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AN ELECTRICAL ENGINEERING PERSPECTIVE ON NEUROMODULATION – CHARACTERISTICS OF THE "MAGNETIC STIMULATION" PROCEDURE

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Clinical neuroscience supports several therapeutic technologies based on the application of electrical stimuli to different areas of the nervous system, with a neuromodulation effect. Among the known procedures, Transcranial Magnetic Stimulation (TMS) is preferred by both practitioners and patients, due to its effectiveness and non-invasive nature.

The paper highlights some technical aspects specific to electrical engineering associated with TMS clinical practice, in order to provide clues regarding the analysis of its operational characteristics and open some optimization perspectives. The content follows several topics such as: (*) brief overview of the TMS principle based on classical electromagnetism; (*) generation of electrical stimuli and efficiency criteria; (*) discussing the concept of "Activation Function"; (*) evaluation of TMS characteristics by numerical analysis. An illustrative case study approach by numerical finite element method analysis is performed on a typical TMS configuration.

Keywords: Neuromodulation; Transcranial Magnetic Stimulation (TMS); Electromagnetic induction; Numerical analysis; Finite Element Method (FEM)

1. Introduction

Experts from different scientific areas – medicine, engineering, exact sciences – have long been performing convergent research to develop the innovative domain of *neural engineering*, aiming to address challenges related to specific nervous system disorders or functional improvement. The history of medicine includes various therapeutic practices based on stimulation of excitable tissue (nervous, muscular, and sensory), performed in a more or less rigorous manner. Only the proper evolution of technologies and communications during the last decades revealed the power of interdisciplinary cooperation. On such foundations, the concept of *neuromodulation* is apt to bring together and enhance

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the value of a large group of interventional technologies and related neurological effects as part of *neural engineering* [1], [2].

The International Neuromodulation Society (INS) [3] was founded in 1989 by a group of physicians from Western Europe; interdisciplinarity was adopted as one of the fundamental principles, first among medical interests and shortly after, adding technical expertise and industry support, needed for the creation and optimization of the required interventional equipment. At the same time, INS quickly enlarged its membership worldwide and funded several national societies that organized joint meetings, scientific events, dissemination sessions, publications, etc., contributing to the very fast-growing profile of this new medical specialty.

One of the most comprehensive definitions of *neuromodulation* is formulated by INS as a new medical field that "*employs advanced medical device technologies to enhance or suppress the activity of the nervous system for the treatment of disease*" and "*these technologies include implantable as well as non-implantable devices that deliver electrical, chemical or other agents to modify brain and nerve cell activity reversibly*" [3]. Although *neuromodulation* began to be known in the early1960s as a class of therapies for pain treatment by deep stimulation of the brain and spinal cord (known as TENS – Transcutaneous Electrical Nerve Stimulation), it rapidly enhanced its interventional area. Now we can see applications for depression, Parkinson's disease, bipolar disorder, metabolic disorders, sphincter control, addiction, epilepsy, and the list is in continuous growth.

The techniques used in neuromodulation are not entirely new; for example, around the turn of the 20th century, various procedures of electrical stimulation (either invasive or non-invasive) were already applied in neuro-psychiatric clinics, and the physicist Jaques Arsène d'Arsonval was performing his famous experiments producing magneto-phosphenes that later inspired a team of British researchers led by A.T. Barker, to launch the Transcranial Magnetic Stimulation (TMS) method in 1985, together with adequate clinical equipment to performing it [4], [5], [6].

Today, clinical neurosciences accept several *therapeutic neuromodulation technologies* and continuously improve them in practice. A selection of such currently known procedures (inspired by recently published literature [7], [8], [9]) follows here the criterion of invasiveness:

- *Non-invasive techniques:* Transcranial Magnetic Stimulation (TMS), Repetitive TMS (rTMS), Deep Brain Stimulation (DBS), Transcranial Direct Current Stimulation (tDCS), Transcranial Electrical Stimulation (TES), Electro Convulsive Therapy (ECT), Transcutaneous Electrical Nerve Stimulation (TENS).
- *Invasive techniques:* Vagus Nerve Stimulation (VNS), Deep Cerebral Stimulation (DCS), Intracortical Electrical Stimulation (ICES).

All the names of the technologies listed above are suggestive in terms of principle and application technique; they have in common the generation of electrical stimuli on nervous circuits, targeted to the site of action (along the axons or at the synaptic sites).

Most medical applications of *neuromodulation* target the central nervous system, especially the brain. The technology is based on the activation or inhibition of neurons - the cell physiology is affected at the level of transmembrane ionic transport, with influence on the transmission through the nervous network of electric signals carrying information; it mainly addresses categories of cells belonging to deep cortical structures (projection neurons, local interneurons, as well as glial cells), which are activated or inhibited in the process. Applied stimuli elicit functional or behavioral responses that can trigger and control *neuroplastic activity* - physiological and pathological plasticity processes are expected to be activated. *Neuroplasticity* explains animal evolution by adaptation to environmental and social conditions and recovery of the nervous system (especially the brain) after injuries; due to life challenges, the nervous system proves its ability to self-reorganize, to change its topology, to enhance or diminish certain functions [10].

