1985 first used the current method of transcranial magnetic stimulation (TMS) [30]. It was painless in most subjects.

TMS is a non-invasive method that can be applied to modulate neural tissue activity in the human brain. Depending on the stimulation parameters, it can excite or inhibit the desired brain region or function. The TMS pulse is generated by applying a short pulse of electric current to the TMS coil placed over the target area [31]. The TMS circuit includes a high-voltage power supply that charges a bank of capacitor, which is then rapidly discharged through a fast electronic switch into the TMS coil. This creates a rapidly changing magnetic pulse with a magnetic field perpendicular to the applied current. The magnetic field can penetrate the skull and induce a transient electric field (EF) on the cortex, which activates the neurons [31]. Due to the shape of the EF, the depth of penetration is limited, and TMS is mainly associated with cortical structures rather than subcortical parts of the brain [32]. Previous studies on TMS have shown its variety of applications in routine tests of central motor pathways, as well as locating, mapping and outlining cortical speech and motor areas for presurgical and radiotherapy planning [10–14].

2.2.2. Electromagnetic field

Maxwell’s equations describe electromagnetic phenomena. For a charge density $\rho$ and a current density $\mathbf{J}$, they are defined as

\begin{align}
\nabla \cdot \mathbf{D} &= \rho \\
\nabla \cdot \mathbf{B} &= 0 \\
\nabla \times \mathbf{H} &= j \omega \mathbf{D} + \mathbf{J} \\
\nabla \times \mathbf{E} &= -j \omega \mathbf{B},
\end{align}

where $\mathbf{E}$ is the electric field, $\mathbf{H}$ is the magnetic field, $\mathbf{B}$ is the magnetic induction, $\mathbf{D}$ is the electric induction, and all fields are position ($\mathbf{r}$) and frequency ($\omega$) dependent. From (2.2), the magnetic induction $\mathbf{B}$ can be extracted in terms of a vector potential $\mathbf{A}$:

$$
\mathbf{B} = \nabla \times \mathbf{A}.
$$

Substituting this in equation (2.4) results in
\[
\n\nabla \times (\vec{E} + j\omega \vec{A}) = 0, \tag{2.6}
\]

from which it follows that

\[
\vec{E} = -j\omega \vec{A} - \nabla \phi, \tag{2.7}
\]

where \( \phi \) is the scalar potential. Moreover, it holds that

\[
\nabla \times (\nabla \times \vec{A}) = \nabla (\nabla \cdot \vec{A}) - \nabla^2 \vec{A}. \tag{2.8}
\]

Let us consider first the case where the coil is placed in a vacuum, and where the current density in the coil is given by \( \vec{J}_{\text{coil}} \). In the magnetostatic approximation, \( j\omega \vec{D} \) can be neglected in equation (2.3). Combining equation (2.8) and (2.3), and using the Coulomb gauge, i.e. \( \nabla \cdot \vec{A} = 0 \), results in

\[
\nabla^2 \vec{A} = -\mu_0 \vec{J}_{\text{coil}}, \tag{2.9}
\]

since \( \vec{B} = \mu_0 \vec{H} \) in vacuum, where \( \mu_0 \) is the permeability of vacuum. The solution of equation (2.9), known as the Biot-Savart law, is given by:

\[
\vec{A}(\vec{r}, \omega) = \frac{\mu_0}{4\pi} \int_{\text{coil}} \vec{J}_{\text{coil}}(\vec{r}', \omega) \frac{d^3 \vec{r}'}{||\vec{r} - \vec{r}'||}, \tag{2.10}
\]

where the position vector \( \vec{r}' \) is integrated over the whole current distribution. If the current through the coil is uniform over its cross section, it holds that

\[
\vec{J}_{\text{coil}}(\vec{r}, \omega) = \frac{I(\omega)}{A} \hat{\tau}(\vec{r}), \tag{2.11}
\]

where \( I(\omega) \) is the current in the coil in the frequency domain, i.e. the Fourier transform of the current in time domain \( I(t) \), \( A \) the cross-sectional area of the wire, and \( \hat{\tau}(\vec{r}) \) the unit vector tangent at the point \( \vec{r} \) along the coil, pointed in the direction of the positive current. Hence,

\[
\vec{A}(\vec{r}, \omega) = \frac{\mu_0 I(\omega)}{4\pi A} \int_{\text{coil}} \frac{\hat{\tau}(\vec{r}') \times (\vec{r} - \vec{r}')}{||\vec{r} - \vec{r}'||^3} d^3 \vec{r}'. \tag{2.12}
\]

\[
\vec{B}(\vec{r}, \omega) = \nabla \times \vec{A} = \frac{\mu_0 I(\omega)}{4\pi A} \int_{\text{coil}} \frac{\hat{\tau}(\vec{r}) \times (\vec{r} - \vec{r}')}{||\vec{r} - \vec{r}'||^3} d^3 \vec{r}. \tag{2.13}
\]

And in time domain,

\[
\vec{B}(\vec{r}, t) = \frac{\mu_0}{4\pi} I(t) \int_{\text{coil}} \frac{d(\vec{r}') \times (\vec{r} - \vec{r}')}{||\vec{r} - \vec{r}'||^3}. \tag{2.14}
\]

Since the coil is positioned in a vacuum (or air), \( \rho = 0 \) and \( \vec{D} = \epsilon_0 \vec{E} \), where \( \epsilon_0 \) is the permittivity of vacuum, and hence \( \nabla \cdot \vec{E} = 0 \). Therefore \( \phi = 0 \), such that the electric field is only determined by the vector potential \( \vec{A} \), and given by \( \vec{E} = -j\omega \vec{A} \). Note that an alternating current is required to induce an electric field, since otherwise \( \omega = 0 \).
Things become different if the coil is located near a human head. Biological tissues are known to be non-magnetic, and therefore

\[ \vec{B}(\vec{r}, \omega) = \mu_0 \vec{H}(\vec{r}, \omega). \]  

However, the dielectrical properties are inhomogeneous, anisotropic and dispersive.

The schematic view of the coil current, magnetic field and induced current in the brain produced by a simple circular coil are demonstrated in Figure 2.4. The coil is placed tangentially to the scalp surface, and the magnetic field is generated perpendicular to the plane of the coil. The induced EF produces electrical current loops perpendicular to the magnetic flux plane. The intensity of the induced EF decreases dramatically as a function of distance from the coil. Consequently, the TMS has an effect mostly superficially under the windings of the coil [33]. The intensity of TMS should be increased significantly to perform deep brain stimulation, which may lead to stimulating facial nerves and cause pain [34].

![Diagram of current, magnetic field, and induced current](image)

Figure 2.4: The schematic representation of the current in a circular magnetic coil, the induced current in the brain and the lines of magnetic flux. Figure modified from [35].

2.2.3. Coils

There are two commonly used TMS coil geometries for either clinical or research purposes: circular and figure-of-eight coils. The first generation of TMS coils, the circular coil, stimulates a relatively large area (Figure 2.5.a). The circular coil is placed with its edge tangential to the scalp. It can be used in studies, which lack information about the exact location of the target area, and thus a larger area needs to be stimulated.

