Department of Engineering Physics and Mathematics Laboratory of Biomedical Engineering Helsinki University of Technology Espoo, Finland

# Transcranial Magnetic Stimulation: Modelling and New Techniques

Jarmo Ruohonen

Dissertation for the degree of Doctor of Technology to be presented with due permission for public examination and debate in Auditorium F1 at Helsinki University of Technology (Espoo, Finland) on the 4th of December, 1998, at 12 o'clock noon.

Espoo 1998

# Acknowledgements

The work for this thesis was carried out in the BioMag Laboratory of the Helsinki University Central Hospital and in the Centre of Biomedical Engineering of the Italian National Research Council.

The supervisor of the work was Professor Toivo Katila; I am grateful for his invaluable support. I also want to thank the instructors, Docent Risto Ilmoniemi and Professor Ferdinando Grandori. During the years 1993–1998, I have worked for 3 years in the group of Ferdinando Grandori, who has given me excellent guidance since I was an undergraduate student. On the other hand, during the BioMag years I have enjoyed greatly the innovative and challenging atmosphere created by Risto Ilmoniemi.

Team work made the topic of the thesis both "magnetic" and "stimulating". Paolo Ravazzani deserves my warmest thanks for many discussions and friendship. I want to thank my co-workers in the TMS project: Pekka Kahri, Janne Kamppuri, Jari Karhu, Martti Kesäniemi, Pekka Kähkönen, Marko Ollikainen, Reeta Varonen and Jyri Ylöstalo; especially, I thank Juha Virtanen. I thank all collaborators in Helsinki and in Milan. Special thanks are due to Antti Korvenoja, Vadim Nikouline, Juha Huttunen, Eero Pekkonen, Luisa Portoni and Gabriella Tognola.

My brain was stimulated for the first time in 1993 by Marcela Panizza and Jan Nilsson (Fondazione Maugeri, Castel Goffredo). I thank them for explaining the basics of physiology and engineering behind TMS. Professor Giancarlo Comi (San Raffaele, Milan) I want to thank for the positive attitude toward my work.

I wish to express my gratitude to Professor Claudia Tesche and Professor Guglielmo d'Inzeo for reviewing the manuscript of this thesis.

I am very grateful for the love and support of my parents Ritva and Leo, my brother Jari and my dear Laura.

This work was financially supported by TEKES, the Italian National Research Council, the Finnish Cultural Foundation, the Italian Cultural Institute, the Italian Ministry for Foreign Affairs, the Runar Bäckström Foundation and the Finnish Foundation for Inventions.

# Contents

List of publications	••••••
List of abbreviations	3
1 INTRODUCTION	4
2 BASIC PRINCIPLES AND HISTORY 2.1 Basic principles 2.2 History of non-invasive brain stimulation	<b>5</b> 5 7
<b>3 MODELLING OF MAGNETIC STIMULATION</b>	8
<ul><li>3.1 The induced electric field</li><li>3.2 Electrophysiology of excitation</li><li>3.3 Locus of excitation</li></ul>	
4 INSTRUMENTATION	20
<ul> <li>4.1 Available types of stimulators and coils</li> <li>4.2 About optimisation of the stimulator</li> <li>4.3 Coil construction and fabrication</li></ul>	20 22 23 23 24
5 NEW ADVANCED TECHNIOUES	
5 NEW ADVANCED TECHNIQUES 5.1 Computer-assisted TMS 5.2 Multichannel TMS 5.3 TMS-compatible EEG	25 25 27 28
<ul> <li>5 NEW ADVANCED TECHNIQUES</li></ul>	25 25 27 28 30
<ul> <li>5 NEW ADVANCED TECHNIQUES</li></ul>	25 25 27 28 30 30 32
<ul> <li>5 NEW ADVANCED TECHNIQUES</li></ul>	25 25 27 28 30 30 32 33
<ul> <li>5 NEW ADVANCED TECHNIQUES</li></ul>	25 25 27 28 30 30 32 33 33
<ul> <li>5 NEW ADVANCED TECHNIQUES</li></ul>	25 27 28 30 30 30 31 33 33 33 34 35
<ul> <li>5 NEW ADVANCED TECHNIQUES</li></ul>	25 25 27 28 30 30 32 33 33 34 35
<ul> <li>5 NEW ADVANCED TECHNIQUES</li></ul>	25 25 27 28 30 30 32 33 33 33 35 37

# List of publications

This thesis consists of an overview and the following publications:

- I Jarmo Ruohonen, Paolo Ravazzani and Ferdinando Grandori. An analytical model to predict the electric field and excitation zones due to magnetic stimulation of peripheral nerves. *IEEE Transactions on Biomedical Engineering* 42, 158–161, 1995.
- II Jarmo Ruohonen, Paolo Ravazzani, Jan Nilsson, Marcela Panizza, Ferdinando Grandori and Gabriella Tognola. A volume-conduction analysis of magnetic stimulation of peripheral nerves. *IEEE Transactions on Biomedical Engineering* 43, 669–678, 1996.
- III Paolo Ravazzani, Jarmo Ruohonen, Ferdinando Grandori and Gabriella Tognola. Magnetic stimulation of the nervous system: induced electric field in unbounded, semi-infinite, spherical, and cylindrical media. Annals of Biomedical Engineering 24, 606–616, 1996.
- IV Jarmo Ruohonen, Marcela Panizza, Jan Nilsson, Paolo Ravazzani, Ferdinando Grandori and Gabriella Tognola. Transverse-field activation mechanism in magnetic stimulation of peripheral nerves. *Electroencephalography and clinical Neurophysiology* 101, 167–174, 1996.
  - V Jarmo Ruohonen, Paolo Ravazzani, Risto Ilmoniemi, Giuseppe Galardi, Jan Nilsson, Marcela Panizza, Stefano Amadio, Ferdinando Grandori and Giancarlo Comi. Motor cortex mapping with combined MEG and magnetic stimulation. *Electroencephalography* and clinical Neurophysiology Supplement 46, 317–322, 1996.
- VI Jarmo Ruohonen, Juha Virtanen and Risto Ilmoniemi. Coil optimization for magnetic brain stimulation. *Annals of Biomedical Engineering* 25, 840–849, 1997.
- VII Jarmo Ruohonen and Risto Ilmoniemi. Focusing and targeting of magnetic brain stimulation using multiple coils. *Medical & Biological Engineering & Computing* 36, 297–301, 1998.
- VIII Risto Ilmoniemi, Juha Virtanen, Jarmo Ruohonen, Jari Karhu, Hannu Aronen, Risto Näätänen and Toivo Katila. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *NeuroReport* 8, 3537–3540, 1997.

# List of abbreviations

CT	Computed tomography
EEG	Electroencephalography
EMG	Electromyography
EP	Evoked potential
ERP	Event-related potential
ES	Electrical stimulation
FEM	Finite element method
fMRI	Functional magnetic resonance imaging
MEG	Magnetoencephalography
MEP	Motor-evoked potential
MNE	Minimum-norm estimation
MRI	Magnetic resonance imaging
MT	Motor threshold
NIRS	Near-infrared spectroscopy
PET	Positron emission tomography
PNS	Peripheral nervous system
rTMS	Repetitive transcranial magnetic stimulation
SPECT	Single photon emission computed tomography
TCES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
3D	Three-dimensional

# 1 Introduction

The use of non-invasive neuroimaging has increased explosively in recent years. Details of the functioning of the human brain are revealed by measuring electromagnetic fields outside the head or metabolic and hemodynamic changes using electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), nearinfrared spectroscopy (NIRS) or functional magnetic resonance imaging (fMRI). This thesis deals with transcranial magnetic brain stimulation (TMS), which is a direct way of manipulating and interfering with the function of the cortex, thus complementing conventional neuroimaging.

Brain stimulation with TMS is achieved from the outside of the head using pulses of electromagnetic field that induce an electric field in the brain. TMS has numerous applications in the study, diagnosis and therapy of the brain. TMS can either excite the cortex or disturb its function. The observed excitatory effects are normally muscle twitches or phosphenes, whereas in the "lesion" mode TMS can transiently suppress perception or interfere with task performance.

The aim of this thesis was to develop physical understanding of magnetic stimulation and to build models that could provide new insights for utilising the technique. For this purpose, two principal issues had to be addressed: 1) macroscopic electromagnetic fields in the tissue, for which models are developed in Publications I–III, and 2) understanding of the neuronal responses, considered in Publications IV and V. Then, the models developed were used as a basis for engineering modifications that would increase the utility of TMS, the emphasis being on the optimisation of the stimulating coils (Publication VI) and on the use of multiple coils in a whole-scalp array (Publication VII). Publication VIII presents the concurrent use of TMS and high-resolution EEG, showing that the combination is effective for mapping the functional connections in the brain.

The models and procedures were developed in parallel with the design and construction of TMS instrumentation for computer-assisted stimulation.

# 2 Basic principles and history

## 2.1 Basic principles

Neurones can be excited by externally applied time-varying electromagnetic fields. In TMS, excitation is achieved by driving intense pulses of current I(t) through a coil located above the head. The source of activation is the electric field **E** induced in the tissue, obtained from Faraday's law:

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t},\tag{1}$$

where **B** is the magnetic field produced by the coil, given by the Biot–Savart law:

$$\mathbf{B}(\mathbf{r},t) = \frac{\mu_0}{4\pi} I(t) \oint_C \frac{d\mathbf{l}(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} .$$
(2)

The integration is performed with the vector *d***I** along the coil windings *C* and  $\mu_0 = 4\pi \times 10^{-7}$  H/m is the permeability of free space.

The pulses of current are generated with a circuit containing a discharge capacitor connected with the coil in series by a thyristor. With the capacitor first charged to 2–3 kV, the gating of the thyristor into the conducting state will cause the discharging of the capacitor through the coil. The resulting current waveform is typically a damped sinusoidal pulse that lasts about 300  $\mu$ s and has a peak value of 5–10 kA. The electrical principles have been outlined, *e.g.*, by Jalinous [72,73].

Figure 1 summarises the chain of events in TMS. The induced  $\mathbf{E}$  is strongest near the coil and typically stimulates a cortical area of a few centimetres in diameter. TMS pulses cause coherent firing of neurones in the stimulated area as well as changed firing due to synaptic input. At microscopic level,  $\mathbf{E}$  affects the neurones' transmembrane voltage and thereby the voltage-sensitive ion channels. Brain imaging tools can be used to detect the associated electrical currents and changes in blood flow of metabolism. In motor-cortex stimulation, peripheral effects can be observed as muscle activity with surface electromyography (EMG). Moreover, there may be behavioural changes, for instance, impaired task performance.



FIGURE 1. Principles of TMS. Current I(t) in the coil generates a magnetic field **B** that induces an electric field **E**. The lines of **B** go through the coil; the lines of **E** form closed circles. The upper-right drawing illustrates schematically a lateral view of the precentral gyrus in the right hemisphere. Two pyramidal axons are shown, together with a typical orientation of the intracranial **E**. The electric field affects the transmembrane potential, which may lead to local membrane depolarisation and firing of the neurone. Pyramidal axons are likely stimulated near bends, as illustrated here, but also other mechanisms exist (see, section 3.2) and other neurones may be stimulated. Macroscopic responses can be detected with functional imaging tools (EEG, PET, fMRI, NIRS and SPECT = single photon emission computed tomography), with surface EMG, or as behavioural changes.

# 2.2 History of non-invasive brain stimulation

Stimulation of the exposed human cerebral cortex with electrical currents was first described by Bartholow in 1874 [11]; the currents elicited movements of the opposite side of the body. Electrical brain stimulation is today possible non-invasively using scalp electrodes [96]. However, transcranial electrical stimulation (TCES) is very painful and hence of limited value.

The first experiments with magnetic stimulation were conducted by d'Arsonval in 1896 [36]. He reported "phosphenes and vertigo, and in some persons, syncope," when the subject's head was placed inside an induction coil. Later, many scientists reported the phenomenon of magnetophosphenes, that is, visual sensations caused by the stimulation of the retina due to changing magnetic fields [10,15,41,92,155,159].

Magnetic *nerve* stimulation was accomplished only several decades later, first in the frog by Kolin *et al.* [79] in 1959 and then in the human peripheral nerve by Bickford and Fremming [17] in 1965. The latter authors used an oscillatory magnetic field that lasted 40 ms. The resulting long-lasting activation interval made it impossible to record nerve or muscle action potentials, and the work was not pursued further. In the following years, the technique was investigated only occasionally [68,87,118].

In 1982, Polson, Barker and Freeston [128] described a prototype magnetic stimulator for peripheral nerve stimulation. They used 2-ms-duration pulses and recorded, for the first time, motor-evoked potentials (MEPs) obtained by median nerve magnetic stimulation. In present-day devices, the pulse duration is typically shorter.