As one can observe, the definition of *neuromodulation* and its medical applications listed above point to the advanced technologies and engineering methods, replacing or complementary to targeted pharmaceutical agents (administered for long periods and producing many side effects). Current trends show a preference for non-chemical interventions and for the use of devices capable of generating electric fields targeted precisely to a particular nervous system location. The electrical stimulus is delivered either by galvanic contact (electrodes implanted or applied on the skin) or by the non-invasive method based on electromagnetic induction, commonly referred to as *magnetic stimulation*.

2. Considerations on TMS Procedures

Magnetic stimulation is a method to produce an electric field (and the corresponding stimulus) inside the exposed body, through electromagnetic induction; non-invasiveness is the most appreciated aspect of the therapy, as it avoids surgery, discomfort, and pain and allows external adjustment of stimulus features. The *applicator* (external electric circuit) is inductively coupled with the *receiver* (a conductive target region inside the body), where an electrical current is generated and acts as a stimulus for excitable (mainly nervous) tissue (Fig. 1). Medical applications include stimulation applied to the spinal cord, or the peripheral nervous system, but targeting the cerebral cortex through TMS represents now the most advanced brain modulation technique based on electromagnetic induction.

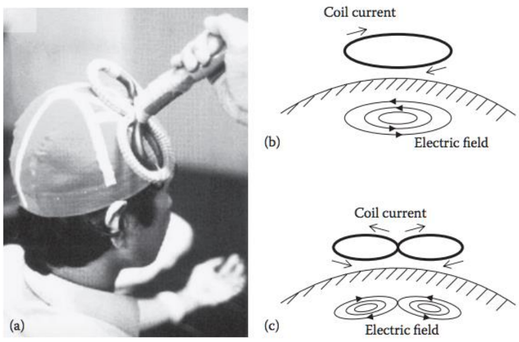


Fig. 1. Basics of TMS applicators: (a) - picture showing a double (figure-of-eight) coil positioned near the head; (b) and (c) - diagrams showing TMS applicators (simple and double current carrying coils) and the effect of electromagnetic induction inside the head, *i.e.,* induced electric field and induced currents (electric stimuli) (picture after [11])

2.1 Physics of the TMS Technology

A glimpse of the practice and effects of TMS is suggestively presented in Fig. 1 [11], while the succession of electromagnetic field phenomena and laws is synthesized in Fig. 2 and explained further.

Magnetic field applicators are inductive elements; various structures are used in TMS applications, from a simple or a double coil to more sophisticated configurations dedicated to specific medical goals. The electric circuit of the applicator, fed by variable current, generates a magnetic field (same waveform as current), following the *magnetic circuit law* (reduced to *Ampère's theorem* in this simplified case). The inductive magnetic field spreads unconstrained into non-magnetic space (such as air and tissues); its amplitude decreases with distance from the applicator.

Faraday's law for electromagnetic induction quantifies the *induction principle* (by magnetic field variation in time, in this case); it is further applied to explain the generation of the induced electric field, which occurs in space, wherever the varying magnetic field is present. The local amplitude depends on the amplitude of the magnetic field and its rate of change over time; still, it is not affected by the physical properties of the local environment, which explains the effective delivery of "the stimulus" through less-conductive tissues such as skin, skull, fat, unlike the case of electrical stimulation. It should be noted that a simplified theory model is shown here, which highlights the main electromagnetic phenomena; only the primary induced electric field $\mathbf{E_{in}}$ is considered (as dominant) in the model, while the reaction components are negligibly small.

The induced electric field generates local current density inside each material (tissue), according to *the conduction (or Ohm's) law*; local current density is proportional to local electrical conductivity σ – good conductors convey higher current densities.

Stimulus or ***Activating function (AF)*** is defined in terms matching the specific electric circuit model used for the cell membrane; for example, *the cable model of axons* (based on the circuit with distributed parameters shown in Fig. 3) operates with:

- $AF = r_e i_s$ in *electrical stimulation*, with r_e - the electric resistance corresponding to the extracellular space around the axon, and i_s – the locally applied stimulation current [12], [13], and
- $AF = \partial E_{in,x} / \partial x$ in *magnetic stimulation,* where only the component of ($\nabla \cdot \mathbf{E_{in}}$) along the direction of the fiber is the active quantity [14], [15]. *AF* depends on the spatial orientation of the induced electric field $\mathbf{E_{in}}$. It could be observed that magnetic stimulation applied to peripheral nerves operates along the axons of motor or sensory neurons; in contrast, in spinal stimulation and TMS, the $\mathbf{E_{in}}$ vector is oriented parallel to the axons of interneurons, which are considered the target of the induced stimulus [11]. The symbols are related to the equations in Fig. 2 and Fig. 3.