On the other hand, the figure-of-eight coil, also called the butterfly coil, is the most widely used TMS coil. As can be seen in Figure 2.5.b, it consists of two circular coils with opposite current flow direction. This configuration leads to a strong EF just below its center. The induced EF strength reduces similarly to the circular coils. The strong and highly concentrated induced EF provides the opportunity to
stimulate small targets precisely. Consequently, the figure-of-eight coils are used in various studies, particularly in studies involving focused targeting of the stimulation, e.g., in cortical mapping.

Figure 2.5: The induced electric field by a circular coil (a), and figure-of-eight coil (b). Figure modified from [36].

There is diversity in figure-of-eight coil parameters between manufacturers. Figure 2.6 shows three coils produced by different companies, which have differences in the distance between the centers, the angle between each coil winding and the number of wire loops.

Figure 2.6: The Nexstim coil (a), the Magstim coil (b) and the Medtronic MC-B70 coil (c). Figure modified from [37].
2.2.4. Waveforms

Two commonly used waveforms in TMS measurements are the monophasic and biphasic waveforms. The first generation of TMS stimulators was capable of producing a monophasic pulse. In the monophasic pulse, the current flows in one direction and its waveform includes one rapid change from zero to peak and then slowly to zero again (Figure 2.7.b)[36]. However, most clinically applied nTMS utilizes the biphasic waveform, in which the current flows in both directions and the waveform consists of one damped sine pulse [36](Figure 2.7.a). The time required for recharging in the biphasic pulses is shorter due to the return of a significant portion of energy to the capacitors. On the contrary, in the monophasic pulses, most of the energy is dissipated as heat. Previous studies have reported the better efficiency and effectiveness in the biphasic waveform against monophasic waveform [38–41]. Importantly, it should be noticed that the waveform can affect the optimal coil orientation to elicit responses [42,43].

![Figure 2.7: Biphasic current pulse (a). Monophasic current pulse (b).](image)

2.2.5. Pulse sequences

The most common pulse sequences in TMS studies are single-pulse, paired-pulse and repetitive TMS (rTMS) pulses [36]. In the single pulse stimulation, TMS pulses are administered to the subject with a long pause, i.e., inter-stimulus interval (ISI) between the pulses generally more than 3 s [36]. The ISI is defined to prevent producing cumulative neural effects [44]. The paired-pulse stimulation includes two pulses with a short ISI followed by a longer pause prior to next stimuli [36]. The repetitive TMS (rTMS)
is performed by a train of stimuli with an ISI 1 s or less [36]. Each pulse sequence has its effects on the neural tissue which needs to be considered before utilization [36,45,46].

2.2.6. Navigated TMS

TMS evokes a physiological response, which can be measured by the EMG. This feature enables targeting and mapping the cortical motor areas [4]. For this purpose, TMS has been combined with neuronavigation to accurately localize and stimulate the functionally active areas of the motor cortex. In the navigated TMS (nTMS), the individual MRI is registered by anatomical landmarks (usually three) obtained from the MRI and skin. The registration is completed by adding a set of surface points on the skin around the head [47]. To save the coil direction, the TMS coil has been equipped with several trackers, which enable the online tracking of coil coordinates. TMS becomes a more accurate and reproducible tool by using online navigation provided by nTMS technology [48]. Accordingly, the stimulation can be targeted to a desired cortical structure, and the coil location, direction and the estimation of the induced EF can be visualized online. The procedure can be seen in Figure 2.8. The direction of the coil, with respect to the head, is checked online to find the most efficient position and direction. Moreover, all information about the coil direction and location are stored and can be checked after the measurement.

Figure 2.8: The basic principle of nTMS. By using subject’s head tracker and digitizing pen, the head is co-registered with the subject’s MRI (a). The movement of TMs coil is tracked by its reflective parts and is shown and records by device (b). The MR images are used to localize the cortical target for the stimulation (c). The nTMS device monitor; the coil location and EMG responses can be seen online during the measurement (d).

2.2.7. Physiological basis

TMS has been applied widely since its introduction in 1985 [35,49], but the exact neurophysiological mechanisms and the excited brain sites are still not fully understood. At sufficient intensities, the
induced EF causes the depolarization of the membrane followed by an initiation of the action potential, and neuron activation. Changing the membrane potential leads to activation of the cells with high concentration of the voltage-gated sodium channels. It finally leads to the action potential by exceeding a threshold value of the membrane potential [50].

There are theoretical and experimental studies on the peripheral nerve stimulation, which show that the gradient of the EF along the long straight axon plays a vital role in the changes of the membrane potential and the activation of the cell. Based on the studies, the stimulation occurs when the gradient decreases rapidly along the direction of the nerve [51–54]. However, the recent findings show that the mentioned mechanism does not apply to the axonal bends or axons terminal [53,55–58] (Figure 2.9).

![Diagram](image.png)

Figure 2.9: TMS mostly activates neural axons at two points: axon termination point (a) and axon bending point (b). Black arrows show the induced electric field, and it has the maximum gradient along the axon at these points. Figure modified from [31].

Since the axonal bends and terminations provide additional sites of depolarization even without strong gradient field, different mechanisms are likely to be involved in cortical stimulation [56,59,60]. Furthermore, the cortical neurons have different orientations in relation to the induced EF due to differences in the cortical regions, the gyral folding and the types of neurons and their axons. The heterogeneity and anisotropy of the electrical activity in different parts of the brain is another point, which affects the site of stimulation [20,61,62]. Moreover, the stimulation intensity and pulse shape have an influence on the induced EF [63–65]. To sum up, the mentioned factors demonstrate the level of complexity in the simulation of the brain stimulation.

TMS stimulates the motor cortex generating activity in the cellular layers of the motor cortex [2,66,67]. The cortical neural response to TMS is composed of a direct (D) and few indirect (I) waves [67]. The D waves are the initial volley of the induced activity, which is produced by the direct activation in layer L5 neurons. On the other hand, indirect activation of the large pyramidal neurons by the layer II and III
neurons generates later volleys which are called the I waves [68]. The temporal effect of these subsequent waves occurring about 1.4 ms apart generates the final activation of the entire motor tract of a target muscle [41].

Their characteristic latencies are thought to be related to the coil orientation, the level of muscle contraction, the type of waveforms and the stimulation intensity [64,69–71].

2.2.8. Cortical mapping

In the modern nTMS devices, the EMG responses are linked with the stimulation site, and the induced EF can be observed online [8,72,73]. Using the information of EMG and the stimulation sites provides a detailed map of the responses, called the cortical map [74–77].

Traditionally, motor cortex mapping has been related to the mapping of the brain areas, which evoke observable or recordable activity in the desired muscle. Although the complete understanding of the mechanism is still missing, it seems that the primary motor cortex in the precentral gyrus holds the large scale somatotopic organization of the individual muscles. It is also speculated that the primary motor cortex encodes the movements and kinetic parameters [78,79].

There are several studies, which have focused on the effects of TMS motor mapping in the pre-surgical applications. nTMS was found to be useful for surgical planning in 75% of the patients and changed the treatment plan in more than 50% of the patients [80,81]. nTMS also had an impact on 79% of the planned surgical treatments with brain tumors in the motor eloquent regions [82].