In 1985, the Sheffield group achieved successful transcranial magnetic stimulation [9] and made the first clinical examinations [6]. TMS proved valuable for probing the motor pathways: in healthy subjects, stimulation over the motor cortex causes twitches in hand muscles in about 25 ms, while many neurological conditions manifest slower conduction. Another important characteristic of TMS is that it is painless, the subject usually feeling only a not uncomfortable sensation of scalp being pinched. The encouraging results led into commercialisation of TMS by Novametrix Ltd. (predecessor of Magstim Company).

Since 1985, magnetic stimulator technology has remained mostly unchanged. Whereas early research used circular coils, today devices are usually equipped also with an 8-shaped, or figure-of-eight coil proposed by Ueno [157]. The 8-shaped coil induces a more concentrated electric field than the circular coil, resulting in better control of the spatial extent of the excitation. Another important development is repetitive TMS (rTMS) capable of delivering trains of stimuli at 1–50 Hz. rTMS was first produced by Cadwell Laboratories in 1988 and is today one of the most quickly growing areas of TMS research.

The reader may get a detailed overview of the history and principles of magnetic stimulation, for instance, from Refs. [5,49].

# 3 Modelling of magnetic stimulation

Models of magnetic stimulation are of great importance in the investigation of the locus, extent and mechanisms of stimulation, in the interpretation of experiments and in the design of effective instrumentation. Modelling can be divided into two important separate parts: 1) the computation of the macroscopic electromagnetic fields due to current in the coil, and 2) the response of neurones as a result of electrical charges that the macroscopic field builds up on their membranes.

This section also outlines experimental results about the locus of activation and about the dominant cellular mechanisms.

### 3.1 The induced electric field

Generally, the shape of the electric field induced in the tissue depends on 1) the shape of the induction coil, 2) the location and orientation of the coil with respect to the tissue, and 3) the electrical conductivity structure of the tissue.

The total electric field in the tissue is the sum of *primary* and *secondary* electric fields, the primary field  $\mathbf{E}_1$  being induced by the changing magnetic field  $\mathbf{B}(t)$  from the coil, as stated by Eqs. 1 and 2. In conductors,  $\mathbf{E}_1$  causes a flow of current  $\mathbf{J} = \sigma \mathbf{E}_1$ ,  $\sigma$  being the conductivity. Any conductivity changes along the path of the current cause nonuniformity of electric charges, giving rise to an electrostatic potential *V*, the negative gradient of which is the *secondary* field  $\mathbf{E}_2 = -\nabla V$ . Expressing **B** in terms

of the vector potential **A**, *i.e.*,  $\mathbf{B} = \nabla \times \mathbf{A}$ , the total **E** is [70]:

$$\mathbf{E} = \mathbf{E}_1 + \mathbf{E}_2 = -\frac{\partial \mathbf{A}}{\partial t} - \nabla V.$$
(3)

The potential V obeys Laplace's equation,  $\nabla^2 V = 0$ . Equation 3 has been solved for the unbounded space [54] and for simple conductor shapes such as the semi-infinite space [42], spheres [43], and infinite-length cylinders [44,45]. Other shapes and inhomogeneities have been modelled numerically [23,37,106,139,149,157].

## 3.1.1 The relationship between TMS and MEG

TMS is the converse of MEG, which uses a number of sensor coils to measure the magnetic field generated by electrical currents associated with neural activation. Because of the converse relationship, several results obtained in connection with MEG have relevance to TMS, and vice versa. The **E** induced in the brain by TMS can be obtained using the same formulas that in MEG give the sensor coil signal due to known intracranial currents [Publications I–III]. The theoretical link is constituted by the reciprocity theorem [29,61,80]:

$$\int_{V} \mathbf{J}^{\mathrm{P}}(\mathbf{r}) \cdot \mathbf{E}(\mathbf{r}) \, dv = -\frac{dI(t)}{dt} \int_{C} \mathbf{B}_{\mathrm{J}}(\mathbf{r}') \cdot d\mathbf{a}(\mathbf{r}') \,, \tag{4}$$

where  $\mathbf{B}_{J}$  is the external magnetic field at  $\mathbf{r'}$  produced by a primary current distribution  $\mathbf{J}^{P}$  inside the volume conductor *V* approximating the head. Vector  $d\mathbf{a}$  is a vector normal to an arbitrary surface spanned by the windings of the induction coil *C* and the current in the coil is I(t). Both calculations are to be conducted for the same geometry. The reciprocity holds for linear and inhomogeneous space and for anisotropic space with symmetric permittivity and permeability tensors [80]. Moreover, it is required that I(t) be of low frequency, *i.e.*, quasi-static. These conditions can be considered to exist in magnetic stimulation.

On the other hand, the flux  $\boldsymbol{\Phi}$  through an MEG sensor coil due to an intracranial current  $\mathbf{J}^{\mathrm{P}}$  can be written in terms of a sensitivity function  $\mathbf{L}$ , called *lead field* for the coil [60]:

$$\boldsymbol{\Phi} = \int_{C} \mathbf{B}_{\mathbf{J}} \cdot d\mathbf{a} = \int_{V} \mathbf{L} \cdot \mathbf{J}^{\mathbf{P}} dv \,. \tag{5}$$

From Eqs. 4 and 5, the solution for **E** in TMS is obtained by assuming that the MEG coil is used for stimulation instead of flux measurement. Driving the coil with current I(t), the induced field is:

$$\mathbf{E}(\mathbf{r}) = -\frac{dI(t)}{dt} \mathbf{L}(\mathbf{r}) .$$
 (6)

The lead field at  $\mathbf{r}$  can be computed by calculating the flux coupled into the coil by the magnetic field due to an arbitrary current dipole (a short element of current) immersed in the tissue at  $\mathbf{r}$  [60]. This is the *forward problem*, which has been solved explicitly for simple conductor shapes such as spheres [65,148] and spheroids [35].

Primary currents perpendicular to the lead field do not couple flux into the sensor coil, which prevents localisation of such sources in the brain with MEG. The converse is true in TMS: no field is induced in directions perpendicular to the lead field.

#### 3.1.2 Field shaping with multiple coils

With multiple coils, *i.e.*, channels, the TMS excitation field can be electronically shaped by changing currents in the coils individually (see, chapter 5.2). Field shaping aims at finding the optimal currents in *n* coils to realise a field that is as close as possible to a desired field configuration **P**. Publication VII formulates the TMS field-shaping problem as the minimisation of the norm  $\int (\mathbf{E} - \mathbf{P})^2 dv$  between **P** and the actual field **E**. The resulting optimal coil currents are then obtained from the column vector  $\mathbf{J} = (dI_1/dt, ..., dI_n/dt)^T$  [Publication VII]:

$$\mathbf{J} = -\mathbf{L}^{\dagger} \mathbf{P} , \qquad (7)$$

where  $\mathbf{P} = (\int \mathbf{P} \cdot \mathbf{L}_1 dv, ..., \int \mathbf{P} \cdot \mathbf{L}_n dv)^{\mathrm{T}}$  and  $\mathbf{L}$  is a square matrix with elements  $\mathbf{L}_{ij} = \int \mathbf{L}_i \cdot \mathbf{L}_j dv$  (i, j = 1, ..., n). The pseudoinverse of  $\mathbf{L}$  is  $\mathbf{L}^{\dagger}$ . The resulting  $\mathbf{E}$  is then

$$\mathbf{E} = -\sum_{i=1}^{n} (\mathbf{L}^{\dagger} \mathbf{P})_{i} \mathbf{L}_{i} , \qquad (8)$$

where  $(\mathbf{L}^{\dagger}\mathbf{P})_i$  is the *i*th element of vector  $\mathbf{L}^{\dagger}\mathbf{P}$ . Eq. 8 is analogous with the MEG minimum-norm estimate (MNE) of the intracranial current density that best explains the measured data [60]. Eq. 8 holds also for TCES, provided that electrical lead fields are used and the coils' rates of change of current in vector  $\mathbf{J}$  are replaced by electrode currents.

The field-shaping problem is not generally exactly solvable, there being infinitely many **P** that cannot be realized. Therefore, different target field configurations **P** can lead to the same solution. MNE is one possible solution, but not necessarily the best. These conclusions do not change with the number of coils. When the goal is to minimise the extent of the stimulating field, search algorithms give better results [Publication VII], since the mathematical formulation of the MNE procedure implies a tendency to diffuse solution fields. The great advantage of MNE-based field shaping is that once  $\mathbf{L}^{\dagger}$  is computed for the given coil array, the optimal coil currents for any **P** are obtained by simple matrix multiplication.

### 3.1.3 No 3D focusing

Many interesting studies would emerge if it were possible to focus the induced  $\mathbf{E}$  in depth, that is, to obtain a field that is strong in deep brain structures and weak in the structures above. Unfortunately, focusing in depth is not possible with any combination of TMS and/or TCES. Heller and van Hulsteyn [61] have proved mathematically that at quasi-static frequencies the field is always stronger on the boundary than in the interior of any volume-conductor compartment with constant conductivity. For spherically symmetric conductors, the maximum field within the conductor is always on the outer surface. Coil designs capable of 3D TMS focusing are occasionally suggested, but doomed to failure.

In non-spherical conductors with varying conductivity, it is possible that  $\mathbf{E}$  is maximal in a deep low-conductivity region. Since such regions can pin the locus of the field maximum, smooth changing of the site of neuronal excitation is not possible. This means that focusing in depth can not be realised.

#### 3.1.4 Spherical head model

In MEG, a widely used approximation of the conductivity geometry of the head is the spherical model. It has been shown that the spherical model is appropriate for superficial parts of the head [59]. Since TMS can not effectively reach deep structures and can not be focused in depth, it follows from the reciprocity that the spherical model must be applicable also to TMS. The spherical model must be used so that the sphere fits the local radius of curvature of the inner surface of the skull near the area of interest. The mathematical formulation is found in Refs. [61,65,148].

Publication III examined the effects of spherical boundaries. Fig. 2 displays the magnitude of the induced  $\mathbf{E}$  in the unbounded and sphere models for circular and 8-shaped TMS coils. The spherical model is seen to decrease the strength of  $\mathbf{E}$ , but the distribution of the field is similar in the two models. When the circular coil is tilted erect above the head (Fig. 2b, coil axis tangential to the sphere surface), the electric field induced in the sphere is much smaller than in the unbounded model. In the absence of the boundary the maximum field value is the same for the tangential and erect coils (Figs. 2a and 2b, top). The boundary effects disappear for any coil whose axis passes through the sphere centre [29,61]. This is the main reason why motor responses are more easily elicited with a circular coil flat on the vertex than with other orientations.



FIGURE 2. Contour maps of the strength of **E** on an 8-cm-radius spherical surface for the unbounded (top) and spherical medium (bottom). (a) Tangential, laterally shifted circular coil; (b) erect circular coil; and (c) 8-shaped coil. Projections of the coils are depicted with thick continuous lines. The diameter of the coils was 40 mm and  $dI/dt = 10^8$  A/s. The coils had 10 turns. The peak value of **E** is given below each plot. The depth of the spherical surface below the coil was 15 mm.

The Ampère–Laplace law, which is the continuous counterpart of the Biot–Savart law in Eq. 2, implies that in all axially symmetric conductor shapes the induced  $\mathbf{E}$  along any rotational axis vanishes on that axis [Publication I]. This means that  $\mathbf{E}$  is never oriented towards the centre of the sphere.

#### 3.1.5 Models of the limbs and the spine

Cylinder-shaped volume conductors can be used to model limbs. Publications I and II derived analytical solutions to **E** and its gradient  $\partial E_x/\partial x$  in a prolate spheroid as well as in unbounded and semi-infinite conductors. An analytical solution is available also in the infinite-length circular cylinder [44,45]. Finite-length cylinders have been analysed numerically [37,115,139].



FIGURE 3. The induced  $\partial Ex/\partial x$  in unbounded (*top*) and prolate spheroidal (*bottom*) models due to circular and 8-shaped coils. The field plane was 10 mm below the coil plane. Contour step is 0.5 kV/m<sup>2</sup>. The zero contours are dotted and the negative contours dashed. Projections of the coils are depicted with thick continuous arcs. Both wings of the 8-shaped coil comprised 5 turns of 50 mm in radius; the edge-tangential coil had 10 turns. The spheroid's radius was 40 mm and its length 1 m and  $dI/dt = 10^8$  A/s. The inserts show the geometry, coil orientations and field plane (dark rectangle). Adapted from Publication II.

In peripheral stimulation, an important activating feature of **E** is thought to be its gradient along the axon,  $\partial E_x/\partial x$  (chapter 3.2). Fig. 3 dis-

plays the  $\partial E_x/\partial x$  induced in the spheroid and unbounded medium for a circular and an 8-shaped coil. The pattern of  $\partial E_x/\partial x$  is similar in the models, but its strength is less in the spheroid. It was calculated in Publication II that with typically used coil orientations the field in a cylinder-shaped conductor is 70–80% of the field in the unbounded volume. This agrees with simulations made by others [45] as well as with *in vivo* measurements [93]. The usefulness of the simplified cylinder-shaped models is limited because the computation is time-demanding and the inaccuracy of the unbounded model is small when estimating the shape of **E**.