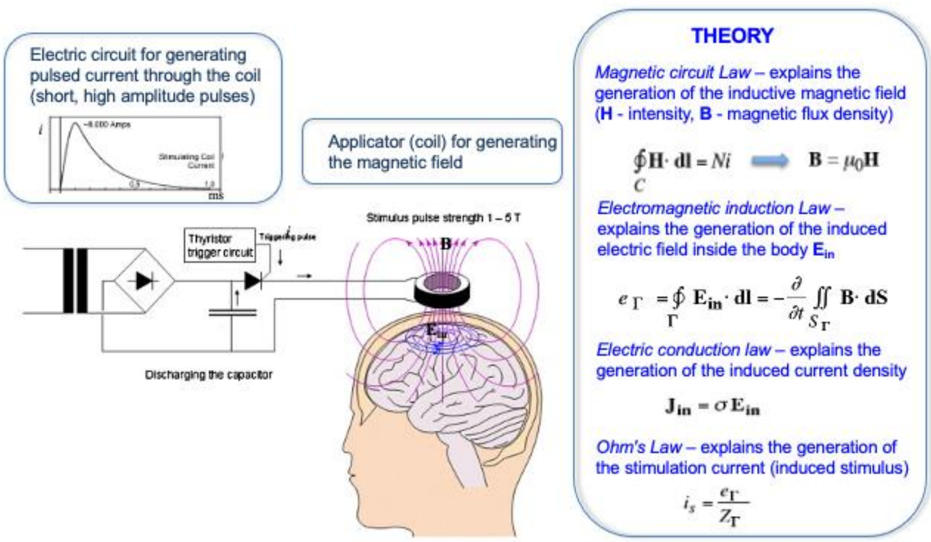


Fig. 2. Principle of TMS when reaction effects are neglected (picture of the circuit after [13])

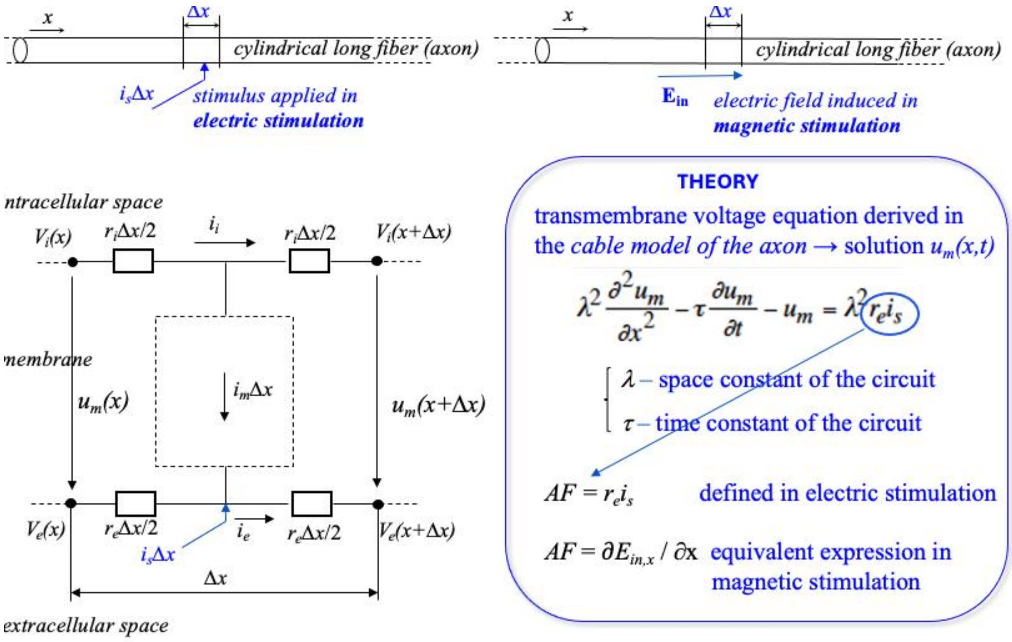


Fig. 3. Electric versus magnetic stimulation in the *cable model of the axon*; definition of *AF* (after [15])

In practice, stimulus quantification is determined by the practitioner following several tests of each patient's reactivity; recordings of signals showing stimulus and reaction are used to determine *a strength-duration* dependence that could provide data on the *stimulus threshold* in the motor response. Different threshold criteria are set in theory, generally based on quantifying the induced electric field distribution. In numerical simulation, it is easier to identify a target volume where a certain quantity of energy is delivered, and literature shows different implementations of effective excitation criteria (over-threshold stimulation) [8].

It is evident from TMS theory that the effectiveness of the stimulus (magnitude at the target) depends on several features provided by the technology: the amplitude of the current through the coil and its rapid rate of change, the number of turns ($N \cdot i$ – the ampere-turns of the applicator), the position of the applicator (orientation and distance to the target inside the brain), the electrical conductivity of the target tissue (σ).