2.2.9. Motor evoked potential

The motor evoked potential (MEP) is induced by the TMS when targeted on the primary motor cortex of the selected muscle (Figure 2.10). The MEP is indicative of the corticospinal motor tract excitability [83] and integrity [84]. Since MEP typically relates to either resting or active state of the muscle, it is recorded non-invasively using the surface EMG [85]. One of the main applications of the MEPs is in presurgical mapping, in which the different cortical areas are differentiated by the MEP responses and them the cortical areas are located and outlined [80,86,87].
2.3. TMS simulation

EF calculations based on numerical methods are increasingly used in TMS. The EF calculation has been used to first design new coils and then characterize the spatial pattern of the induced EF [12]. However, this is far from the ultimate goal, which is using EF calculation as a standard tool for the planning and analysis of TMS.

In order to determine the TMS-induced EF, two methods have been used so far, using a simplified head models or realistic head models (Figure 2.11). In the early studies, the field calculation have been done with simple geometries such as infinite half planes and spheres [15,37]. However, calculations based on the simplified geometries are only able to demonstrate the gross features of the field distribution. During last few years, using MRIs resulted in creating accurate head models [13]. Recent studies compared the EF calculation by the realistic head models with a simplified one and found a substantial deviation between the simplified head model results and those determined by realistic head models [18,72,88]. On the other hand, the EF calculation based on the realistic head model has its issues such as the time-consuming creation of the head models and using a sophisticated software solution for the numerical techniques [12].

Figure 2.10: The surface EMG electrodes (a). The MEP response in the resting state measured by EMG (b). If the target muscle is at rest during TMS, a resting MEP may be evoked.
Practically, the simulation of TMS can be used in different aspects. It has potential to be used as a quantitative measure of the stimulation “dose” and to improve the reproducibility of TMS. This can be either within the same subject where the aim is to equalize the dose applied to different brain areas, or between different subjects where the goal is to apply the same dose to a particular brain area [12].

Some issues and challenges remain in the EF calculations. Firstly, there are some uncertainties in the models. Secondly, it is challenging to establish a clear link between the induced EF and physiological stimulation effects. Finally, there are difficulties in the usability of these tools. The challenges mainly come from the limited knowledge about the brain tissue and the neurons. Although the anatomical accuracy of the head models has been significantly increased [89,90], the uncertainties in tissue conductivities and permittivity at the low frequencies (< 10 kHz) have raised difficulties [12,91].

Several packages, such as FreeSurfer [92] (surfer.nmr.mgh.harvard.edu) and BrainVoyager (Brain Innovation, The Netherlands) [93], have been developed to reconstruct the cortical hemispheres from the MRI data. Parcellation of the different brain areas and segmentation of the different tissue-types are two initial key steps in EF calculation. Thielsher et al. [13] have performed a valuable survey, in order to study the effect of biophysical and geometrical properties of the stimulated tissue, i.e., the conductivity differences between CSF, WM and GM in combination with the gyral geometry. They have defined four different tissue properties on the realistic head model in addition to simple head geometry (Table 2.1). Importantly, in one case they selected the conductivities of WM, GM, CSF based on the most frequently reported values (typical case), and in another case they chose the tissue conductivities homogeneously. In the homogeneous case, the same conductivity was considered for the three tissues inside the skull, which is the most similar case to a spherical model.
Table 2.1: Conductivities (in [S/m]) used in [13].

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Typical</th>
<th>Worst case 1</th>
<th>Worst case 2</th>
<th>Homogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM</td>
<td>0.126</td>
<td>0.105</td>
<td>0.291</td>
<td>0.276</td>
</tr>
<tr>
<td>GM</td>
<td>0.276</td>
<td>0.61</td>
<td>0.61</td>
<td>0.276</td>
</tr>
<tr>
<td>CSF</td>
<td>1.654</td>
<td>1.52</td>
<td>1.52</td>
<td>0.276</td>
</tr>
<tr>
<td>Skull</td>
<td>0.010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>0.465</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consequently, they showed that the realistic head models generally exhibited higher EF at the gyral crowns, compared with the spherical head model. They reported up to 55% increase in higher peak values for the induced EF in the typical case compared to a spherical model, which shows the effect of geometry and segmentation on TMS-induced EF. Due to the higher field strengths at the gyral crowns and lips in the realistic head model, its focality was increased compared to the results of the spherical model. They speculated that these results are mainly because of conductivity changes at the CSF-GM and GM-WM boundaries, due to the complex gyral folding. They emphasized the robustness of their finding by using worst case configuration which demonstrated increased focality of the fields induced in GM compared with the spherical head model (Figure 2.12).

Figure 2.12: Maximum EF for all cases. By taking the gyrification pattern into account the results show higher maximal EF values, compared to the two less complex models (sphere, FEM homogeneous). Figure traced and modified from [13].

Next challenge in EF calculation arises from the diversity in conductivity and permittivity values reported in the literature, which can be addressed to either error in the measurement or individual variability. The impact of this variability explained above and also studied in [94], in a complicated computational way. Moreover, poor understanding of the type and position of the neurons causes the next problem. Neurons are strongly affected by the induced EF, and the diversity of their types, shapes, orientations, and biophysical properties results in uncertainties in the simulation results [95]. According to the experiments and observations, the EF peaks at the gyral crown. Consequently, the simulations
mainly have focused on this part, which is most affected by the TMS [13,96]. Other TMS measurements and imaging studies have reported an important hypothesis. They hypothesized that the highest field strength is obtained when the EF direction is perpendicular to the gyrus [97], and the strongest activation can be observed within the sulci.

The last challenge arises from the numerical method used for EF calculations. The newest and most promising approach is combining the finite element method (FEM) with accurate head models constructed of structural MRIs. However, the complexity of the integration of FEM with an automated segmentation of the MRIs for head modeling [90] has decelerated the development of EF calculation tools.
2.4. SimNIBS

SimNIBS is an open-source software, which integrates the established software for neuroimaging, computer graphics, and FEM calculation into one easy-to-use solution. FreeSurfer [92] and FSL [98] are software used widely in the neuroscience research and have to be installed in parallel with SimNIBS. They are employed for the segmentation of MR images. Moreover, SimNIBS consists of tools for meshing (Gmsh and meshfix [99,100]) and finite element calculations (GetDP [101]).

The SimNIBS TMS simulation is based on three main steps: head mesh generation, field calculation, and post-processing (Figure 2.13).

![SimNIBS workflow diagram](image)

Figure 2.13: The SimNIBS workflow.

2.4.1. Head mesh generation

The first step in SimNIBS workflow is generating a subject-specific tetrahedra head mesh by using structural MR images. The head model is created from T1-weighted and (optionally) T2-weighted MR images. Using both MR images creates better skull segmentations. The most time-consuming step in SimNIBS is accomplished via a bash script “mri2mesh” which is based on the FreeSurfer and FSL.
2.4.1.1. Segmentation

The different tissues are segmented from the MR images, and the borders between the skin, skull, cerebrospinal fluid (CSF), including lateral ventricles, gray matter (GM) and white matter (WM), are extracted. The cerebellum and brain stem are considered as WM. Shortly, in the segmentation part, the WM, GM, cerebellum, and brain stem are segmented by using the T1-weighted image in FreeSurfer. CSF surface and the lateral ventricles are segmented by T1-weighted and T2-weighted (if added as an input) MR images in FSL BET and BETSURF.