As to the modelling of the spine, finite element method (FEM) modelling has revealed that bones and inhomogeneities in the spinal neurogeometry affect greatly the induced  $\mathbf{E}$  [106]. The well-conducting cerebrospinal fluid reduces notably the field in the less conducting spinal cord [91,150]. This explains the inadequacy of stimulating the spinal cord magnetically.

#### 3.1.6 Realistic models

At least in principle, the shape of the conductivity boundaries of the head, spine and limbs can be obtained from MR images. This information can be used to reconstruct realistic models of the conductivity geometry, although MRI does not give the value of the conductivity or information about possible conductance anisotropy.

A few studies have investigated using FEM modelling how anisotropies and inhomogeneities affect the TMS-induced electric field [23, 37,106,162]. The main result has been that the induced **E** is maximal in the regions of low conductivity. The preferential direction of **E** in anisotropies has been found to be along the direction of lower conductivity. The peak value of **E** in heterogeneous tissue models was 50–100% of the value in the homogeneous unbounded model. These results indicate that regions of low conductivity can channel the direction of **E** in the brain or spine and pin the location of its maximum value.

To conclude, simplified models such as the sphere are satisfactory for explaining gross features of the induced electric field, especially if the area of interest is superficial and the model geometry agrees reasonably well with the local curvature of the body.

# 3.2 Electrophysiology of excitation

The electric field  $\mathbf{E}$  sets free charges into coherent motion both in the intra- and extracellular spaces. Basically, any part of the cell membrane interrupting this motion of the charges becomes depolarised or hyperpolarised. In practice, however, the basic cellular mechanisms are unclear, although the macroscopic electromagnetic fields are well understood. Modelling of TMS at cellular level is very qualitative because of complex cell shapes and, *e.g.*, the effects of background neuronal activity.

This chapter overviews the present status of modelling the cellular response to magnetic stimulation.

## 3.2.1 Cable model

The subtreshold behaviour of the transmembrane potential V, measured from the resting potential, is described by the cable equation [12,95, 133,153]:

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} - \tau \frac{\partial V}{\partial t} - V = f(x,t) , \qquad (9)$$

where  $\lambda$  and  $\tau$  are the fibre's length and time constants, respectively; the coordinate *x* measures the distance along the axon. The activating function, *f*, describes the sources of excitation; its computation requires information about the coil and its location as well as about the tissue surrounding the fibre. From Eq. 9, the axon is depolarised where *f* is negative and hyperpolarised where it is positive.

Equation 9 holds as such for bent axons and in its compartmental form also for myelinated and finite-length axons [111]. The axon dynamics, described by the Hodgkin–Huxley model, can be included in the cable equation [12,138], but the mathematical treatment becomes non-linear and complicated. Provided that the electric field inside the axon can be assumed to be axial, the resulting activating function f in magnetic stimulation is [138]:

$$f = \lambda^2 \partial E_{\rm x} / \partial x , \qquad (10)$$

where  $\partial E_x/\partial x$  is the gradient of the component of **E** along the axon; *f* is also known as Rattay's activating function [131]. Fig. 4a illustrates that no activation occurs with a uniform field along the axon, whereas Figs. 4b and 4c depict the gradient activation mechanism for straight and bent axons.

Publications II and IV provide evidence that Eq. 10 is incomplete, since also the field component transverse to the axon,  $E_T$ , affects V. The potential difference across the axon is of the order of  $2RE_T$ , where R is the axon radius [81,137]. Thus, Eq. 10 must be changed accordingly, giving the *modified* activating function:

$$f = \lambda^2 \partial E_{\rm x} / \partial x - 2RE_{\rm T}.$$
<sup>(11)</sup>

The ratio of the transverse and gradient field mechanisms is independent of the axon size. A schematic illustration of the axon membrane polarisation in a transverse field is shown in Fig 4d.



FIGURE 4. A schematic illustration of the activation mechanisms. The axon membrane polarisation is sketched for different externally applied electric field patterns (arrows): (a) uniform **E** along the axon, no change from the resting state; (b) gradient activation, with  $\partial E_x/\partial x \neq 0$ ; (c) bent axon in uniform **E**, depicting only the gradient activation; (d) transverse activation, with **E** locally across the axon; (e) axon terminating in uniform **E**. D and H denote depolarisation and hyperpolarisation, respectively. Although not illustrated, it is assumed that **E** is equal outside and inside the cells.

#### 3.2.2 Geometrical factors affecting the excitability

Neuronal excitability changes because of various geometrical factors, *e.g.*, axon terminals, bending, branching, nonuniformity and tapering and volume-conductor nonuniformities [137]. Especially, bends and terminations are thought to play a key role in TMS [90]. High effective  $\partial E_x/\partial x$  values are achieved at bends even in homogeneous **E** [1,63] (see, Fig. 4c). In thin curved axons, the relative contribution from the transverse field  $E_T$  (Eq. 11) is small as compared to  $\partial E_x/\partial x$ .

Computer simulations [111] and in vitro experiments [110] suggest

that if the coil is placed close to the end of axon, or the axon is short (< 6-8 cm), the axon membrane is preferentially depolarised at the end by the field component parallel to the axon. This is illustrated in Fig. 4e for an axon terminating in a uniform field.

The cable equation (Eq. 9) applies for isolated axons, but in fibre bundles the nearby axons may change the extracellular potential significantly. Both the excitability and the locus of activation vary with the position of the fibre in the bundle [108,109].

#### 3.2.3 Strength-duration relationship

The cell membrane behaves as a leaky integrator with a time constant of about 150  $\mu$ s, and hence the shorter the pulse, the less energy is required for excitation [8,111,119]. On the other hand, the minimum pulse intensity is achieved when the effective pulse duration is greater than the chronaxie time of the neurone. Fig. 5 depicts the energy–duration and strength–duration curves for TMS while holding the coil inductance and circuit resistance constant and changing the capacitance. The efficiency is at maximum with brief intense pulses, but this solution requires a low capacitance and a high capacitor voltage. The maximal useful voltage is limited by the availability and price of power electronics components.



FIGURE. 5. Calculated normalised threshold capacitor energy and peak value of **E** as function of zero-to-peak rise time. Values are normalised to rise time of 100  $\mu$ s. Circuit inductance  $L = 20 \ \mu$ H and resistance  $R = 50 \ m\Omega$ . The capacitance C ranged from 20 to 600  $\mu$ F. Current shape was biphasic and membrane time constant  $\tau = 150 \ \mu$ s. Although not shown, the energy–duration curve levels off at a constant value for very short pulses.

## 3.3 Locus of excitation

The locus and mechanisms of activation are of great consequence when looking for the optimal shape of  $\mathbf{E}$  to activate specific cortical patches or when interpreting measurements. This section presents some relevant experimental results separately for distal, spinal root and brain stimulation.

#### 3.3.1 Distal nerve stimulation

Recalling the theory presented in chapter 3.2.1, there are two expected mechanisms of activation in distal nerve stimulation: the gradient and transverse field mechanisms. Experimentally, the site of activation has been argued to be at the negative peak of  $\partial E_x/\partial x$  [13,110,111,115,132, 133,138], but some reports display strong activation with coil orientations that induce no  $\partial E_x/\partial x$  along the nerve [34,57,78,89,117]. Publication IV was aimed at addressing this discrepancy. For this purpose, the locus of activation, determined from the latency of surface EMG responses, was mapped with different coil placements. The modified activating function (Eq. 11), which includes the contribution from both gradient and transverse fields, was found to predict well the locus of activation. Thus, these results suggest that there is no discrepancy, but that two separate mechanisms are responsible for the membrane depolarisation.

Bones change notably the induced field distribution as well as the elicited neuronal activation. For instance, Maccabee *et al.* [91] stimulated sheep phrenic nerve in a saline container. Insertion of solid plastic cylinders near the nerve caused preferential activation from points of the nerve near the plastic. Something similar has been observed in facial nerve stimulation, where the greatest excitability was at the exit from the temporal bone [135].

#### 3.3.2 Stimulation of the spine and spinal roots

The present magnetic stimulators are not powerful enough to stimulate directly the descending spinal tracts [26,27], since the spinal bones attenuate greatly the induced **E** (chapter 3.1.3). On the other hand, *spinal roots* can be stimulated magnetically, but the response latency does not change smoothly with coil position [26]. This is thought to be because the roots are bent near the neural foramen, which serves as a high-excitability

point. Another source of changed excitability is the complicated bone geometry.

#### 3.3.3 Brain stimulation

Characteristic dimensions of the shapes of cortical neurones are small compared with the distances over which the induced electric field varies. Hence, cortical neurones are likely to be activated at terminations (Fig. 4e) or at axonal bends (Fig. 4c), where the effective gradient of **E** along the axon can be great. Consequently, TMS activation most probably takes place at the maximum of the externally applied **E**. The contribution of the transverse activation mechanism is small since the axons are thin. On the other hand, **E** can be maximal in low-conductivity regions, which could help to determine the site of stimulation, but also complicates the study of the activating mechanisms.

Comparative results from localisation of the somatosensory cortex with TMS and other methods support that the activation occurs at the maximum of **E**. Recently, Krings *et al.* [82,83] compared TMS maps with direct cortical stimulation results, finding agreement to within less than 5–10 mm. The site of maximal **E** in TMS has been found to agree with the localisation results from MEG [103,104,146,Publication V] and PET [167] to within 10–20 mm. Similarly, fMRI, PET and TMS have localised the frontal eye field to the precentral gyrus [22,127]. Despite the agreement between results from TMS and functional imaging, different neuronal structures may be involved.

Not only the strength, but also the direction of the induced  $\mathbf{E}$  in the brain affects the locus and strength of activation. The motor activation is strongest when the cortical  $\mathbf{E}$  in the contralateral precentral gyrus is in the posterior-to-anterior direction. This possibly means that TMS of the primary motor cortex preferentially activates elements in the posterior bank of the precentral sulcus that are parallel to the induced field [121], or at bends [90]. This is different from MEG, which reflects postsynaptic activity [60]. Hence, although there is a reciprocity between the macroscopic field theory for MEG and TMS, different cellular-level phenomena are involved.

TMS is thought to affect neurones in the cortex, rather than deep parts of the corticospinal tract [101]. Corticospinal neurones are presumably activated transsynaptically at low TMS intensities, since the response latency to TMS is often 2 ms longer than to TCES [38,144], which stimulates the corticospinal neurones directly. On the other hand, intense TMS pulses often yield latencies similar to TCES, suggesting direct activation of the corticospinal axons.

At cellular level, TMS is thought to excite axons rather than the cell body or other parts of the neurones [88] since the measured chronaxie [8] and intervals for facilitation [145] in peripheral motor axonal and brain excitation are similar.

The mechanisms of repetitive TMS (rTMS) have not been examined so far. The electromagnetic theory and the cable theory for single-pulse TMS remain unchanged for rTMS. However, it is possible that at high repetition rates the cellular-level effects of rTMS differ from those of singlepulse TMS.

# 4 Instrumentation

## 4.1 Available types of stimulators and coils

There are two stimulator types: single-pulse devices and repetitive TMS (rTMS) devices that generate trains of stimuli at 1–60 Hz. Commercial equipment are provided by three main manufacturers: Cadwell Laboratories, Inc. (Kennewick, USA), Magstim Company, Ltd. (Whitland, UK) and Medtronic Dantec NeuroMuscular (Skovlunde, Denmark).

Dantec and Magstim have add-on modules to their single-pulse devices that can be used to drive one coil with two to four pulses separated by 1 ms to 1 s. These devices are called paired-pulse or quadruple-pulse stimulators. Two stimulator units can be used together to drive separate coils to stimulate different regions at the same time or in quick succession. This TMS mode is called double-pulse TMS.

The rTMS devices operate at 10–60 Hz at 40–100% of the maximum intensity of single pulses. The duration of sustained operation is limited by coil heating to 100–1,000 pulses at maximum power. With proper coil cooling, the duration of the stimulus train can be made unlimited. Cadwell makes coils with continuous water cooling, whereas Magstim makes aircooled coils.

The current pulse properties vary among manufacturers. Three pulse

waveforms are available: i) monophasic, *i.e.*, rapid rise from zero to peak and slower decrease to zero; ii) biphasic, *i.e.*, one damped sine pulse; and iii) multiple-cycle damped sine pulse. The Dantec MagPro model is equipped with a switch that allows selection between monophasic and biphasic pulse shapes. Most of the Magstim devices use a monophasic pulse. Cadwell devices generate a biphasic pulse, although earlier MES-10 units had a multiple-cycle sine pulse. Rapid charging of the capacitors requires that the rTMS devices use biphasic currents. The initial direction of the current in the coil can be switched in some Dantec stimulators.