2.2 Technical Aspects in TMS

After testing some neuromodulation technologies in a clinical environment and assessing their efficiency and accessibility, the implementation in clinical practice started to develop on a large scale only after 2008, when the TMS technique received approval from the Food and Drug Administration (FDA - the internationally recognized authority of the US for health-related practices, devices, and substances). In the beginning, FDA approved TMS as a therapy for the treatment of major depression in adults, performed with the Neurostar TMS System, which rapidly became a successful commercial device (DEN070003) [16]. A wide range of protocols based on TMS (classical, repetitive, deep, guided by neuro-navigation, etc.) emerged after 2008 for the treatment of psychiatric and neurological disorders. Psychotherapists, too, have recently begun to include TMS in their neurofeedback protocols. Both practitioners and patients agree on the advantages derived from the non-invasive character of the method [17], [18]. Some other stimulation devices and accessories (commercial systems fabricated by several medical device companies) were rapidly developed and approved worldwide for clinical use, aiming to broaden TMS utility and improve technical aspects of the technology and systems; for example, the paper [1] includes a selection of eight neural engineering devices produced in the US and tailored for specific electrical stimulation goals, which obtained approval from FDA in a short time interval 2013-2018. A suggestive timescale of the technical evolution of clinical TMS devices approved by the FDA is presented in [16]; it highlights the spectacular growth, under our eyes, of this technology addressed to mental health care and based on electrical engineering principles and equipment.

Figure 2 shows the electrical circuit used, in principle, to feed the applicator by a pulsed current. To get such a waveform, it seems necessary to analyze the circuit and properly dimension its elements; Fig. 4 shows the structure of the circuit in more detail. The pulse is obtained when a capacitor C discharges on the R-L load in the circuit, powering the applicator (Fig. 4 left). The dynamic response of the circuit is described by a set of differential equations (Fig. 4 right).

Short monophasic pulses (especially fast-growing, as in Fig. 5.a) are used in various protocols: isolated pulses (1 ms duration, with the peak at 0.1 ms and very high amplitude in the order of kA) as in classical TMS [19], or many successive bursts, like in rTMS - repetitive pulses, either at low frequencies (LF rTMS < 1 Hz) or at high frequencies (HF rTMS > 5 Hz), in trains lasting from seconds to tenths of seconds. One current rTMS protocol is the Theta Burst Stimulation (TBS) using HF bursts mode at 50 Hz in continuous (cTBS) or intermittent (iTBS) trains of pulses, as in Fig. 5.b. [20].

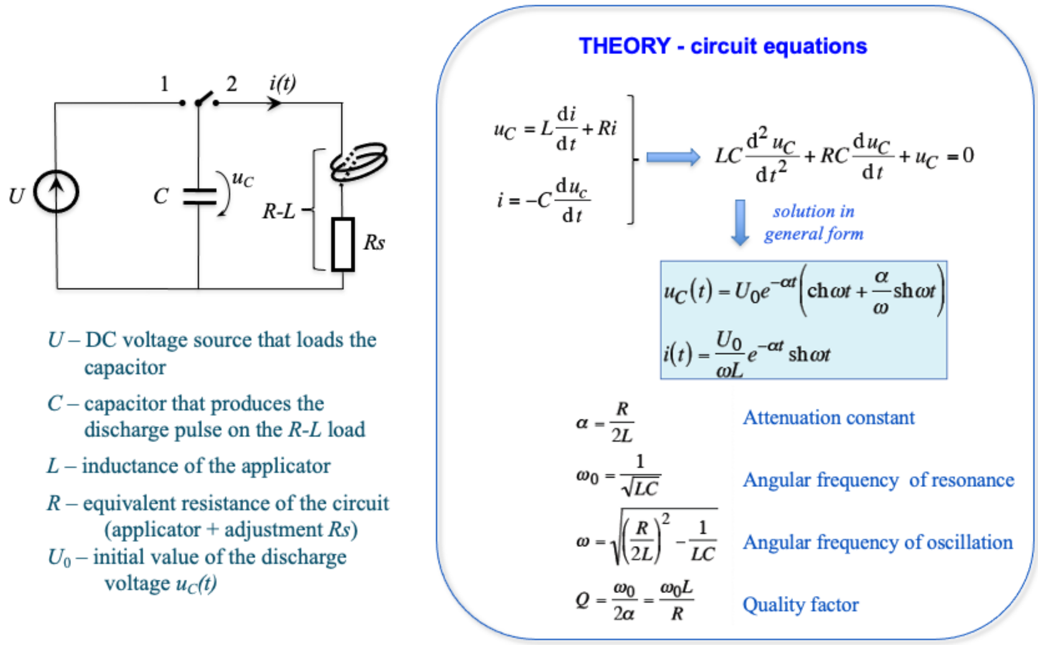
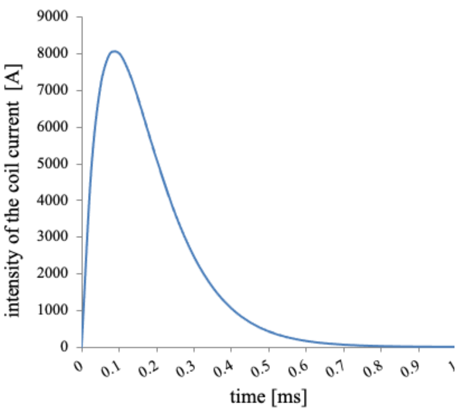