2.4.1.2. Optimization and decoupling

The critical point in constructing an appropriate model for volume meshing is to create surfaces carefully. This step is performed by MeshFix [102] and extended with custom-written functions. In this part, MeshFix removes the overlaps and self-intersections and finally optimizes the triangle mesh quality (Figure 2.14).

Figure 2.14: The intersected triangles in the mesh before and after MeshFix optimization. Figure modified from [90].

The decoupling is performed to reduce the complexity of the problem. It is implemented by assuming that

- ventricles are embedded in the WM
- WM is inside the GM
- CSF surrounds the GM, the brain stem and the cerebellum
- the skull contains the CSF and is completely covered by skin.

To improve the mesh quality, MeshFix is utilized again for removing the self-intersections, intersections between neighboring surfaces and overlaps between the triangles. Thereafter, it optimizes the spatial uniformity of the distribution of the vertices while preserving the surface shape.
2.4.1.3. **Volume meshing**

In the volume meshing, the triangle meshes (2D) are transformed into volume meshes (3D). Thus, the subvolumes for the lateral ventricles, WM, GM, cerebellum and brain stem, CSF, skull, and skin are created using the optimized surface meshes from the previous step. Then, by using Gmsh, the subvolumes are filled. Finally, to improve the numerical properties of the mesh, the quality of the tetrahedra is optimized [103] (Figure 2.15.b). The SimNIBS GUI can display the scalp and gray matter surfaces of the 3D head model (Figure 2.16).

![Figure 2.15: An example of meshing results. Cutaway views of the surfaces (a). The T1-weighted image overlaid onto the segmented tissues (b). The red lines belong to the final optimized surfaces. The original FreeSurfer results for the WM and GM are green lines.](image)

2.4.2. **Field calculation**

To calculate the EF, the tissue conductivity has to be assigned to the five brain tissues: WM, GM, CSF, skull, and skin. It can be done either by diffusion tensor imaging (DTI) or using standard conductivity...
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values reported in the literature. The default conductivity values in SimNIBS shown in table 2.1 [13,17]. The lateral ventricles are considered as CSF and the brain stem and cerebellum as WM.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Conductivity (S/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM</td>
<td>0.126</td>
</tr>
<tr>
<td>GM</td>
<td>0.276</td>
</tr>
<tr>
<td>CSF</td>
<td>1.654</td>
</tr>
<tr>
<td>Skull</td>
<td>0.010</td>
</tr>
<tr>
<td>Skin</td>
<td>0.465</td>
</tr>
</tbody>
</table>

The TMS-induced EF is calculated in three steps: positioning the coil above the desired target location, calculation of the magnetic vector generated by the coil, and the FEM-based calculation of the EF.

In the SimNIBS GUI, the position of the coil is defined by clicking on the scalp or brain surfaces; the first click determines the position of the coil centers and the second click determines the orientation.

The TMS coil can be either described by the dipole model or by means of a 3D volume file that contains the pre-calculated $A$ (the magnetic vector potential) field. By using the dipole model, the magnetic vector potential can be easily determined via summing up the contributions of all the dipoles modeling the coil [13].

The magnetic vector is determined at each node after positioning the coil, which is used for the EF calculation. The FEM-based calculation of the TMS-induced EF is performed by using a quasi-static regime assumption [13,104]:

$$\bar{E} = -\nabla \varphi$$  \hspace{1cm} (2.16)

In the case of TMS, the electric field $\bar{E}$ is determined as

$$\bar{E} = -\frac{\partial A}{\partial t} - \nabla \varphi.$$  \hspace{1cm} (2.17)

Based on the previous studies, it is assumed that the displacement currents can be neglected. The Galerkin method is used in the FEM solver to determine $\varphi$ (electric potential) at the nodes. Finally, the induced EF and current densities are calculated by using Equation (2.17). A simulation can be easily copied and modified in the GUI, e.g. to explore the impact of a specific feature, such as the chosen conductivity values, on the field distribution.

2.4.3. Post processing:

In order to post-process the results, SimNIBS uses Gmsh to visualize the head meshes and the results of electric field estimation (Figure 2.17). Moreover, the SimNIBS team has written several Matlab
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functions for the flexible post processing of the results. For instance, the functions are able to compare and merge data [90].

Figure 2.17: Gmsh post-processing toolbox.
3. Material and methods

3.1. TMS measurement

TMS measurements were done on two healthy right-handed subjects. The measurements were performed at the Department of Neurophysiology in Kuopio University Hospital (KUH), Kuopio, Finland. The local ethical committee (permission 72/2016) approved the research project, and all volunteers signed written informed consent. The imaging and measurements were originally performed for another study [105].

3.1.1. Imaging and instrumentation

Three dimensional T1-weighted magnetic resonance images (MRIs) were obtained by using 3T MRI scanner (Philips Achieva 3.0T TX, Philips, Eindhoven, The Netherlands) with a resolution of 1mm and TR = 8.22 ms, TE = 3.78 ms, flip angle = 8°, voxel size = 1 × 1 × 1 mm. In this study, the NBS system 4.3 prototype (Nexstim Plc., Helsinki, Finland) with an air-cooled figure-of-eight coil was used (Figure 3.1). During the nTMS measurements, EMG data from three hand muscles, the first dorsal interosseus (FDI), abductor digiti minimi (ADM) and abductor pollicis brevis (APB) were measured with a system-integrated EMG device (Nexstim Plc., Helsinki, Finland).
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3.1.2. Measurement Protocol

The measurement session was started by roughly mapping the cortical motor representation of the FDI muscle in the left hemisphere with nTMS. The central sulcus and “hand knob” were used as the anatomical landmarks. The cortical representation area for the target muscle was located by applying single-pulse nTMS with an ISI of at least 5s [44] on the precentral gyrus. The optimal cortical representation target, commonly called the hotspot, was defined as the location where the stimulation induced the highest MEPs.

By using single-pulse nTMS and checking the MEP response in the FDI muscle, the appropriate coil location and direction were found. Accordingly, the resting motor threshold (rMT), i.e. the minimum stimulus intensity that generated a MEP response of at least 50 µV at rest, was calculated for the stimulation target using single-pulses with the system-integrated MT-tool [38].

Subsequently, seven stimulation targets were selected along the precentral gyrus, one at the hotspot of the FDI muscle, and three targets both medially and laterally from the hotspot, 1 cm apart. Targets were numbered in the lateral-medial order from 2 to 7 (Figure 3.2). TMS coil at was rotated at each target in the tangential plane in order to estimate the optimal coil direction at the targets. The rMT of the FDI muscle was determined in the estimated optimal coil direction at each target.
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Thereafter, the MEP amplitudes as a function of coil rotation at the hotspot and targets 3–6 were measured in order to estimate the optimal direction accurately. The coil was rotated within ±135 degrees from the optimal direction with 10 pulses given in each 45° sector.