The current pulse duration is typically 200–300  $\mu$ s for biphasic and about 600  $\mu$ s for monophasic pulses. The peak current generated by the commercial devices is 2–8 kA. Operating voltage of TMS devices is typically 2–3 kV and the power consumption 2–3 kW at maximum stimulus intensity.

The standard stimulating coils are either circular or 8-shaped. Some Cadwell coils are drop-shaped with one rectangular edge (Focalpoint<sup>TM</sup>); the benefit from the shape is questionable. Magstim sells 8-shaped cone coils with angled wings that fit the head and Dantec has a similar circular cone coil. The cone coils are somewhat more effective than planar ones, but at the cost of focality. The diameter of the coils ranges from 50 to 150 mm. The coils are usually wound of 10–30 concentric turns of rectangular copper wire (gauge, *e.g.*, 1×5 mm<sup>2</sup>), resulting in an inductance of 15–30  $\mu$ H.

Prototype four-leaf coils have been presented with four coplanar wings [140] suitable for peripheral stimulation. Another new idea is the so-called half-toroid ("slinky") coil, which is wound with the turns in different angles while maintaining the tangency along one edge [134,171].

The TMS equipment developed and used at the BioMag Laboratory has two independent stimulator channels that are controlled by a computer. The maximum stimulus repetition rate is 1 Hz at full intensity and the system operates at 3 kV. The coils are 8-shaped and water-cooled and their outer diameter ranges from 30 to 50 mm. The current pulse shape is biphasic with rise time ranging between 70 and 100  $\mu$ s depending on the coil.

TABLE 1.
Definition and importance of main figures of merit for the optimisation and the
evaluation of magnetic stimulators.

Figure of merit	Quantity to be minimised	Importance	
Stimulator's efficacy	Input power	Stimulus repetition rate	
Coil's efficacy	Peak magnetic energy	Price, weight and size of components	
Coil heating	Temperature rise / pulse	Duration of pulse trains and of sustained operation	
Focality	Area bound by the half- maximum of <b>E</b>	Spatial resolution	

## 4.2 About optimisation of the stimulator

Publication VI addresses the optimisation of the TMS coil and the selection of the power electronics components. The optimal design depends on the application and how different qualities are weighted. Optimisation should hence begin by selecting the quality criteria and the weighting rules for computing the costs. The key task is to identify the members of three variable categories:

- constraints, e.g., safety regulations
- quantity/quantities to be minimised, e.g., fabrication costs
- adjustable parameters, *e.g.*, coil dimensions.

The most important physical quantities that determine the quality of magnetic stimulators are listed in Table 1; Publication VI gives the formulas to calculate their values. Unfortunately, the quantities are competing, *e.g.*, focal coils have a lower efficacy than otherwise similar coils.

As a rule, the coil is the main item to be optimised. Publication VI focused on minimising the stimulator's power consumption by changing the coil's winding structure and wire gauge. The procedure could improve especially the efficacy of small coils by winding them into solenoids instead of flat spirals. This procedure has been applied to design small water-cooled coils for the TMS equipment at the BioMag Laboratory. In the literature, the results of coil optimisation have remained of little use since the definition of the "optimum" has been omitted [86,105,116]. In one study, a mathematical method was used to maximise the focality by changing the coil shape [141]. The resulting most focal coil shape was found to be roughly 8-shaped.

## 4.3 Coil construction and fabrication

Coil design must always be taken into account when constructing TMS equipment. Effective design is hindered by the high amount of energy that must be driven through the coil in a very brief time. In brain stimulation this energy is about 500 J, which would suffice to lift a weight of 1 kg to a height of 50 m.

The intense submillisecond current pulses cause strong expanding and compressing forces in the coil. The forces are even tens of kilonewtons and thus the cross-sectional wire size must be large and the potting material resistant. The forces are proportional to the peak energy in the coil. Optimally, the coils are wound so that the forces are compressing in the direction where the coil touches the head.

In rTMS, an additional trouble is that tens of W/Hz of power is dissipated in the coil. The coil being usually placed against the head, according to the safety standards its surface temperature must not exceed 41°C. One should also avoid high wire temperatures (100–120°C), since these deteriorate insulation, decreasing safety and the coil's life time. Built-in temperature sensors and effective cooling can be used to guard against excessive temperatures.

Problems with power consumption and coil heating can be alleviated by reducing the coil's resistance, determined by the wire gauge and coil geometry [Publication VI]. When the cross-sectional dimensions of the wire exceed 1 to 2 mm, the skin and proximity effects change the current distribution in the wire [154], and may increase the direct current resistance significantly. Striped, foil or litz wire can be used to reduce the skin and proximity effects. The skin effect causes the current to flow mainly on the surface of thick wire; hence, tubular wire can be used without affecting the resistance. Liquid coolant can then flow inside the wire, as it is done in the BioMag Laboratory's TMS coils.

The voltage over the coil's connectors may be 3 kV and depending on how the coil is wound the voltage across adjacent turns can be from 200 to 1,000 V. The wire insulation (varnish, film, mylar paper) must have the necessary dielectric strength and resist chemical solvents of the potting material (epoxy resin, polyurethane foam). The electrical and liquid coolant contacts must be tightly fastened and well insulated.

The intense current gives rise to a clicking sound from the coil, cables and capacitor, exceeding 100 dB near the coil. To reduce the noise from the coil, researchers at the BioMag Laboratory are investigating the possibility to encapsulate the coil in vacuum or place a vacuum shield between the coil and the subject [67].

## 4.4 Focality of stimulation

The capability to concentrate, or focus, the induced  $\mathbf{E}$  to small cortical patches deserves special attention since it limits the spatial resolution of TMS. Focusing is possible in two dimensions only [61] (see chapter 3.1.3).

A convenient measure of focality in TMS is the area of the spherical surface bound by the half-maximum of **E**, listed in Table 2 for some presently available commercial coils. Table 2 lists also the peak **E** values obtained while driving the coils with  $dI/dt = 10^8$  A/s; in practice, the dI/dt values vary among manufacturers. For comparison, the same values are given for a hexagonal array of 19 circular coils, partially realised at the BioMag Laboratory (chapter 5.2). The focality of the multichannel array is superior due to the use of many coils that are smaller than normal [Publication VII].

The 8-shaped coil is much more focal than the circular coil. In practice, however, the circular coil is sometimes preferred over the 8-shaped coil because motor responses can be promptly evoked without need for precise coil positioning. The 8-shaped coil is chosen for better control of excitation. The focality and the strength of stimulation depend on the coil size and on the distance from the coil, both degrading quickly with increasing depth. For very small radius the focality levels off at a constant value.

Characteristics of some coils. Circular coils were placed edge-tangentially and 8-
shaped coils tangential to the scalp. The array coils pointed to the centre of the head.
The computation was done on a 80-mm-radius spherical surface 20 mm below the
coils. The spherical model was used and $dI / dt = 10^8$ A/s.

TABLE 2.

Manufacturer	ID / OD	N	Focality	Peak E
	[mm]	[turns]	[cm <sup>2</sup> ]	[V/m]
	Circul	ar coils		
Cadwell <sup>a</sup>	72 / 85	14	96	170
Dantec <sup>b</sup>	74 / 94	11	103	130
Magstim (type 9762) <sup>c</sup>	40 / 94	15	96	130
8-shaped coils				
Cadwell <sup>a</sup>	42 / 54	14 (×2)	18	210
Dantec (type B55) <sup>b</sup>	34 / 54	11 (×2)	18	150
Magstim (type 9790) <sup>c</sup>	56 / 87	9 (×2)	33	180
	BioMag 19	-coil arrays		
BioMag 19 array	OD 30	30	7	55 <sup>d</sup>
BioMag 19 array	OD 40	30	12	105 <sup>d</sup>

ID = inner diameter; OD = outer diameter. <sup>a</sup> Approximate geometry from [143]; <sup>b</sup> from [115]; and <sup>c</sup> from [73]. <sup>d</sup> Value when the sum of the absolute dI/dt values in all coils is  $10^8$  A/s.

# 5 New advanced techniques

## 5.1 Computer-assisted TMS

In currently available commercial TMS systems the coil is positioned manually above the head, the location of the coil being determined on the basis of skull landmarks. Although TMS is used enthusiastically, users strongly criticise the difficulties of focusing the activation in desired targets. Because of the large coils and manual placement, the reproducibility and repeatability are often poor.

Computer-assisted stereotactic TMS is under development at the HUCH BioMag Laboratory. The essence of computer-assisted TMS is an intelligent user-interface, by aid of which the operator may plan, perform, monitor and document the experiments in a controlled and reproducible manner. An important part of the software is the calculation of the electric field induced in the brain. Stereotactic stimulus targeting is made possible by 3D localisation of the coil/coils with respect to the head and by displaying the MR images on the computer screen. The BioMag system is realised using a motorised coil holder and frameless stereotaxy based on a 3D electromagnetic pointer. The concept of computer-assisted TMS is illustrated in Fig. 6.



FIGURE 6. Computer-assisted TMS. System comprises gantry, patient chair, computer, control and power electronics circuits and power source. One or a few coils may be used, or an array of many coils.

Computer-assisted TMS enables new useful concepts for brain research. Stereotactic targeting allows stimulation of a given location in the cortex or a given anatomical structure. For instance, the functional organisation of the brain can be studied with a greatly improved spatio-temporal resolution. The stimulus may be modified both spatially and temporally during tasks in order to identify the cortical areas that are necessary for the task and the order in which they process the data.

In computer-assisted TMS, information from brain imaging techniques can be used in planning the stimulation parameters as well as in the display and interpretation of the results. In particular, digitisation of the coil position on the MRI provides anatomical information of the stimulated location [83,102], which enables stereotactic TMS, that is, precise stimulation of selected anatomical locations. Stereotaxy allows selection of the stimulation intensity level on the basis of calculating the actually induced electric field in the target area instead of defining it as a percentage of the maximum stimulator output or motor threshold. Frameless stereotaxy system and stimulus targeting software have been realised in the BioMag Laboratory.

The merging of TMS with functional neuroimaging tools provides additional benefits. The concurrent use of TMS with PET, fMRI and EEG has already been demonstrated for the study of connectivity maps and the reactivity of the stimulated cortex [18,127,Publication VIII]. Likewise, MEG can give the location of specific cortical functional units in advance.

#### 5.2 Multichannel TMS

Multichannel TMS [64], theoretically examined in Publication VII, refers to the use of multiple independently controlled stimulating coils. It has a number of advantages over stimulation with one coil, offering an alternative solution for stereotactic TMS. One can stimulate multiple loci in one shot, or with short delay between the pulses. The operator can also alleviate the nuisance caused by the activation of undesired structures by suppressing the field at selected locations. Moreover, it is possible to quickly scan brain regions since the coils need not to be moved during scanning. The use of multiple coils improves the mapping resolution since the stimulating field can be made more concentrated. The shaping of the field can be effectively solved using the MNE procedure described in Publication VII and chapter 3.1.2.

Publication VII analysed the properties of multichannel TMS; Fig. 7 shows some of the results. Coil size is an important factor that determines the focality and the power required to obtain a given stimulation intensity; the number of coils is less important, yet significant. The focality depends

on the location of the target point with respect to the coils, being the best below points where the coils touch each other. Multichannel TMS can clearly improve the focality; with the present commercial single-coil devices the focality is  $10-15 \text{ cm}^2$ , while levels of a few cm<sup>2</sup> are attainable with multiple small coils. The focality is improved at the cost of increased power consumption.



FIGURE 7. Left: Focality of cap-shaped array as function of number of coils n. Coil diameter is between 15 and 40 mm. Right: Normalised power required to induce a given peak value of **E**. Adapted from Publication VII.

Multichannel TMS can also be used to produce sham stimulation by selecting the coil currents so that the electric field induced in the brain is small, but the subjective sensations due to scalp stimulation and coil click can be predicted to be similar to real TMS [147].

The main drawback of multichannel TMS is that it is much more expensive than computer-assisted stereotactic TMS with one coil. This is because the power electronics design as well as the power source and mechanical construction are more complicated.

#### 5.3 TMS-compatible EEG

The brain's electrical activity related with the TMS pulse can be detected with EEG [2,32,84,97,151]. The EEG amplifiers are, however, prone to external disturbance and in the studies cited the recording of the EEG to TMS has been possible only using 2 to 3 electrodes located so that the disturbance from the TMS pulse is little.

Publication VIII presents a TMS-compatible EEG system. The BioMag high-resolution EEG system allows free positioning of all its 60 electrodes

[66]. The EEG is artefact-free in just a few ms after the stimulus pulse; problems with the artefacts are dealt with sample-and-hold circuits that pin the amplifier outputs at a constant level during the TMS pulse [158]. Scalp burns resulting from the eddy current in the electrodes can be avoided using low-conductivity materials. The electrodes are optimally small and have a cut that interrupts the path of the eddy current [142].