Fig. 4. The electrical circuit producing the pulsed current that powers the applicator and theory of the circuit

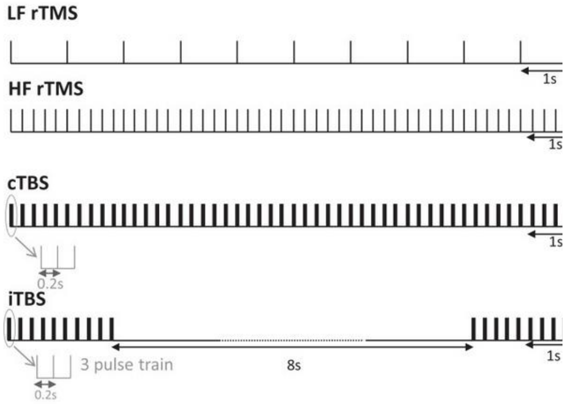
The short monophasic current pulse (as in Fig. 5.a) is best equated by *the critically damped response* of the circuit of Fig. 4, which results for $\alpha = \omega_0$, *i.e.*, $R = 2\sqrt{L/C}$ and $Q = 1/2$. Equation (1) shows the expression of the current, where the coefficients are provided by the appropriate design of the applicator and by the choice of the circuit parameters.

$$i(t) = \frac{U_0}{L}\, t\, e^{-\alpha t} \tag{1}$$

Commercial applicators for TMS are simple coils (circular and figure-of-8 coils, like in Fig. 1 or models shown in [19] or in the promotional documentation provided by the companies), usually made of solid rectangular copper wire and a relatively small number of turns (< 20), encased in insulating material. They generate high-density magnetic flux around the coils (peak values of 1.5 – 2.5 T at the coil's surface) and induce electric fields of 150 – 180 V/m inside the brain at the stimulation zones. The pulsed current waveform allows for brief thermal overloads; there are also models of applicators with forced cooling systems.



a. Monophasic pulse of current
(1 ms, peak: 8 kA at 0.1 ms)



b. Pulsed waveforms for rTMS (up to down): continuous train of pulses (LF rTMS and HF rTMS) and Theta Bursts Stimulation (TBS) (iTBS and cTBS) (after [20])

Fig. 5. Current waveforms through the inductive applicator

For research purposes, the literature proposes a wide variety of shapes and positioning of stimulation coils (e.g., double-cone or batwing coils, or with circuits distributed around the scalp like Halo or Hesed coils), following optimization criteria like targeting deeper zones in the cortex [21], [22], [23], [24], [25], best focalization of the stimulus [26], [27], minimizing side effects such as inhibition (close to stimulation areas), excessive heating of coils and others.

3. Numerical Analysis for the Study of TMS

Numerical analysis of the electromagnetic field problem associated with TMS procedures takes advantage of the research experience (methods and tools) provided by electrical engineering. It successfully replaces experiments for optimizing applicators' design (*i.e.,* finding the best match between the applicator's design and its performance for medical utility) and for preparing personalized therapeutic interventions by simulation. Measurements could not determine *E*-field distribution and other electromagnetic characteristics inside the body, but numerical simulation efficiently provides such data for various applicator configurations.

3.1 Formulation of the Numerical Model

It is common knowledge that simulation models are built on a set of *idealization assumptions* that make the numerical approach possible without significant changes to the realistic representation and provide practical value for medicine.

Electromagnetic problem. The frequency range of the signals involved in most electromagnetic field neuromodulation therapies, including TMS, is in the lower non-ionizing spectrum (< 10 kHz), which is associated with the *quasi-static approximation*; some consequences follow:

- the electric field strength active in stimulation is commonly the result of two factors: electromagnetic induction and interface polarization (as a reaction to the induced electric field); numerical implementation could thus operate with the magnetic vector potential **A** and the electric potential V, as in eq. (2)

$$\mathbf{E} = -\partial \mathbf{A}/\partial t - \nabla V, \text{ where } \mathbf{A} \text{ is introduced by } \mathbf{B} = \nabla \times \mathbf{A}; \tag{2}$$

  if the reaction of induced electric currents is neglected (an assumption suitable especially for homogeneous body models), the electric field equation reflects only induction, and eq. (2) becomes $\mathbf{E} = \mathbf{E_{in}} = -\partial \mathbf{A}/\partial t$;
- numerical implementations commonly solve the magnetic field equation for **A,**

$$\sigma\left(\frac{\partial \mathbf{A}}{\partial t}\right) + \nabla \times \left(\frac{1}{\mu}\nabla \times \mathbf{A}\right) = \mathbf{J_e} \tag{3}$$

  where σ is the electrical conductivity, μ is the magnetic permeability (human tissues are non-magnetic materials $\mu = \mu_0 = 4\pi 10^{-7}$ H/m), and $\mathbf{J_e}$ represents the current density applied externally (*i.e.,* the current density through the applicator);
- the characteristic dimensions of the exposed body are much smaller than both, the penetration depth and the electromagnetic field wavelength; phase and amplitude alteration of the inductive magnetic field are thus negligible, and the electromagnetic field is transmitted by conduction and diffusion, while propagation phenomena are neglected;
- biological tissues are considered relatively good electro-conductive materials (the dielectric nature is insignificant);
- when the current through the applicator has a harmonic waveform, *the time-harmonic operation mode* can be applied with the complex form representation of quantities; if the induction current has a pulsed waveform (Fig. 5.a), the electromagnetic field problem should be solved in *the transient operation mode*.