Finally, motor mapping was performed for the FDI muscle. Mapping was started from the anatomically identified “hand knob” since this is the presumed anatomical location for the hand motor function [106]. The direction of the induced current was kept perpendicular to the nearest sulcus during the mapping. After locating the site eliciting the highest amplitude MEPs for the target muscle, the coil was turned within ±90° in a tangential plane in this location. This was conducted to find the coil angle producing the highest MEPs, since the optimal angle may not always be perpendicular to the gyrus [107]. The mapping of the motor area was done by the intensity of 105% of rMT at the hotspot. The mapping started from the hotspot and extended until no responses were observed.

Throughout the measurement, EMG was measured at 3 kHz from the right relaxed hand using disposable Ag-Cl electrodes (Figure 3.3). MEPs with a peak-to-peak amplitude of at least 50μV were accepted as responses. The muscles were selected due to their adjacent and overlapping representation areas in the cortex for simultaneous activation [108] and their typical application in TMS studies and clinical therapies [109].
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3.2. SimNIBS simulation

SimNIBS simulation consists of the building a coil model, generating the head mesh and simulating the experimentally determined coil locations.

The overall workflow designed in this thesis is shown in Figure 3.4. First, the head mesh is constructed by the subject’s MR images. After that, the pipeline creates new SimNIBS run file based on the measurement session, head mesh, and MR images generated by the SimNIBS. The induced EF can be visualized in either Gmsh or Matlab.

Figure 3.3: The EMG electrodes used in the study. Three muscles, including the first dorsal interosseous (FDI), abductor pollicis brevis (APB) and abductor digiti minimi (ADM), were utilized to study the MEPs.
3.2.1. Coil modelling

One of the main questions in the TMS studies is to determine the site and size of the stimulated cortex. The initial step for answering this question is generating a realistic TMS coil model. In this thesis, a general code has been written by the author to create models for different figure-of-eight coils using the method introduced by Ravazzani [15] and Thielcher [37]. In this method, the coil area is divided into subregions (Figure 3.5) and dipoles are placed perpendicular to the coil in the center of each subsurface (Figure 3.6).
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The ideal figure-of-eight coil can be modeled by two circular disks. Each circle is divided into the rings, and each ring is divided into elements (Figure 3.5). The dipoles are placed in the center of each element. Each ring has inner and outer radii, which are used to calculate the area of the subregion. Since the current rotates in opposite directions in each wing, also the dipoles have opposite directions in the wings (Figure 3.6).

Figure 3.6: Dipole model of the idealized coil. The dots represent the position of dipoles. The large arrows indicate the z-direction of the dipoles.

As opposed to the ideal coil, the real TMS coil (e.g. Magstim and Nexstim coil) has several wire loops in each wing (Figure 3.7). Thereby, the dipoles are weighted by the area of the subsurface and the amount of current around them. Moreover, the height of the wire and the plastic chassis should be taken into account in the real TMS coil. These information were gathered from X-ray images of the different coils.

Figure 3.7: Nexstim coil, photos and X-ray images.
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In this thesis, a custom Matlab function is written to model the Nexstim nTMS coils. The inputs of the function are the distance between the wing centers, wire height, the plastic chassis thickness, the number of rings, the number of elements in each ring, and the outer radius, all taken from X-ray images of the coils. The code calculates the location of the center in each element (X, Y and Z coordinates) and determines the magnetic dipole of each element based on the explained method [15,37]. To calculate the center of each element, the locations of four nodes, which surround the element, are determined. The location of the center is assumed to be the average of these four points in X and Y directions. Furthermore, another Matlab function is written to generate the TMS coil file (ccd-file) based on the Magstim coil ccd-file, available in the SimNIBS example file.

3.2.2. Head mesh generation

The function “mri_to_mesh” (Figure 3.8) has been written to perform the head mesh generation. It employs the SimNIBS tools to generate the tetrahedral head mesh from the T1-weighted and T2-weighted structural MR images. Although it can be run with the only T1-weighted image, it creates better skull segmentations by using the both MR images.

```matlab
% Choose T1 image (.nii.gz)
% Choose T2 image (.nii.gz)
% The code runs the command in unix line

function mri_to_mesh(T1,T2,Name)

if nargin==0
    unixstr=['mri2mesh --all ',Name,' ',T1,' ',T2];
    unix(unixstr)
end

if nargin==2
    unixstr=['mri2mesh --all ',Name,' ',T1];
    unix(unixstr)
end
if nargin<2
    T1= uigetfile(...
        ['*.nii.gz','nifti file(.nii.gz)',...,'Choose T1 Image',' ']);
    T2= uigetfile(...
        ['*.nii.gz','nifti file(.nii.gz)',...,'Choose T2 Image',' '];
    Name=input('Please select the name of Model: ',s);
    unixstr=['mri2mesh --all ',Name,' ',T1,' ',T2];
    unix(unixstr)
end

end
```

Figure 3.8: mri_to_mesh function.

The “mri_to_mesh” function should be run in Linux since it uses the “mri2mesh” tool of SimNIBS. The argument “--all” in this code tells mri2mesh to run all reconstruction steps, including volume meshing. In the next step, the code asks for the “subject ID”. mri_to_mesh creates a head mesh named
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“subject ID.msh”, a folder named “fs_subject ID” that contains the FreeSurfer results, and a folder named “m2m_subject ID” that contains the file needed for volume meshing. By calling “mri2mesh --all” the first time for the dataset, it runs FreeSurfer using the T1-weighted (and T2-weighted) MR image as an input. This step is quite time-consuming and takes ~10 hours.

To visualize the head mesh, the Gmsh software can be used. The user can select the desired tissue (1: WM, 2: GM, 3: CSF, 4: Bone, 5: Scalp for volumes). The equivalent surfaces have the same number as the volume, added by 1000 (Figure 3.9).

![Figure 3.9: Head mesh generated by the “mri2mesh” function.](image)

Since the Gmsh is quite slow, two custom Matlab codes were written based on the open-source Gmsh binary format (functions “mesh_to_mat” and “head_visualization”). Likewise, in the “head_visualization” function, the user is able to choose the desired tissue: 1: WM, 2: GM, 3: CSF, 4: Bone, 5: Scalp for volumes. The equivalent surfaces have the same number as the volume, added by 1000 (Figure 3.10).
3.2.3. SimNIBS pipeline

Here the new pipeline allowing for the semiautomatic field calculations based on the FEM is presented. The pipeline starts by transforming the TMS coil location, direction from MRI to the SimNIBS coordinate system, and ends by generating the new SimNIBS run file.

The pipeline includes one main Matlab function, which is assisted by the five supporter functions. All functions have been written by the author except two functions, namely “dicm_hdr” and “nii_tool” obtained from DICOM to NIfTI converter and NIfTI tool and viewer, respectively [110]. Figure 3.11 shows the overall workflow designed for the pipeline.
3.2.3 Pipeline inputs

The designed pipeline needs the following inputs to generate the new SimNIBS run file:

- T1-fs weighted MR image: saved in “m2m_subject ID” folder
- T1-fs weighted MR image: saved in “m2m_subject ID” folder
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- The TMS measurement file (.nbe) generated
- The head mesh file (explained in the previous section)
- Prepared SimNIBS run file (needs to be in .mat file extension)

The T1fs, T1fs conform images and the head mesh file are generated by the SimNIBS using the “mri_to_mesh” function (details in Section 3.2.2). The measurement file is exported from the Nexstim nTMS device after the measurement. A SimNIBS run file including the head mesh and coil information should be saved by the user in the mat form (the detailed description is in Section 3.2.3.4).