Concurrent use of TMS and EEG has three basic uses. 1) EEG can be used to locate the neuronal activity elicited by TMS, and its spread to other regions, so as to determine reactivity and connectivity patterns. 2) One can study how the brain processes information from the periphery by determining temporo-spatially the effects of TMS on evoked and eventrelated potentials (EPs and ERPs). 3) EEG can be used when TMS is applied as a treatment to monitor for any abnormality, or to control on-line the efficacy of the treatment. Many more applications will become feasible with better understanding of the interaction of the TMS fields and the neurones, and of the head as a volume conductor.



FIGURE 8. Contour maps of scalp potentials recorded with 60-channel EEG after left motor cortex TMS. Activity is drawn at selected latencies between 9 and 29 ms post-stimulus time. The contour spacing is 0.4  $\mu$ V; negative potentials are shaded. The inter-stimulus interval was 2 s and 150 EEG responses to TMS at an intensity slightly below motor threshold (90% MT) were averaged. In the drawings, the head is seen from above, the nose pointing up.

Publication VIII displayed the distribution and spread of the TMS-

evoked EEG activity when the parietal or occipital lobe was stimulated. Figure 8 shows the scalp potential distribution elicited by TMS over the left hand-motor area from one healthy subject. As in Publication VIII, the early activity is dominantly near the stimulated regions. After that, also the opposite hemisphere becomes activated, indicating transcallosal signal transmission. At later time points, not shown in Fig. 8, interpretation of the activation patterns becomes complicated since many cortical regions are active simultaneously and there will be also evoked potentials due to the activation of the scalp and of the auditory pathways.

# 6 Safety

TMS has been used since 1985; today, thousands of stimulators are in use. The present understanding is that single-pulse TMS is safe, if general guidelines are respected. However, high-frequency rTMS may have undesired effects (seizures, pain from muscle contraction, arm jerking, crying, transient hemianopia). New guidelines for TMS and rTMS are needed since in the last few years the number of pulses has risen from hundreds to thousands in one examination [19].

## 6.1 Known adverse effects

Some immediate side effects to TMS are known. Seizure induction is the most serious of them. Single-pulse TMS has produced seizures in patients [28,47,62,75], but never in healthy subjects. In epileptic patients, there is to date only one report of seizure definitely triggered by singlepulse TMS [28]. Instead, rTMS at rates of several Hz has caused seizures even in volunteers with no neurological problems or history of epilepsy [24,99,123,165].

A frequent harmless, but uncomfortable, effect is a mild headache, which is probably caused by the activation of scalp and neck muscles. The headache may persist after the end of stimulation session and responds well to mild analgesics.

TMS is accompanied by loud clicking sound from the coil that can exceed 100 dB near the coil [152]. Most sound energy is in the frequency range 2–7 kHz. The noise may exceed criteria limits for sensorineural

hearing loss [31].

It is assumed that harmful effects of TMS are related to the induced electric field, since the body tissue is transparent to low-frequency magnetic fields. Heating of the brain is of the order of  $10^{-6}$  °C/pulse and unlikely to cause deleterious effects [5]. Theoretical maximum power dissipation from rTMS in the whole brain is about 3 mW/Hz [39]. Mild burns from scalp electrodes [123] can be avoided using special-designed electrodes [142].

Many tests, including blood pressure, pulse rate, balance, gait and serum prolactin and cortisol levels [71,123,166], have revealed no statistically significant changes after TMS. The same is true for cognitive tests; naturally, naming and verbal fluency tasks can be transiently disturbed by TMS. Documented consistent changes include at least a lateralised effect on immune functions (T-lymphocytes) [4] and changes in thyroidstimulating hormone levels after prefrontal stimulation [53].

Spontaneous EEG following TMS has been found to be normal. Izumi *et al.* [69] reported slowing of the EEG at 150 ms post-TMS and other changes lasting 400–600 ms, but these findings are not necessarily relevant for the safety of TMS since similar changes are caused by sensory stimuli. Generally, EEG is not a good test of safety since it is not sensitive to mild or additive cellular dysfunction. However, monitoring of the EEG during rTMS may be useful in order to stop the experiment if abnormalities appear.

The few existing histopathological studies have not found any definite TMS-related changes. In one study, rTMS (2,000 pulses at 20 Hz) was performed in two patients who were assigned to temporal lobectomies because of medically intractable epilepsy [48]. Histologic study of the surgical specimen did not show any lesions attributable to TMS. Most animal models have failed to find negative effects from TMS [169]. One study in rats reported microvacuolar changes when using very high stimulus intensities [94]; these findings have been criticised by other authors [163]. A study in the cat did not reveal any acute adverse changes following TMS, assessed by cortical blood flow, blood pressure and heart rate measurements [46].

## 6.2 Guidelines

Guidelines for safe TMS and rTMS have not been conclusively established. The following text lists some general recommendations. For reviews, see Refs. [136,163].

In the USA, clinical investigations for the FDA (Food and Drug Administration) approval of TMS are underway, but prompt FDA approval is unlike. According to the FDA, TMS at frequencies of  $\geq$  1 Hz always carries significant risk, whereas certain studies using lower frequencies may not [163].

Protocols should exclude individuals with intracranial metallic or magnetic objects. The magnetic field of the TMS coil will attract ferromagnetic objects and repel nonmagnetic conductors. This force increases quickly with size and conductivity of the object. TMS should never be administered in the vicinity of any implanted electronic devices, since it may disturb their function.

The experimenter should take into account possible seizures when working with single-pulse TMS in patients and always with rTMS. Already when designing experiments, one should keep in mind the great medical and social impact that a seizure may have on the subject's wellbeing. Generally, spread of excitation in the brain can lead to tonic-clonic seizures. For safe rTMS, there is a tradeoff between the maximum stimulus intensity and the pulse rate: it has been recommended that the excitability spread is avoided if at 100% of motor threshold (MT) the pulse rate is below 10 Hz and at 150% MT below 1 Hz [123,163,166]. The duration of the inter-train interval and the number of trains changes the safe limits, at least when the inter-train interval is less than 5 s [24].

When stimulating non-motor areas, it is important to note that strong brain activation can occur without subjective sensations or other observable effects. It is more adequate to limit TMS on the basis of the calculated electric field intensity and distribution. There is no experience of the seizure threshold with widespread activation such as might be available with a whole-scalp TMS array.

Hearing protection aids are recommended for both the examiner and the patient, although safety regulations would allow 1,000–10,000 pulses daily [152]. The new devices by Magstim Company are reasonably quiet, so that hearing protection is normally unnecessary.

Since voltages of up to 4 kV can be present in the TMS equipment, the coil must never be connected or disconnected before the capacitor is fully discharged. The coils and cables should be regularly checked for visible failures. The stimulator case must be opened by authorised persons only.

It is extremely important for the future of TMS/rTMS that the experimenters document all harmful effects and the stimulation parameters that produced them. If possible, rTMS experiments should be videotaped and the EEG recorded. Good documentation is crucial for the updating of guidelines for safe use.

# 7 Applications

Recording of motor-evoked potentials (MEPs) has made TMS a routine tool to probe the conduction of the brain's descending motor pathways. Interest in TMS is now rapidly increasing also in the basic research: TMS has already been used, *e.g.*, to transiently suppress visual detection, halt speech, induce verbal memory errors, impair learning, localise cerebral functions and explore cortical excitability and intracortical connectivity.

This section briefly outlines selected clinical and therapeutic applications as well as uses in basic brain research [25,40,114,160]. Magnetic stimulation of the PNS is not considered here.

### 7.1 Clinical use

Since the first TMS studies the clinical focus has been on measuring the excitability thresholds and motor conduction in patients with motor deficits. TMS has revealed altered excitability thresholds and response latencies in several clinical circumstances, including multiple sclerosis [7], motor neurone disease [16] and cervical spondylosis [20]. TMS has provided new significant information about many diseases, but, at least presently, the diagnostic value of TMS is limited because it lacks sensitivity [56].

Since motor deficits are common in stroke and head and spinal injuries, TMS may be used to acquire objective evidence as to the severity of pyramidal tract damage [85,112]; this complements the anatomical evidence derived from CT and MRI, and the clinical evidence based on the acute impairment. It has been suggested that TMS responses would reflect the prognosis of recovery from stroke, at an early stage [130].

TMS may provide a quick and inexpensive way of locating functionally important cortical areas in patients assigned to brain surgery [82,103,104,168]. Likewise, rTMS can be used to lateralise speech [74,164], although the reliability has been called into question [99].

TMS shows promise in pharmaceutical research because TMS-related indices can give additional evidence of the functional efficacy of medication, the indices being, for instance, spatio-temporal changes in the cortical reactivity and excitatory and inhibitory responses. In their pioneering study, Ziemann *et al.* [170] observed consistent changes in specific TMS responses when the type of epileptic medication was changed (GABAergic *vs.* sodium channel–blocking drugs). Similarly, Puri *et al.* [129] found accelerated TMS responses in untreated schizophrenia, pointing up the potential additional value of TMS in psychiatric disorders.

#### 7.2 Basic brain research

In cognitive and behavioural sciences, TMS is used to turn off noninvasively the function of specific cortical regions to produce temporarily artificial lesions. This allows functional identification of areas of the brain that are important for the given task. Earlier, such studies were limited to animals or human individuals with pathology. In studies of how the brain processes external input, TMS may be used to impair performance by disturbing relevant signals, but also to improve performance by disturbing irrelevant and competing signals [161].

Pioneering studies have used TMS to study, for instance, the encoding of objects and space in memory [107], visual pathways [3,14,100], speech [33,156], and callosal connections [32,98]. Plasticity of the cortical topography has been studied with TMS in patients suffering from stroke [21,58] or amputations [76] as well as in normal volunteers. Using rTMS, it was recently shown that the visual cortex in the blind processes functionally relevant information [30]. Also, rTMS has been used to show plasticity of the finger representation area during learning of a finger tapping task [122].

## 7.3 Therapeutic use

A recent revolutionary finding is that rTMS may have therapeutic potential in patients with medication-resistant depression. George *et al.* [52] reported robust benefit in 2 and slight benefit in 2 of 6 patients; Pascual-Leone *et al.* [124] found remarkable benefit in 11 of 17 patients lasting at least some weeks. Other studies have reproduced the effects [51,77]. In the depression therapy trials some 1,000 pulses of 10-Hz rTMS have been administered daily to the left dorsolateral prefrontal cortex for several consecutive days. Interestingly, in healthy subjects rTMS to left prefrontal areas appears to have an opposite effect, triggering crying [99,120].

Despite promising results, the efficacy of rTMS in depression treatment has so far not been clinically proven. The debate on how to affirmatively assess its efficacy is underway. However, rTMS may challenge electro-convulsive therapy (ECT) [77].

Treatment with TMS has been studied also in several psychiatric disorders, including schizophrenia [50] and obsessive-compulsive disorder [55]. Therapeutic applications may evolve also in the neurological field. Repetitive TMS may speed up movements [125] and reset tremor [126] in Parkinson's disease and reduce spasticity in multiple sclerosis [113]. Moreover, it has been speculated that rTMS at 1 Hz could have a normalising effect on excitability threshold in epileptogenic regions [166].

# 8 Summary

Transcranial magnetic stimulation (TMS) refers to excitation of the human brain by means of electromagnetic induction, allowing one to interfere non-invasively with the function of the cerebral cortex. TMS is well-established in the investigation of many neurological conditions that affect the motor pathways. In addition, TMS shows great promise in basic brain research, creating transient functional lesions in healthy volunteers. Moreover, various therapeutic applications are presently evolving that employ trains of TMS pulses.

In this thesis, models of the central physical and engineering aspects underlying TMS were developed. Two principal realms were studied. First, the calculation of the macroscopic electromagnetic fields due to TMS was explored. Publications I and II derived a model that describes the macroscopic fields in cylinder-shaped volume conductors, whereas Publication III investigated the spherical head model. Second, the neuronal responses resulting from the macroscopic field were considered. Publication IV compared the theory with experimental results from peripheral nerve stimulation, providing new direct evidence of how and where the neurones are activated. Publication V compared the locating of the sensorimotor cortex with TMS and MEG, finding a fairly good agreement, which information provides invaluable evidence of the locus of TMS activation and suggests that TMS can be used in locating the motor cortex.

As a second major effort of the thesis, models were used as a starting point towards more effective TMS instrumentation. Publication VI presented a procedure to optimise stimulator coils, the results indicating that the presently available coils are far from being optimal. Publication VII derived the mathematical theory for the effective use of multiple TMS coils, advantage of which is improved targeting and focusing of stimulation. Publication VIII demonstrated the feasibility of concurrent use of TMS and EEG, one of the applications being the mapping of functional connections in the brain.