Computational domain and Boundary conditions. Numerical simulation in TMS requires representing the magnetic field source (applicator) and the exposed body (head, preferably with its realistic shape and anatomical structure). Since the electrical circuits (coils) and human tissues are good electric conductors compared with the air, their boundaries are electrically insulated ($\mathbf{n}\cdot\sigma\mathbf{E} = 0$). All the components inside the domain are non-magnetic materials, allowing the magnetic field to spread freely in space; that is why an artificially set boundary surface should close the entire domain by a *magnetic insulation condition* ($\mathbf{n}\mathrm{x}\mathbf{A} = 0$). Of course, the boundary (*e.g.,* a spherical surface surrounding the head and applicator) should be set far enough from the magnetic field source to perturb field distribution minimally. If the numerical code allows a thin spherical layer with "infinite elements" could mimic free space, providing an economy of numerical resources.

Anatomical structure and Physical properties. The literature currently shows various anatomy representations for use in numerical simulation of TMS, from half-plane and spherical or oval head, with homogeneous or layered anatomical structure, up to realistic head models, with anatomical details built by domain reconstruction from CT or MR images. For example, the importance of accurate anatomical representation is highlighted when stimulation is assessed deep within cortical regions, such as sulci versus gyri locations [28].

Physical properties are assigned according to the model structure: equivalent properties for homogeneous built subdomains and specific values if anatomy components are identified. Biological tissues are non-magnetic, but dielectric properties could be taken from databases with measured electrical conductivity and permittivity for various human and animal tissues over a large frequency spectrum of non-ionizing electric fields [29]. The low-frequency range is of particular interest for TMS, where tissues behave as relatively good electrical conductors; conductivities for some typical head tissues suitable for TMS numerical simulation are shown in Table 1 (from the database [30]); values are constant over the low-frequency range, up to approx. 10 kHz.

Table 1

Electrical conductivities (in S/m) for several head tissues at low frequency (from [30])

Skull / Bone	0.02	Cerebellum	0.12	Fat	0.02
Gray matter	0.1	Cerebrospinal fluid	2	Muscle	0.33
White matter	0.06	Cornea	0.42	Eye vitreous humor	1.5

Magnetic field source. The applicator in TMS needs to be accurately modeled, either the widespread single round coil and the figure-of-eight coil, or one more complicated structure designed to enhance specific features (focalization on deep structures, minimization of side effects, etc.). The magnetic field amplitude and distribution depend primarily on the current, the number of turns and the configuration of the applicator and secondarily on the actual dimensions of wires; in simplified models, coil representation with filiform wires is also acceptable, but precise position relative to the body is required because the current path is significant for the magnetic field distribution.

Numerical method. The Finite Difference Time Domain (FDTD) method and the Impedance Method are often used for electromagnetic analyses in time (especially dynamic regimes); still, there are disadvantages regarding accuracy in representing anatomical details through voxelization. At the same time, the Finite

Element Method (FEM) allows for best realistic representations of geometry (shapes and structures); it is used mainly for steady-state and harmonic problems, but transient analysis is also possible.

3.2 Case Study – FEM Analysis of TMS Electromagnetics

An illustration of some commonly applied ideas in numerical simulation, along with a study tracing the waveforms of the primary electromagnetic quantities involved in TMS, is presented next. The case study concerns a model of the human head under the impact of a circular stimulation coil fed by a pulsed current, and the numerical analysis is performed by FEM in Comsol Multiphysics. The results are intended to verify the overall performance of the procedure in a transient analysis.

Significant design data. The human head is represented by a numerical model derived from the Specific Anthropomorphic Mannequin (SAM) described in the EN 62209-1:2005 standard. The inhomogeneous head geometry is adapted here from a homogeneous model of the Comsol library, adding significant anatomical elements with equivalent electrical conductivities: skull, eyeballs (with vitreous humor-like conductivity), and brain (with grey matter-like conductivity) (Table 1). The circular coil is similar to Magstim 200 models [19], having 14 turns, 50/110 mm inner/outer diameters, and 17.5 mm height. For convenience, the study starts by positioning the coil symmetrically above the head, as in Fig. 6. A spherical surface bounds the computation domain at a sufficient distance from the head and coil so as not to constrain the magnetic field distribution; some tests have been performed to satisfy this condition reasonably, especially concerning the magnetic field distribution inside the head.