In the primary function, “simnibs_pipeline”, input files should be added in addition to choosing the desired session and its stimulation intensity. Likewise, the names of the T1-weighted MR images, the measurement file and its desired session to simulate, head mesh file, and prepared SimNIBS file need to be added at the beginning. The intensity of stimulation can be chosen in this section. Figure 3.12 shows the first part of the function where the user can add the input files.

```matlab
function simnibs_pipeline

clear all;
close all;
addpath('support\\')

t1_file='T1fs.nii.gz';   % T1fs MR image name
t1_conform='T1fs_conform.nii.gz'; % T1 conform MR image name
nbe_file='test.nbe'; % Measurement file name
session='mapping_right_hemis'; % The measurement session which you want to simulate
msh_file='subject_10.5T.msh'; % The head mesh file name
run_file='sim.mat'; % The prepared SimNIBS run file name

import_all(nbe_file);
[c_loc,c_dir]=transform_m(t1_file,t1_conform,session);
mesh_to_mat(msh_file,0);
cr_simnibs(msh_file(1:end-4) '.mat'),run_file,c_loc,c_dir,di);
```

Figure 3.12: Input section of the “simnibs_pipeline” function.

The “simnibs_pipeline” function begins by exporting all measurement sessions and converting the head mesh file into the “mat” format. Then, by using the “transform_m” function, it changes the coordinate system and creates new SimNIBS run file by “cr_simnibs” function.

3.2.3.2. Exporting sessions from the Nexstim measurement file (“import_all” function)

Nexstim produces a measurement (.nbe) file that includes landmark points, stimulation targets and stimulation sessions for each TMS measurement. Each stimulation session in measurement file consists of all stimulation information, such as the intensity, coil location, coil direction, and maximum induced EF location in the brain. However, in order to perform simulation automatically, this information should be extracted as a Matlab file. Therefore, a function named “import_all” has been written to accomplish this goal. This code extracts all information of each sequence in separate mat files in the same folder.
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3.2.3.3. Coordinate system transformation (“transform_m” function)

The stored locations in the measurement file are in a coordinate system represented by the voxel indexes. However, the coordinate system in the SimNIBS is based on continuous coordinates.

The “transform_m” function has been written to implement the transformation from the voxel indexes to the continuous coordinates. It reads the header of the two T1 images created by SimNIBS, in addition to the session points, which the user tends to convert. The input MR images are the “T1.fs.nii.gz” and “T1fs_conform.nii.gz” placed in “m2m_subject ID” folder by SimNIBS automatically after generating the head mesh.

There are three different methods that attach continues coordinates to the voxels [111]. The s_form matrix method has been used in the pipeline. The voxel index coordinates are referred to as \((i,j,k)\) and the continuous coordinates are referred to as \((X, Y, Z)\). The \((X, Y, Z)\) axes are related to a subject-based coordinate system.

To transform the coordination systems, the sform matrix is used. This method gives the locations of the voxel centers in the \((X, Y, Z)\) coordinate system. The \((X, Y, Z)\) coordinates are given by a general affine transformation of the \((i,j,k)\) indexes:

\[
\begin{bmatrix}
X \\
Y \\
Z \\
1
\end{bmatrix} = \begin{bmatrix}
srow_x(0) & srow_x(1) & srow_x(2) & srow_x(3) \\
srow_y(0) & srow_y(1) & srow_y(2) & srow_y(3) \\
srow_z(0) & srow_z(1) & srow_z(2) & srow_z(3) \\
0 & 0 & 0 & 1
\end{bmatrix} \begin{bmatrix}
i \\
j \\
k \\
1
\end{bmatrix}
\]

The srow_* vectors are in the NIfTI header. However, SimNIBS changes the NIfTI image to make the model, and also the header of the NIfTI images generated by SimNIBS is changed. Thus, this method only can be used for converting the point locations from the voxel indices to on continuous coordinates in the T1fs NIfTI image. We found that the head model created by SimNIBS is in the “conformed” space, which is the standard model for FreeSurfer. Therefore, the affine transformation was needed for transforming the points from the standard NIfTI image to the conformed image (Figure 3.13).
Material and methods

The SimNIBS transformation between voxel indices and surface coordinates based on FreeSurfer conventions was employed. Therefore, in the last step of transforming the points from MRI to SimNIBS coordinates, the continuous coordinates from Equation (3.1) were transformed into the voxel indices in the “conformed” image space. It was done by using the inverse matrix of sform formed by the conformed image header (Equation 3.2), and finally, they were transformed to surface coordinates \((X, Y, Z)\) by using Equation (3.3).

\[
\begin{bmatrix}
    i_{\text{conform}} \\
    j_{\text{conform}} \\
    k_{\text{conform}} \\
    1
\end{bmatrix}
= 
\begin{bmatrix}
    \text{srow}_x(0) & \text{srow}_x(1) & \text{srow}_x(2) & \text{srow}_x(3) \\
    \text{srow}_y(0) & \text{srow}_y(1) & \text{srow}_y(2) & \text{srow}_y(3) \\
    \text{srow}_z(0) & \text{srow}_z(1) & \text{srow}_z(2) & \text{srow}_z(3) \\
    0 & 0 & 0 & 1
\end{bmatrix}^{-1}
\begin{bmatrix}
    X \\
    Y \\
    Z \\
    1
\end{bmatrix}
\]

\((3.2)\)

\[
\begin{bmatrix}
    X \\
    Y \\
    Z \\
    1
\end{bmatrix}
= 
\begin{bmatrix}
    -P_d\text{im}_x & 0 & 0 & \left(\frac{N_x}{2} + 1\right)P_d\text{im}_x \\
    0 & P_d\text{im}_y & 0 & -\left(\frac{N_y}{2} - 1\right)P_d\text{im}_y \\
    0 & 0 & P_d\text{im}_z & -\left(\frac{N_z}{2}\right)P_d\text{im}_z \\
    0 & 0 & 0 & 1
\end{bmatrix}
\begin{bmatrix}
    i_{\text{conform}} \\
    j_{\text{conform}} \\
    k_{\text{conform}} \\
    1
\end{bmatrix}
\]

\((3.3)\)

where \(N_x, N_y, N_z\) are the numbers of voxels in \(x, y,\) and \(z\) directions, respectively. \(P_d\text{im}_x, P_d\text{im}_y,\) and \(P_d\text{im}_z\) are the voxel dimensions in \(x, y,\) \(z\)-direction, respectively.

Lastly, the pipeline saves the converted points in the folder called “transformed” in the same path.

3.2.3.4. Creating SimNIBS run file (“cr_simnibs” function)

There are two ways to run the simulations in SimNIBS: adding the coil position and direction manually (Figure 3.14), or creating a SimNIBS run the file automatically. Since each TMS stimulation sequence
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contains a vast number of stimulations, the first approach is time-consuming and increases the occurrence user-made errors.