In conclusion, sound physical theories are the cornerstone of any significant progress in TMS instrumentation. For instance, while frameless stereotaxy is gradually becoming the standard way of locating the TMS coil with respect to anatomical structures, precise targeting of the stimulation to predefined cortical loci is not possible without modelling the actually realised electromagnetic fields. Important advances also come along with the merging of TMS with other neuroimaging tools. In fact, combined use of different methods is a shared trend in brain imaging and in clinical neuroscience.

# List of references

- [1] Abdeen MA and Stuchly MA. Modeling of magnetic field stimulation of bent neurons. *IEEE Trans Biomed Eng.* **41**, 1092–1095. 1994.
- [2] Amassian VE, Cracco RQ, Maccabee PJ and Cracco JB. Cerebello-frontal cortical projections in humans studied with the magnetic coil. *Electroenceph clin Neurophysiol.* 85, 265–272. 1992.
- [3] Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell A and Eberle L. Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroenceph clin Neurophysiol.* 74, 458–462. 1989.
- [4] Amassian VE, Henry K, Durkin H, Chice S, Cracco JB, Somasundaram M, Hassan N, Cracco RQ, Maccabee PJ and Eberle L. Human immune functions are differentially affected by left-sided versus right-sided magnetic stimulation of temporo-parieto-occipital cortex. *Neurology.* 44 (Suppl 2), A133. 1994.
- [5] Barker AT. An introduction to the basic principles of magnetic nerve stimulation. *J Clin Neurophysiol.* 8, 26–37. 1991.
- [6] Barker AT, Freeston IL, Jalinous R and Jarratt JA. Clinical evaluation of conduction time measurements in central motor pathways using magnetic stimulation of the human brain. *Lancet.* 1, 1325–1326. 1986.
- [7] Barker AT, Freeston IL, Jalinous R and Jarratt JA. Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery*. 20, 100–109. 1987.
- [8] Barker AT, Garnham CW and Freeston IL. Magnetic nerve stimulation: the effect of waveform on efficiency, determination of neural membrane time constants and the measurement of stimulator output. *In* Levy WJ, Cracco RQ, Barker AT and Rothwell JC. Editors. *Magnetic Motor Stimulation: Basic Principles and Clinical Experience*. Amsterdam: Elsevier Science. 227–237. 1991.
- [9] Barker AT, Jalinous R and Freeston I. Non-invasive magnetic stimulation of the human motor cortex. *Lancet.* **1**, 1106–1107. 1985.
- [10] Barlow HB, Kohn HL and Walsh EG. Visual sensations aroused by magnetic fields. Am J Physiol. 148, 372–375. 1947.
- [11] Bartholow R. Experimental investigations into the functions of the human brain. *Am J Med Sci.* **67**, 305–313. 1874.
- [12] Basser PJ and Roth BJ. Stimulation of myelinated nerve axon by electromagnetic induction. *Med Biol Eng Comput.* **29**, 261–268. 1991.
- [13] Basser PJ, Wijesinghe R and Roth BJ. The activating function for magnetic stimulation derived from a three-dimensional volume conductor model. *IEEE Trans Biomed Eng.* **39**, 1207–1210. 1992.
- [14] Beckers G and Zeki S. The consequences of inactivating areas V1 and V5 on visual motion perception. *Brain.* 118, 49–60. 1995.

- [15] Beer B. Über das Auftrafen einer objective Lichtempfindung in magnetischen Felde. *Klin Wochenschr.* 15, 108–109. 1902.
- [16] Berardelli A, Inghilleri M, Cruccu G, Mercuri B and Manfredi M. Electrical and magnetic transcranial stimulation in patients with corticospinal damage due to stroke or motor neurone disease. *Electroenceph clin Neurophysiol.* 81, 389–396. 1991.
- [17] Bickford RG and Fremming BD. Neural stimulation by pulsed magnetic fields in animals and man. *6th Int Conf Med Electr Biol Eng.* Tokyo. Abstract 7-6. 1965.
- [18] Bohning DE, Shastri A, Nahas Z, Lorberbaum JP, Andersen SW, Dannels WR, Haxthausen EU, Vincent DJ and George MS. Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation. *Invest Radiol.* 33, 336–340. 1998.
- [19] Brown P. Shocking safety concerns. *Lancet.* **348**, 959. 1996.
- [20] Brunholzl C and Claus D. Central motor conduction time to upper and lower limbs in cervical cord lesions. *Arch Neurol.* 51, 245–249. 1994.
- [21] Caramia MD, Iani C and Bernardi G. Cerebral plasticity after stroke as revealed by ipsilateral responses to magnetic stimulation. *Neuroreport.* 7, 1756–1760. 1996.
- [22] Carter N and Zee DS. The anatomical localization of saccades using functional imaging studies and transcranial magnetic stimulation. *Curr Opin Neurol.* 10, 10– 17. 1997.
- [23] Cerri G, De Leo R, Moglie F and Schiavoni A. An accurate 3-D model for magnetic stimulation of the brain cortex. J Med Eng Technol. 19, 7–16. 1995.
- [24] Chen R, Gerloff C, Classen J, Wassermann EM, Hallett M and Cohen LG. Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Electroenceph clin Neurophysiol.* **105**, 415–421. 1997.
- [25] Chokroverty S. Magnetic Stimulation in Clinical Neurophysiology. Boston: Butterworth. 1990.
- [26] Chokroverty S, Deutsch A, Guha C, Gonzalez A, Kwan P, Burger R and Goldberg J. Thoracic spinal nerve and root conduction: a magnetic stimulation study. *Muscle Nerve.* 18, 987–991. 1995.
- [27] Chokroverty S, Flynn D, Picone M, Chokroverty M and Belsh J. Magnetic coil stimulation of the human lumbosacral vertebral column: site of stimulation and clinical applications. *Electroenceph clin Neurophysiol.* 89, 54–60. 1993.
- [28] Classen J, Witte OW, Schlaug G, Seitz RJ, Holthausen H and Benecke R. Epileptic seizures triggered directly by focal transcranial magnetic stimulation. *Electroenceph clin Neurophysiol.* **94**, 19–25. 1995.
- [29] Cohen D and Cuffin BN. Developing a more focal magnetic stimulator. Part I: some basic principles. J Clin Neurophysiol. 8, 102–111. 1991.

- [30] Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Faiz L, Dambrosia J, Honda M, Sadato N, Gerloff C, Catalá MD and Hallett M. Functional relevance of cross-modal plasticity in blind humans. *Nature*. 389, 180–183. 1997.
- [31] Counter SA, Borg E and Olofsson A. Oto-traumatic effects of computer simulated magnetic coil impulse noise: analysis of mechanisms. *Acta Oto-Laryngol.* 113, 699–705. 1993.
- [32] Cracco RQ, Amassian VE, Maccabee PJ and Cracco JB. Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. *Electroenceph clin Neurophysiol.* 74, 417–424. 1989.
- [33] Cracco RQ, Amassian VE, Maccabee PJ and Cracco JB. Flow of symbolic visual information from retina to vocalization. 6th Symp on Clinical Use of Magnetic Stimulation. Kyoto, Japan. 28–30. 1995.
- [34] Cros D, Day TJ and Shahani BT. Spatial dispersion of magnetic stimulation in peripheral nerves. *Muscle Nerve*. **13**, 1076–1082. 1990.
- [35] Cuffin BN and Cohen D. Magnetic fields of a dipole in special volume conductor shapes. *IEEE Trans Biomed Eng.* 24, 372–381. 1977.
- [36] d'Arsonval A. Dispositifs pour la mesure des courants alternatifs de toutes fréquences. *C R Soc Biol. (Paris).* **3**, 450–457. 1896.
- [37] D'Inzeo G, Esselle KP, Pisa S and Stuchly MA. Comparison of homogeneous and heterogeneous tissue models for coil optimization in neural stimulation. *Radio Sci.* 30, 245–253. 1995.
- [38] Day BL, Thompson PD, Dick JP, Nakashima K and Marsden CD. Different sites of action of electrical and magnetic stimulation of the human brain. *Neurosci Lett.* 75, 101–106. 1987.
- [39] De Leo R, Cerri G, Balducci G, Moglie F, Scarpino O and Guidi M. Computer modelling of brain cortex excitation by magnetic field pulses. *J Med Eng Technol.* 16, 149–156. 1992.
- [40] Devinsky O. Electrical and magnetic stimulation of the central nervous system. Historical overview. Adv Neurol. 63, 1–16. 1993.
- [41] Dunlap K. Visual sensations from the alternating magnetic field. *Science*. **33**, 68–71. 1911.
- [42] Durand D, Ferguson S and Dalbasti T. Effect of surface boundary charge on neuronal magnetic stimulation. *IEEE Trans Biomed Eng.* 39, 58–64. 1992.
- [43] Eaton H. Electric field induced in a spherical volume conductor from arbitrary coils: application to magnetic stimulation and MEG. *Med Biol Eng Comput.* 30, 433–440. 1992.
- [44] Esselle KP and Stuchly MA. Quasi-static electric field in a cylindrical volume conductor induced by external coils. *IEEE Trans Biomed Eng.* 41, 151–158. 1994.
- [45] Esselle KP and Stuchly MA. Cylindrical tissue model for magnetic field stimula-

tion of neurons: effects of coil geometry. *IEEE Trans Biomed Eng.* **42**, 934–941. 1995.

- [46] Eyre J, Flecknell P, Kenyon B, Koh T and Miller S. Acute effects of electromagnetic stimulation of the brain on cortical activity, cortical blood flow, blood pressure and heart rate in the cat: an evaluation of safety. *J Neurol Neurosurg Psychiatry*. 53, 507–513. 1990.
- [47] Fauth C, Meyer BU, Prosiegel M, Zihl J and Conrad B. Seizure induction and magnetic stimulation after stroke. *Lancet.* 339, 362. 1992.
- [48] Gates JR, Dhuna A and Pascual-Leone A. Lack of pathological changes in human temporal lobe after transcranial magnetic stimulation. *Epilepsia.* 33, 504–508. 1992.
- [49] Geddes LA. History of magnetic stimulation of the nervous system. J Clin Neurophysiol. 8, 3–9. 1991.
- [50] Geller V, Grisaru N, Abarbanel JM, Lemberg T and Belmaker RH. Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. *Prog Neuro-Psychopharm & Biol Psychiatry.* 21, 105–110. 1997.
- [51] George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, Greenberg BD, Hallett M and Post RM. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry.* **154**, 1752–1756. 1997.
- [52] George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, Hallett M and Post RM. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport.* 6, 1853–1856. 1995.
- [53] George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, Hallett M and Post RM. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. *J Neurophychol Clin Neurosci.* 8, 172–180. 1996.
- [54] Grandori F and Ravazzani P. Magnetic stimulation of the motor cortex theoretical considerations. *IEEE Trans Biomed Eng.* **38**, 180–191. 1991.
- [55] Greenberg BD, George MS, Martin JD, Benjamin J, Schlaepfer TE, Altemus M, Wassermann EM, Post RM and Murphy D. Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. *Am J Psychiatry*. **154**, 867–869. 1997.
- [56] Hallett M. Transcranial magnetic stimulation: a useful tool for clinical neurophysiology. Ann Neurol. 40, 344–345. 1996.
- [57] Hallett M, Cohen LG, Nilsson J and Panizza M. Differences between electrical and magnetic stimulation of human peripheral nerve and motor cortex. *In Chok*roverty S. Editors. *Magnetic Stimulation in Clinical Neurophysiology*. Stoneham, MA: Butterworth. 275–287. 1990.