Application mode. The *transient analysis* is selected in the low-frequency domain of electromagnetic field problems (AC/DC) and eq. (3) is solved for the magnetic vector potential. The current density through the coil $\mathbf{J}_e$ is given as a function of time, similar to eq. (1), where the respective current follows the pulsed waveform shown in Fig. 5.a (pulse duration - 1 ms, fast rising phase, peak - 8 kA at 0.1 ms). The amplitude of $\mathbf{J}_e$ results as an equivalent for uniform current distribution over the entire cross-sectional area of the coil, neglecting reaction effects.

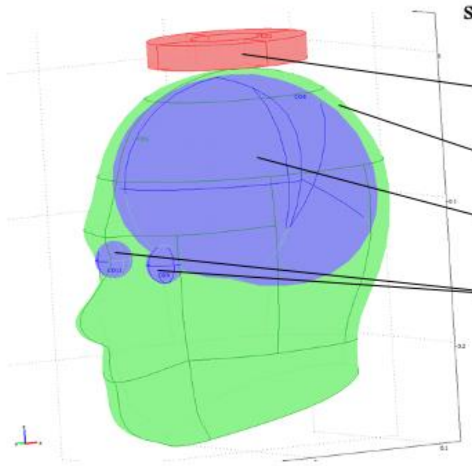
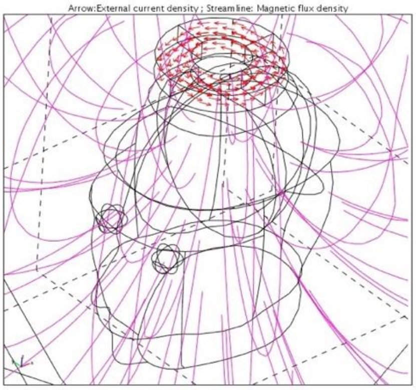


Fig. 6. Model of the human head (derived from the SAM model) and TMS applicator (circular coil)

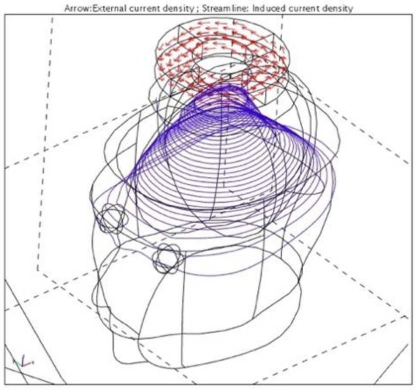
Results. Primary results illustrate the TMS principle in Fig. 7: (a) - magnetic field generation by the current-carrying coil and (b) - induced current density, determined inside the head by electromagnetic induction.

Stimulus localization and focus are essential in TMS. Induced currents follow circular paths, similar to coil projections inside the head, and Fig. 7.b confirms it. In the case of a simple circular coil, the induced electric field and the induced current density reach maximum values in an annular region inside the head, beneath the coil. As a quantitative illustration, Fig. 8 presents linear distributions for the magnitudes of: (a) - *magnetic flux density* $B = |\mathbf{B}| = \sqrt{B_x^2 + B_y^2 + B_z^2}$, and (b) - *induced current density* $J_{in} = |\mathbf{J_{in}}|$ selected at the moment t = 5 μs from the beginning of the pulse; observation lines follow the y direction through the head (parallel to the coil, in the frontal plane) at three distances below the coil (30 mm, 40 mm, 50 mm).

Another interesting result is shown in Fig. 9 and refers to the correlated waveforms of the same fundamental electromagnetic quantities involved in TMS - *magnetic flux density* and *induced current density* - assessed at the same location inside the brain, for the entire duration of the current pulse in the coil (Fig. 5.a). The magnetic flux density has a similar waveform to that of the coil current while its magnitude B decreases with distance from the coil (following *Ampère's theorem*); the strength of the induced electric field $\mathbf{E_{in}}$ is computed by eq. (2), and the induced current density results locally, from the law of electrical conduction ($\mathbf{J_{in}} = \sigma\,\mathbf{E_{in}}$).



a. Current density through the coil (red arrows), magnetic flux density (purple streamlines)



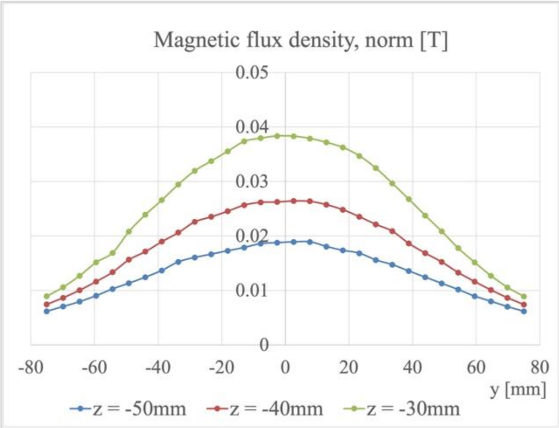
b. Current density through the coil (red arrows), induced current density in the head (blue streamlines)

Fig. 7. Electromagnetic phenomena in TMS: generation of magnetic field and electromagnetic induction effect