![Image of workflow for importing simulation points manually](image1)

**Figure 3.14:** The workflow for importing simulation points manually: (1) Importing head mesh file, (2) Choosing the output folder, (3) Adding TMS poslist, (4) Choosing the desired coil file, (5) Selecting the stimulation intensity, (6) Selecting coil position and direction, (7) Copy poslist. For each stimulation, steps 4 to 7 should be repeated.

On the other hand, creating the SimNIBS run file automatically results in increasing the speed and eliminating the user-made errors. Importantly, this could enable using the pipeline also by non-expert users.

In the last part of the pipeline, the pipeline produces the SimNIBS run file. The pipeline is saved as SimNIBS run file, which contains the head mesh file and coil information. Thereby, it modifies the file with new desired session points. **Figure 3.15** shows the procedure for creating the SimNIBS run file. It includes opening the head mesh file, choosing the coil, selecting one random point, and finally saving the file with “.mat” extension.

![Image of procedure for creating SimNIBS run file](image2)

**Figure 3.15:** an overview for preparing one SimNIBS run file.
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The generated “mat” file is structure array-based, and the coil location and direction are placed in one $4 \times 4$ matrix called “matsimnibs”. The matrix is a rigid-body transformation, which describes a rotation and a translation. These are used to place the coil in the right place and in the right direction. The matrix is formed as:

$$
\begin{bmatrix}
R & 0 & 0 & d \\
0 & 0 & 0 & 1
\end{bmatrix}
$$

in which $R$ is a $3 \times 3$ rotation matrix and $d$ is a $3 \times 1$ translation matrix.

The translation matrix $d$ includes the coil center coordinates in three directions. The rotation matrix, $R$, is much more complicated. It contains three $3 \times 1$ vectors, “newX”, “newY”, and “newZ”, which are placed in matrix $R$ as:

$$
R = \begin{bmatrix}
newX(1) & newY(1) & newZ(1) \\
newX(2) & newY(2) & newZ(2) \\
newX(3) & newY(3) & newZ(3)
\end{bmatrix}
$$

The “newZ” vector is calculated by taking the direction normal to the scalp surfaces. The “newY” is calculated by taking the direction between the coil center and the direction reference point, and then orthogonalizing it. The “newX” is the cross product of the “newY” and “newZ”. Moreover, all vectors need to be normalized so that their norm is 1. Figure 3.16 shows the first and second point added in SimNIBS GUI and its “matsimnibs” matrix created by the SimNIBS.

To create “matsimnibs” matrix, firstly, the head mesh has to be converted into the Matlab file. Then the normal vector to each head mesh triangle needs to be calculated. Finally, three vectors, “newX”, “newY” and “newZ”, are calculated and placed in the SimNIBS run file.

The “cr_simnibs” function performs all the mentioned tasks. First, the head mesh is converted into .mat file by supporting “mesh_to_mat” function, then, the node and face information are read by the code. It forms triangles by “triangulation” function of Matlab, which uses the node and face information. Then, it calculates the normal vectors of each triangle (Figure 3.17), finds the closest triangle by the close function in the scalp to coil position. It calculates all the vectors and forms $R$ and $d$ matrices. Finally, it rewrites the SimNBS run file by the new “matsimnibs” matrices and the stimulation intensity.
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Figure 3.17: The head with triangle mesh. The red arrows are normal vectors to each triangle.

The last step for running the simulation is opening the new SimNIBS run file in SimNIBS software. It can be done by clicking the run button and choosing SimNIBS types file saving. Figure 3.18 demonstrates the procedure.

Figure 3.18: The final step to run a SimNIBS simulation. It only requires the name and type of the file without any file extension. In this step, the “SimNIBS files” must be chosen.

3.2.3.5. Post Processing (“simnibs2_to_mat” and “visualization_simnibs” functions)

In order to visualize the TMS results, two functions were written based on Gmsh binary format, which was converted into the Matlab. First, the “simnibs2_to_mat” function converts the stimulation results
from .msh to the mat. The “visualization_simnibs” function reads the resulted mat file and shows the simulation result in Matlab’s native plotter.

3.3. TMS simulations

In order to compare offline and online TMS mapping, seven points measured by TMS device were simulated in the SimNIBS software using presented pipeline. First, the head mesh was generated for both subjects. Then, the stimulation points were transformed to SimNIBS coordinate system using MRI images. To compare the EF maxima from the online nTMS and simulation, the EF maxima points reported by the nTMS device were also transformed to SimNIBS coordinate system. The new SimNIBS run file was created by the pipeline choosing Nexstim coil and intensity from the measurement. Table 3.1 and Table 3.2 show the stimulation points in voxel indexes and SimNIBS surface coordinate system.

To compare the results of the simulations with those obtained with the nTMS model, the peak focality of the EF were evaluated for each solution. The focality was defined as the GM area in which the field exceeded a certain threshold relative to the peak value. The applied threshold for an identified TMS stimulation focus was chosen to be 90%.

Table 3.1: Stimulation points in voxel indexes and SimNIBS surface coordinate system (calculated by the pipeline) for the first subject.

<table>
<thead>
<tr>
<th>Subject 1</th>
<th>Coil location (Voxel indexes)</th>
<th>Coil location (continues coordinates) [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i</td>
<td>j</td>
</tr>
<tr>
<td>Hotspot (point 1)</td>
<td>139.7</td>
<td>206.9</td>
</tr>
<tr>
<td>point 2</td>
<td>156.6</td>
<td>192.9</td>
</tr>
<tr>
<td>point 3</td>
<td>151.7</td>
<td>197.8</td>
</tr>
<tr>
<td>point 4</td>
<td>147.2</td>
<td>201.3</td>
</tr>
<tr>
<td>point 5</td>
<td>144.2</td>
<td>205.7</td>
</tr>
<tr>
<td>point 6</td>
<td>144.8</td>
<td>206.6</td>
</tr>
<tr>
<td>point 7</td>
<td>143.3</td>
<td>208.4</td>
</tr>
</tbody>
</table>

Table 3.2: Stimulation points in voxel indexes and SimNIBS surface coordinate system (calculated by the pipeline) for the second subject.

<table>
<thead>
<tr>
<th>Subject 2</th>
<th>Coil location (Voxel indexes)</th>
<th>Coil location (continues coordinates) [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i</td>
<td>j</td>
</tr>
<tr>
<td>Hotspot (point 1)</td>
<td>139.3</td>
<td>213.0</td>
</tr>
<tr>
<td>point 2</td>
<td>151.4</td>
<td>203.7</td>
</tr>
<tr>
<td>point 3</td>
<td>148.6</td>
<td>207.3</td>
</tr>
<tr>
<td>point 4</td>
<td>145.2</td>
<td>207.3</td>
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<tr>
<td>point 5</td>
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<td>207.9</td>
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<tr>
<td>point 6</td>
<td>142.8</td>
<td>209.8</td>
</tr>
<tr>
<td>point 7</td>
<td>140.7</td>
<td>211.8</td>
</tr>
</tbody>
</table>
Material and methods

To obtain the distance between the EF maximum point from the online and offline models, Euclidian distance was used (3.5):

\[
d(p, q) = \sqrt{\sum_{i=1}^{n}(q_i - p_i)^2},
\]

(3.5)

where \( p \) and \( q \) are the positions of the first and second points in each direction.