- [58] Hamdy S, Aziz Q, Rothwell JC, Singh KD, Barlow J, Hughes DG, Tallis RC and Thompson DG. The cortical topography of human swallowing musculature in health and disease. *Nature Med.* **2**, 1217–1224. 1996.
- [59] Hämäläinen M and Sarvas J. Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data. *IEEE Trans Biomed Eng.* 26, 165– 171. 1989.
- [60] Hämäläinen MS and Ilmoniemi RJ. Interpreting magnetic fields of the brain: minimum norm estimates. *Med Biol Eng Comput.* **32**, 35–42. 1994.
- [61] Heller L and van Hulsteyn DB. Brain stimulation using electromagnetic sources: theoretical aspects. *Biophys J.* 129–138. 1992.
- [62] Hömberg V and Netz J. Generalised seizures induced by transcranial magnetic stimulation of motor cortex. *Lancet.* **2**, 1223. 1989.
- [63] Hyodo A and Ueno S. Nerve excitation model for localized magnetic stimulation of finite neuronal structures. *IEEE Trans Magn.* **32**, 5112–5114. 1996.
- [64] Ilmoniemi RJ and Grandori F. Device for applying a programmable excitation electric field to a target. Patent FI/100458 (issued 15.12.1997), patent pending EP/94203134. Filed 13.10.1993.
- [65] Ilmoniemi RJ, Hämäläinen MS and Knuutila J. The forward and inverse problems in the spherical model. *In* Weinberg H, Stroink G and Katila T. Editors. *Biomagnetism*, *Applications and Theory*. New York: Pergamon Press. 278–282. 1985.
- [66] Ilmoniemi RJ, Karhu J, Ruohonen J and Virtanen J. Method and apparatus for mapping cortical connections. Patent pending FI/964387 and PCT/FI97/00664. Filed 30.10.1996.
- [67] Ilmoniemi RJ, Ruohonen J, Kamppuri J and Virtanen J. Stimulator head and method for attenuating noise from the stimulating coil. Patent pending FI/974371. Filed 28.11.1997.
- [68] Irwin DD, Rush S, Evering R, Lepeschkin D, Montgomery B and Weggel R. Stimulation of cardiac muscle by a time-varying magnetic field. *IEEE Trans Magn.* 6, 321–322. 1970.
- [69] Izumi S, Takase M, Arita M, Masakado Y, Kimura A and Chino N. Transcranial magnetic stimulation-induced changes in EEG and responses recorded from the scalp of healthy humans. *Electroenceph clin Neurophysiol.* **103**, 319–322. 1997.
- [70] Jackson JD. Classical Electrodynamics. New York: John Wiley & Sons. 1975.
- [71] Jahanshahi M, Ridding MC, Limousin P, Profice P, Fogel W, Dressler D, Fuller R, Brown RG, Brown P and Rothwell JC. Rapid rate transcranial magnetic stimulation—a safety study. *Electroenceph clin Neurophysiol.* 105, 422–429. 1997.
- [72] Jalinous R. Technical and practical aspects of magnetic stimulation. J Clin Neurophysiol. 8, 10–25. 1991.
- [73] Jalinous R. Guide to Magnetic Stimulation. Magstim Company Ltd. 1997.

- [74] Jennum P, Friberg L, Fuglsang–Frederiksen A and Dam M. Speech localization using repetitive transcranial magnetic stimulation. *Neurology*. **44**, 269–273. 1994.
- [75] Kandler R. Safety of transcranial magnetic stimulation. *Lancet.* 335, 469–470. 1990.
- [76] Kew JJM, Ridding MC, Rothwell JC, Passingham RE, Leigh PN, Sooriakumaran S, Frackowiak RSJ and Brooks DJ. Reorganization of cortical blood flow and transcranial magnetic stimulation maps in human subjects after upper limb amputation. *J Neurophysiol.* 72, 2517–2524. 1994.
- [77] Kirkcaldie M, Pridmore S and Reid P. Bridging the skull: electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) in psychiatry. *Convulsive Ther.* 13, 83–91. 1997.
- [78] Kobayashi M, Ueno S and Kurakawa T. Importance of soft tissue inhomogeneity in magnetic peripheral nerve stimulation. *Electroenceph clin Neurophysiol.* 105, 406–413. 1997.
- [79] Kolin A, Brill NQ and Broberg PJ. Stimulation of irritable tissues by means of an alternating magnetic field. *Proc Soc Exp Biol Med.* 102, 251–253. 1959.
- [80] Kong JA. *Theory of Electromagnetic Waves*. New York: John Wiley & Sons. 1975.
- [81] Krassowska W and Neu JC. Response of a single cell to an external electric field. *Biophys J.* 66, 1768–1776. 1994.
- [82] Krings T, Buchbinder BR, Butler W, Chiappa KH, Jiang HJ, Rosen BR and Cosgrove GR. Stereotactic transcranial magnetic stimulation: correlation with direct electrical cortical stimulation. *Neurosurgery.* 41, 1319–1326. 1997.
- [83] Krings T, Naujokat C and Graf v Keyrserlink D. Representation of cortical motor function as revealed by stereotactic transcranial magnetic stimulation. *Electroenceph clin Neurophysiol.* **109**, 85–93. 1998.
- [84] Kujirai T, Sato M, Rothwell JC and Cohen LG. The effect of transcranial magnetic stimulation on median nerve somatosensory evoked potentials. *Electroenceph clin Neurophysiol.* 89, 227–234. 1993.
- [85] Lewko JP, Tarkka IM and Dimitrijevic MR. Neurophysiological assessment of the motor and sensory spinal pathways in chronic spinal cord injury. *Restor Neurol Neurosci.* 7, 225–234. 1995.
- [86] Liu JL and Faust U. Analysis of coil parameters for magnetic stimulation. *Techn Health Care.* 2, 43–52. 1994.
- [87] Maass J and Asa M. Contactless nerve stimulation and signal detection by inductive transducer. *IEEE Trans Magn.* 6, 322–326. 1970.
- [88] Maccabee PJ, Amassian VE, Cracco RQ and Eberle LP. Mechanisms of neuromagnetic stimulation of peripheral nerve. *In Nilsson J, Panizza M and Grandori F.* Editors. *Advances in Magnetic Stimulation: Mathematical Modeling and Clinical Applications.* Pavia, Italy: Salvatore Maugeri Foundation. 117–128. 1996.

- [89] Maccabee PJ, Amassian VE, Cracco RQ, Eberle LP and Rudell AP. Mechanisms of peripheral nervous system stimulation using the magnetic coil. *Electroenceph clin Neurophysiol Suppl.* 43, 344–361. 1991.
- [90] Maccabee PJ, Amassian VE, Eberle L and Cracco RQ. Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerves in vitro: locus of excitation. J Physiol. 460, 201–219. 1993.
- [91] Maccabee PJ, Amassian VE, Eberle L, Rudell A, Cracco RQ, Lai K and Somasundaram M. Measurement of the electric field induced into inhomogeneous conductors by magnetic coils: application to human spinal neurogeometry. *Electroenceph clin Neurophysiol.* 81, 224–237. 1991.
- [92] Magnusson CE and Stevens HC. Visual sensations created by a magnetic field. Am J Physiol. 29, 124–136. 1911.
- [93] Mathis J, Seemann U, Weyh T, Jakob C and Struppler A. The boundary effect in magnetic stimulation. Analysis at the peripheral nerve. *Electroenceph clin Neurophysiol.* 97, 238–245. 1995.
- [94] Matsumiya Y, Yamamoto T, Yarita M, Miyauchi S and Kling JW. Physical and physiological specification of magnetic pulse stimuli that produce cortical damage in rats. J Clin Neurophysiol. 9, 278–287. 1992.
- [95] McNeal DR. Analysis of a model for excitation of myelinated nerve. *IEEE Trans Biomed Eng.* 23, 329–337. 1976.
- [96] Merton PA and Morton HB. Stimulation of the cerebral cortex in the intact human subject. *Nature*. **285**, 227. 1980.
- [97] Meyer BU and Röricht S. Scalp potentials recorded over the sensorimotor region following magnetic stimulation over the cerebellum in man: considerations about the activated structures and their potential diagnostic use. *J Neurol.* **242**, 109–112. 1995.
- [98] Meyer BU, Röricht S and Woiciechowsky C. Topography of fibers in the human corpus callosum mediating interhemispheric inhibition between the motor cortices. Ann Neurol. 43, 360–369. 1998.
- [99] Michelucci R, Valzania F, Passarelli D, Santangelo M, Rizzi R, Buzzi AM, Tempestini A and Tassinari CA. Rapid-rate transcranial magnetic stimulation and hemispheric language dominance: usefulness and safety in epilepsy. *Neurology*. 44, 1697–1700. 1994.
- [100] Miller MB, Fendrich R, Eliassen JC, Demirel S and Gazzaniga MS. Transcranial magnetic stimulation: delays in visual suppression due to luminance changes. *Neuroreport.* 7, 1740–1744. 1996.
- [101] Mills KR. Magnetic brain stimulation: a tool to explore the action of the motor cortex on single human spinal motoneurons. *Trends Neurosci.* 14, 401–405. 1991.
- [102] Miranda PC, de Carvalho M, Conceicao I, Sales Luis ML and Ducla-Soares E. A new method for reproducible coil positioning in transcranial magnetic stimulation

mapping. Electroenceph clin Neurophysiol. 105, 116-123. 1997.

- [103] Morioka T, Mizushima A, Yamamoto T, Tobimatsu S, Matsumoto S, Hasuo K, Fujii K and Fukui M. Functional mapping of the sensorimotor cortex: combined use of magnetoencephalography, functional MRI, and motor evoked potentials. *Neuroradiol.* 37, 526–530. 1995.
- [104] Morioka T, Yamamoto T, Mizushima A, Tombimatsu S, Shigeto H, Hasuo K, Nishio S, Fujii K and Fukui M. Comparison of magnetoencephalography, functional MRI, and motor evoked potentials in the localization of the sensory-motor cortex. *Neurol Res.* 17, 361–367. 1995.
- [105] Mouchawar GA, Nyenhuis JA, Bourland JD and Geddes LA. Guidelines for energy-efficient coils: coils designed for magnetic stimulation of the heart. *Electroenceph clin Neurophysiol Suppl.* 43, 255–267. 1991.
- [106] Mouchawar GA, Nyenhuis JA, Bourland JD, Geddes LA, Schaefer DJ and Riehl ME. Magnetic stimulation of excitable tissue: calculation of induced eddycurrents with a three-dimensional finite-element model. *IEEE Trans Magn.* 29, 3355–3357. 1993.
- [107] Muri RM, Rivaud S, Vermersch AI, Leger JM and Pierrot-Deseilligny C. Effects of transcranial magnetic stimulation over the region of the supplementary motor area during sequences of memory-guided saccades. *Exp Brain Res.* 104, 163–166. 1995.
- [108] Nagarajan SS and Durand DM. Analysis of magnetic stimulation of a concentric axon in a nerve bundle. *IEEE Trans Biomed Eng.* **42**, 926–933. 1995.
- [109] Nagarajan SS and Durand DM. A generalized cable equation for magnetic stimulation of axons. *IEEE Trans Biomed Eng.* 43, 304–312. 1996.
- [110] Nagarajan SS, Durand DM and Hsuing-Hsu K. Mapping location of excitation during magnetic stimulation: effects of coil position. *Ann Biomed Eng.* 25, 112– 125. 1997.
- [111] Nagarajan SS, Durand DM and Warman EN. Effects of induced electric fields on finite neuronal structures: a simulation study. *IEEE Trans Biomed Eng.* 40, 1175– 1188. 1993.
- [112] Netz J, Lammers T and Hömberg V. Reorganization of motor output in the nonaffected hemisphere after stroke. *Brain.* 120, 1579–1586. 1997.
- [113] Nielsen JF, Klemar B, Hansen HJ and Sinkjaer T. A new treatment of spasticity with repetitive magnetic stimulation in multiple sclerosis. J Neurol Neurosurg Psychiatry. 58, 254–255. 1995.
- [114] Nilsson J, Panizza M and Grandori F. Advances in Magnetic Stimulation: Mathematical Modeling and Clinical Applications. Pavia, Italy: Salvatore Maugeri Foundation. 1996.
- [115] Nilsson J, Panizza M, Roth BJ, Basser PJ, Cohen LG, Caruso G and Hallett M. Determining the site of stimulation during magnetic stimulation of a peripheral

nerve. Electroenceph clin Neurophysiol. 85, 253-264. 1992.

- [116] Nyenhuis JA, Mouchawar GA, Bourland JD and Geddes LA. Energy considerations in the magnetic (eddy-current) stimulation of tissues. *IEEE Trans Magn.* 27, 680–687. 1991.
- [117] Olney RK, So YT, Goodin DS and Aminoff JA. A comparison of magnetic and electrical stimulation of peripheral nerves. *Muscle Nerve*. **13**, 957–963. 1990.
- [118] Öberg PÅ. Magnetic stimulation of nerve tissue. Med Biol Eng Comput. 11, 55– 64. 1973.
- [119] Panizza M, Nilsson J, Roth BJ, Grill SE, Demirci M and Hallett M. Differences between the time constant of sensory and motor peripheral nerve fibres: further studies and considerations. *Muscle Nerve.* 21, 48–54. 1998.
- [120] Pascual-Leone A, Catalá MD and Pascual-Leone Pascual A. Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. *Neurology.* 46, 499–502. 1996.
- [121] Pascual-Leone A, Cohen LG, Brasil-Neto JP and Hallett M. Non-invasive differentiation of motor cortical representation of hand muscles by mapping of optimal current directions. *Electroenceph clin Neurophysiol.* 93, 42–48. 1994.
- [122] Pascual-Leone A, Grafman J and Hallett M. Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science*. 263, 1287–1289. 1994.
- [123] Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, Valls-Solé J, Brasil-Neto JP, Wassermann EM, Cohen LG and Hallett M. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroenceph clin Neurophysiol.* 89, 120–130. 1993.
- [124] Pascual-Leone A, Rubio B, Pallardo F and Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet.* 348, 233–237. 1996.
- [125] Pascual-Leone A, Valls-Solé J, Brasil-Neto JP, Cohen LG and Hallett M. Akinesia in Parkinson's disease. I. Shortening of simple reaction time with focal, singlepulse transcranial magnetic stimulation. *Neurology*. 44, 884–891. 1994.
- [126] Pascual-Leone A, Valls-Solé J, Toro C, Wassermann EM and Hallett M. Resetting of essential tremor and postural tremor in Parkinson's disease with transcranial magnetic stimulation. *Muscle Nerve.* 17, 800–807. 1994.
- [127] Paus T, Jech R, Thompson CJ, Comeau R, Peters T and Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *J Neurosci.* 17, 3178–3184. 1997.
- [128] Polson MJR, Barker AT and Freeston IL. Stimulation of nerve trunks with timevarying magnetic fields. *Med Biol Eng Comput.* 20, 243–244. 1982.
- [129] Puri BK, Davey NJ, Ellaway PH and Lewis SW. An investigation of motor func-

tion in schizophrenia using transcranial magnetic stimulation of the motor cortex. *Brit J Psychiatry.* **169**, 690–695. 1996.