In order to characterize the induced field and to compare the results of the created Magstim coil with those obtained with the available Magstim, the peak value EF was assessed.

Although the five created coils in this study, Magstim coil, Nexstim cooled-coil, Nexstim Focal MonoPulse, and Nexstim Focal BiPulse, have different properties and pulse-waveforms which make them incomparable, one simulation for each coil with same intensity and coil location and direction was done, to observe the effect of coil parameters on the induced EF.
The automatic segmentation, meshing and the SimNIBS pipeline designed by the author were successfully tested on two subjects with the accompanied experimental data. The results of EF calculation were compared with the TMS measurements results. Moreover, the resulted EF produced by four different coils were compared.

4.1. Point coordinate transformation

The accuracy of the coordinate system transformation can be assessed by the landmark points used in the TMS measurement. In our TMS measurement protocol, the landmarks are placed on the nose and both ears.

Figure 4.1 shows the landmark points on one of the subject’s head. As can be seen in the figure 4.1, the pipeline worked accurately and points were precisely placed on the head.

Figure 4.1: The nTMS landmark points (nose and ears) with one simulation point on the head generated by the SimNIBS.
4.2. Maximum induced EF location

The maximum EF locations from the online nTMS were compared with the maximum EF from the simulations (offline models). The threshold for maximum EF in simulation was considered as 90% of maximum induced EF. In all 14 stimulations, the closest Euclidean distance between the maximum EF in the online nTMS and the offline model was 9±1 mm. There were only three unique EF maxima in the offline models. Although, the online nTMS EF model was unable to manage more than one EF maxima, the nine SimNIBS models showed multiple EF maxima. Two EF maxima were found in nine of the simulated coil locations. Likewise, three EF maxima were found in three of the simulations, which all belonged to the second subject. The average distance between the online EF maximum point and the second and third closest offline EF maxima were 13±2 mm and 18±3 mm, respectively. The closest offline EF maxima were on average 5 mm lateral, 2 mm anterior, and 5 mm superior to the online EF maxima. Table A.1 in Appendix presents the coil locations, coil intensity and the results from online and offline models for the two subjects. Figure 4.2 shows four simulations, two for each subject, including online and offline EF maxima results.

![Image](image_url)

Figure 4.2: four results of simulations (the upper images belong to subject 1 and the lower images belong to subject 2). The cyan color presents the maximum EF obtained from online nTMS.

4.3. Comparison of EF induced with different coils

In order to compare the created Magstim coil in this study with available Magstim coil in SimNIBS toolbox, simulation with same coil intensity (the intensity used in measurement) was done for each coil
(Figure 4.3). There was only 2.7% between the maximum induced EF values in the coils. The difference may arise from the inaccurate parameters.

Moreover, three different Nexstim coils, which are commonly used in the studies at the Kuopio University Hospital, were modelled and used in the simulations (Figure 4.4). Due to different properties and pulse-waveforms the results are incomparable and only is demonstrated to show the effect of different coil geometry and details on induced EF.
Figure 4.4: Induced electric field using: Magstim coil (a), Nexstim cooled-coil (b), Nexstim Focal MonoPulse coil (c) and Nexstim Focal BiPulse coil (d).
TMS is a non-invasive technique for modulating neurons in the brain via induction of EF. nTMS device, the combination of TMS with a neuronavigation system, is widely used to locate, map and outline cortical speech and motor areas for presurgical planning [112]. Due to the extent of the induced EF, TMS is able to activate neighboring areas. However, the current cortical mapping methods utilize a simplified model of nTMS, which only shows one activated EF maximum point. Thus, the motor areas activated by the nTMS are more likely to be larger and less homogeneous than those obtained from the nTMS system as shown by the results of this thesis. Consequently, using EF distribution could lead to more accurate estimates of the extent of the motor areas. To determine the induced EF distribution, the computational modelling with the real head geometry can be used.

In this thesis, a complete pipeline for TMS field calculation was introduced. The pipeline utilizes the automated segmentation and mesh generation of SimNIBS package to construct an anatomically realistic head model based on MRI. Then, the constructed head model is combined with the measurement session information to create the SimNIBS run file. Lastly, by choosing the new coils created in the thesis, the induced EF is calculated based on the FEM calculation (implemented in the SimNIBS package). Furthermore, the EF visualization can be done by the written Matlab codes. The pipeline was successfully tested on two subjects.

In order to use the tools, the time and manual effort are two key points. The combination of the introduced pipeline, SimNIBS software and postprocessing functions leads to a reduction in time and manual effort significantly. However, the computational time required for the pipeline to complete is still extensive, and is far from real-time applications. Nevertheless, the offline simulation of the more realistic EF distributions requires little effort and can be performed for large sets of data. The created Nexstim coils also allow us to simulate measurements, which have been done by Nexstim nTMS device.

The realistic field calculation based on the accurate head models is the initial step to determine precise EF and understand the underlying biophysical effects of TMS. Its combination with designed pipeline will provide the possibility to simulate a vast number of simulations. The simulations can be done on either healthy subjects or patients. The simulations on healthy subjects may reveal the inter-individual
Discussion

differences in the physiological or behavioral effects of brain stimulation and evaluate the “classic” finding of inter-individual differences in the MT for TMS.

Furthermore, comparing the results of the TMS measurement of patients with the simulations will allow making a conclusion about the effect of tissue abnormalities on the accuracy of nTMS mapping of functional cortical areas in the brain and enhance the accuracy of nTMS mapping by applying computational simulation pipeline.

In the previous studies [113], the spherical head model was used to find the motor representation using a minimum-norm estimate (MNE) [114]. The MNE method is a solution to the inverse problem which can be used to estimate source current distribution in the brain. By using the introduced realistic head model, the EF can be calculated more accurately in order to better nTMS assessment and using as a post-experiment processing part before neurosurgical operation or radiotherapy.

The future aims would be optimization of the pipeline as well as adding multi-compartmental neuron models to the realistic head model. Although the thesis took a big step in TMS simulation, there is still a gap between the ideal pipeline and the current one. Importantly, a function can be written to perform the simulation without a requirement of manual efforts at all. Furthermore, as the recent study by Seo et al. showed, the multi-scale model, including neuron models and realistic head model, can be provided to determine how the EF activates morphologically detailed models of different types. This model takes the calculated EF as an input for calculating the effect of the induced EF on the neurons with high accuracy.

To conclude, this thesis has opened a new way for our group to use the realistic head model clinically and to widen the understanding of how brain responses to the TMS, and how neurological disorders and brain traumas influence the TMS responses. In addition, the developed method provides an opportunity to compare the online nTMS response with the offline model, and to design new TMS coils.
### Appendix A

**Table A.1:** Coil locations, coil intensity and the results from online and offline models for two subjects calculated in this study.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Intensity</th>
<th>First maximum EF location [mm]</th>
<th>Second maximum EF location [mm]</th>
<th>Third maximum EF location [mm]</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>518</td>
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Subject 1

Subject 2

Average

SD
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