- [130] Rapisarda G, Bastings E, de Noordhaut AM, Pennisi G and Delwaide PJ. Can motor recovery in stroke patients be predicted by early transcranial magnetic stimulation. *Stroke.* 27, 2191–2196. 1996.
- [131] Rattay F. Analysis of models for external stimulation of axons. *IEEE Trans Biomed Eng.* 33, 974–977. 1986.
- [132] Rattay F and Aberham M. Modeling axon membranes for functional electrical stimulation. *IEEE Trans Biomed Eng.* 40, 1201–1209. 1993.
- [133] Reilly JP. Peripheral nerve stimulation by induced electric currents: exposure to time-varying magnetic fields. *Med Biol Eng Comput.* **27**, 101–110. 1989.
- [134] Ren C, Tarjan PP and Popovic DB. A novel electric design for electromagnetic stimulation—the Slinky coil. *IEEE Trans Biomed Eng.* 42, 918–925. 1995.
- [135] Rimpiläinen I, Pyykkö I, Blomstedt G, Kuurne T and Karma P. The site of impulse generation in transcranial magnetic stimulation of the facial nerve. Acta Oto-Laryngol. 113, 339–344. 1993.
- [136] Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lücking CH, Maertens de Noordhout A, Marsden C, Murray N, Rothwell JC, Swash M and Thomberg C. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroenceph clin Neurophysiol.* **91**, 79–92. 1994.
- [137] Roth BJ. Mechanisms for electrical stimulation of excitable tissue. Crit Rev Biomed Eng. 22, 253–305. 1994.
- [138] Roth BJ and Basser PJ. A model of the stimulation of a nerve fiber by electromagnetic induction. *IEEE Trans Biomed Eng.* 37, 588–597. 1990.
- [139] Roth BJ, Cohen LG, Hallett M, Friauf W and Basser PJ. A theoretical calculation of the electric field induced by magnetic stimulation of a peripheral nerve. *Muscle Nerve.* 13, 734–741. 1990.
- [140] Roth BJ, Maccabee PJ, Eberle LP, Amassian VE, Hallett M, Cadwell J, Anselmi GD and Tatarian GT. In vitro evaluation of a 4-leaf coil design for magnetic stimulation of peripheral nerve. *Electroenceph clin Neurophysiol.* 93, 68–74. 1994.
- [141] Roth BJ, Momen S and Turner R. Algorithm for the design of magnetic stimulation coils. *Med Biol Eng Comput.* 32, 214–216. 1994.
- [142] Roth BJ, Pascual-Leone A, Cohen LG and Hallett M. The heating of metal electrodes during rapid-rate magnetic stimulation: a possible safety hazard. *Electroenceph clin Neurophysiol.* 85, 116–123. 1992.
- [143] Roth BJ, Saypol JM, Hallett M and Cohen LG. A theoretical calculation of the field induced in the cortex during magnetic stimulation. *Electroenceph clin Neu*-

rophysiol. 81, 47–56. 1991.

- [144] Rothwell JC, Burke D, Hicks D, Stephen J, Woodforth I and Crawford M. Transcranial electrical stimulation of the motor cortex in man: further evidence for the site of activation. *J Physiol.* 481, 243–250. 1994.
- [145] Rothwell JC, Day BL and Amassian VE. Near threshold electrical and magnetic transcranial stimuli activate overlapping sets of cortical neurones in humans. J Physiol. 452, 109P. 1992.
- [146] Ruohonen J, Huotilainen M, Korvenoja A, Aronen H, Ilmoniemi RJ, Kahri P, Karp P, Lehmus S, Näätänen R and Virtanen J. Motor maps with whole-head MEG and magnetic stimulation. 3rd Eur Conf Eng Med. Firenze, Italy. 120. 1995.
- [147] Ruohonen J, Ilmoniemi RJ, Ollikainen M and Virtanen J. Method and apparatus for sham magnetic stimulation. Patent pending FI/981595. Filed 10.7.1998.
- [148] Sarvas J. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Phys Med Biol.* 32, 11–22. 1987.
- [149] Saypol JM, Roth BJ, Cohen LG and Hallett M. A theoretical comparison of electric and magnetic stimulation of the brain. *Ann Biomed Eng.* **19**, 317–328. 1991.
- [150] Scivill IJ, Barker AT and Freeston IL. Finite element modelling of magnetic stimulation of the spine. *Proc 18th Ann Int Conf IEEE EMBS*. Amsterdam, the Netherlands. 1996.
- [151] Seyal M, Browne JK, Masuoka LK and Gabor AJ. Enhancement of the amplitude of somatosensory evoked potentials following magnetic pulse stimulation of the human brain. *Electroenceph clin Neurophysiol.* 88, 20–27. 1993.
- [152] Starck J, Rimpiläinen I, Pyykkö I and Toppila E. The noise level in magnetic stimulation. Scand J Audiol. 25, 223–226. 1996.
- [153] Stuchly MA and Esselle KP. Factors affecting neural stimulation with magnetic fields. *Bioelectromagnetics Supplement*. 1, 191–204. 1992.
- [154] Terman FE. Electronic and Radio Engineering. New York: McGraw-Hill Book Company. 1955.
- [155] Thompson SP. A physiological effect of an alternating magnetic field. Proc R Soc Lond [Biol]. B82, 396–399. 1910.
- [156] Tokimura H, Tokimura Y, Oliviero A, Asakura T and Rothwell JC. Speechinduced changes in corticospinal excitability. *Ann Neurol.* 40, 628–634. 1996.
- [157] Ueno S, Tashiro T and Harada K. Localized stimulation of neural tissue in the brain by means of a paired configuration of time-varying magnetic fields. J Appl Phys. 64, 5862–5864. 1988.
- [158] Virtanen J, Ruohonen J, Ilmoniemi RJ and Näätänen R. Instrumentation for measuring electrical brain responses to transcranial magnetic stimulation. Helsinki University of Technology, Applied Electronics Laboratory. Research Report B1. 1998.
- [159] Walsh P. Magnetic stimulation of the human retina. Fed Proc. 5, 109–110. 1946.

- [160] Walsh V. Brain mapping: Faradization of the mind. Curr Biol. 8, R8-R11. 1998.
- [161] Walsh V and Cowey A. Magnetic stimulation studies of visual cognition. *Trends Cogn Sci.* 2, 103–110. 1998.
- [162] Wang W and Eisenberg SR. A Three-dimensional finite element method for computing magnetically induced currents in tissues. *IEEE Trans Magn.* 30, 5015– 5023. 1994.
- [163] Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroenceph clin Neurophysiol.* **108**, 1–16. 1998.
- [164] Wassermann EM, Blaxton TA, Hoffman E, Pascual-Leone A, Hallett M and Theodore WH. Repetitive transcranial magnetic stimulation (rTMS) of the dominant hemisphere can disrupt visual naming as well as speech in temporal lobe epilepsy patients. *Ann Neurol.* 40, T138. 1996.
- [165] Wassermann EM, Cohen LG, Flitman SS, Chen R and Hallett M. Seizure in healthy people with repeated 'safe' trains of transcranial magnetic stimulation. *Lancet.* 347, 825. 1996.
- [166] Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K and Hallett M. Use and safety of a new repetitive transcranial magnetic stimulator. *Electroen-ceph clin Neurophysiol.* **101**, 412–417. 1996.
- [167] Wassermann EM, Wang B, Zeffiro TA, Sadato N, Pascual-Leone A, Toro C and Hallett M. Locating the motor cortex on the MRI with transcranial magnetic stimulation and PET. *Neuroimage*. 3, 1–9. 1996.
- [168] Wunderlich G, Knorr U, Herzog H, Kiwit JCW, Freund H-J and Rudiger JS. Precentral glioma location determines the displacement of cortical hand representation. *Neurosurgery*. 42, 18–27. 1998.
- [169] Yamada H, Tamaki T, Wakano K, Mikami A and Transfeldt EE. Effect of transcranial magnetic stimulation on cerebral function in a monkey model. *Electroenceph clin Neurophysiol.* **97**, 140–144. 1995.
- [170] Ziemann U, Lönnecker S, Steinhoff BJ and Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol. 40, 367–378. 1996.
- [171] Zimmermann KP and Simpson RK. "Slinky" coils for neuromagnetic stimulation. *Electroenceph clin Neurophysiol.* **101**, 145–152. 1996.

# Summary of publications

The author has done the main work that led to the presented mathematical models and has done all simulations and data analysis for Publications I–II and IV–VII and all work concerning peripheral nerve stimulation in Publication III. The author participated in all stages of the work described in Publication VIII. In all publications the first author was responsible for the experimental paradigm and writing the manuscript.

Publications I–V are the result of a collaboration with researchers at CNR (Milan) and Fondazione Maugeri (Castel Goffredo) and San Raffaele Hospital (Milan). Publications VI–VIII are the result of team work at the BioMag Laboratory (Helsinki).

### Publication I

The reciprocity theory is used to derive an analytical solution to calculate the induced field in homogeneous cylinder-like structures. A prolate spheroid is stretched to approximate circular cylinders. The problem is reduced to the calculation of the magnetic flux coupled into the stimulating coil due to a current dipole inside the spheroid. The induced field is given as an infinite series of associated Legendre functions.

#### Publication II

The reciprocity theory is used to derive the formulas for the electric field and its spatial gradient in the unbounded, semi-infinite and spheroidal volume-conductor models. The models are compared in geometrically different situations by changing the size and shape of the spheroid and the size and position of the stimulating coil. The spheroidal boundary influences the induced field distribution only little, but causes a significant drop in the field strength.

#### Publication III

This paper assesses the boundary effects in the sphere, spheroid and semi-infinite models. The spherical boundary reduces the field to 30–100% of the field in the unbounded model, depending on the coil orientation. Computation of the induced electric field involves the discretisation of the flux integral. A method adopted from biomagnetism studies is applied for selecting optimally 12 integration points. The focality of various coils is assessed with the length of a line on which the field falls to 50%.

## Publication IV

An experimental setup is described for checking the validity of the cable theory to predict cellular response to magnetic stimulation. One result is that peripheral nerve stimulation is predominantly caused by the gradient of the electric field along the nerve, but that also the component of the field transverse to the nerve contributes to the excitation.

#### Publication V

This paper presents a comparison of locating the cortical hand motor representation area using MEG and TMS. The results from the localisation are projected on to MRI slices. The results agree to within 10 mm, suggesting that TMS can be used in locating the motor cortex.

#### Publication VI

The coil's internal structure was optimised by selecting where and how the copper windings should be placed to minimise a given parameter, like the power consumption of the stimulator. It is shown that the power levels of today's repetitive stimulators can be significantly reduced using the described procedure. An example of a realistic case is analysed.

#### Publication VII

This study addresses the theory of shaping the TMS excitation field with arrays of coils. Methodologies familiar from MEG are used to solve the TMS field-shaping problem, *i.e.*, the selection of the coils' driving currents so that the induced electric field is similar to a desired field configuration. A few examples are given and benefits to brain research are briefly discussed.

Errata: page 298, 1st line:  $Q = e_k \delta(\mathbf{r})$ , where  $\delta(\mathbf{r})$  is the delta function; page 298, Eq. 6:  $P_i = \int w(\mathbf{r}) \mathbf{P} \cdot \mathbf{L}_i dv$ ,  $p^2 = \int w(\mathbf{r}) \mathbf{P} \cdot \mathbf{P} dv$ . Symbols  $\mathbf{P}$ ,  $\mathbf{J}$  and  $\mathbf{L}$  denote vectors in Eq. 5 and matrices in Eq. 6.

#### Publication VIII

This publication presents the mapping of the brain's electrical responses to TMS with high-resolution EEG. The method allows the determination of corticocortical and callosal connectivity. Pilot experiments were done that demonstrate the detection of the spread of activity from one hemisphere to the other.