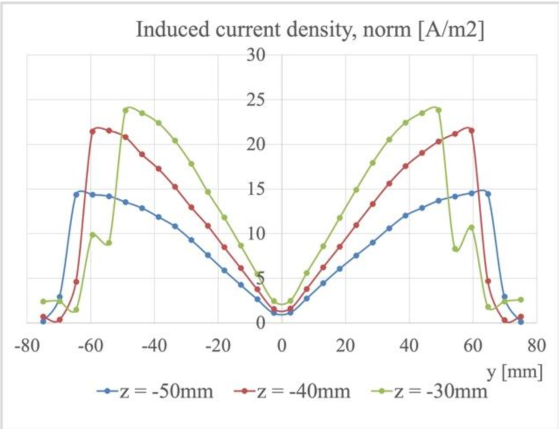
Discussion. The application of *cable theory* based on *AF* quantification (Fig. 3) is less appropriate in TMS than in stimulation of long fibers (spinal or peripheral nerves) due to the complex anatomical structure of the cortex; at the same time, the distribution of the induced current density (J_{in}) appears to be a better indicator of the stimulus.

Although directly related to the coil current (which is the quantity under external control in the TMS process) magnetic field analysis does not provide stimulus-specific information; the waveform and spatial distribution of the stimulus (J_{in}) depend on the waveform of the coil-current and the configuration of the applicator (geometry and position), as shown by correlation of the results in this case study; however, it is clear that the maximum values of the stimulus do not occur at the same locations where B is the largest (Fig. 8), nor when $B(t)$ reaches its peak (0.1 ms as shown in Fig. 9.a).

According to TMS associated electromagnetic theory (sections 2.1 and 3.2) two categories of time evolutions correspond to the quantities involved - **B** and **A** have waveforms similar to *the inductor pulsed current i(t),* while $\mathbf{E_{in}}$ and $\mathbf{J_{in}}$ depend on *the rate of change* (time derivative) of the same current di/dt. This points to the observation that maximum values of J_{in} and B are not synchronized (see waveforms in Fig. 9) and stimulation is most effective during the first instants of the current pulse (t < 0.1 ms). For this reason, t = 5 μs is the time selected to show the results in Fig. 8, considered as relevant for effective stimulation.

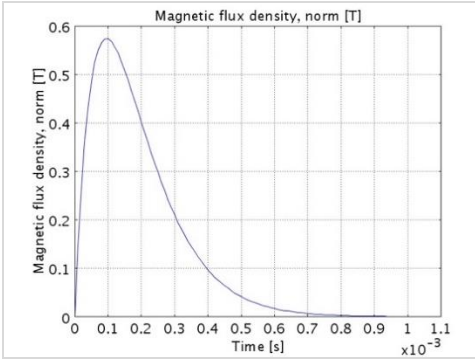


a. Magnetic flux density - $B(y)$

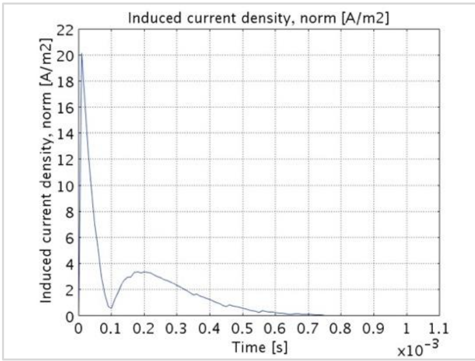


b. Induced current density - $J_{in}(y)$

Fig. 8. Distributions of specific TMS quantities along observation lines crossing the head in the frontal plane, parallel to the coil, for time t = 5μs (distance under the coil: z = -50mm, -40mm, -30mm)



a. Magnetic flux density - $B(t)$



b. Induced current density - $J_{in}(t)$

Fig. 9. Waveforms of TMS quantities during one pulse of the coil current; the values are averaged over a tiny volume of brain tissue centered below the coil (x = 0, y = 30mm, z = -30mm)

The applicator coil and the conductive tissue inside the head are inductively coupled with the specification that the induced current density inside the head is several orders of magnitude (5 – 6) lower than the current density through the inductor coil. Typically, induced electric field strengths above 100 V/m are considered effective in producing nerve stimulation [11], [21], which roughly corresponds to current densities above 10 A/m^2 in the brain.

4. Conclusions

In contemporary times, the rise of neuromodulation techniques is conditioned by:

- the evolution of medical expertise (by the number of practitioners and skills) and patients' access to specialized centers,
- the development of therapeutic technologies (devices and protocols) and their integration into current medical practice (including health insurance coverage).

Engineering will continuously help the domain's growth through the design and fabrication of devices (more efficient, biocompatible, user-friendly) by explaining physical phenomena and processes as much as complex interactions between physiology, anatomic tissues, and electromagnetic fields. In TMS, for example, the distribution of the induced E-field and localization of stimulus are crucial, and measurements cannot determine that type of data. The work presented here highlights the medical utility of theoretical principles, practical approaches specific to electrical engineering, and current technical approaches and skills. Some phenomena of subtle interaction between electromagnetic and biophysical processes could be addressed by numerical simulation, with its collection of specific methodologies and instruments developed and mastered by engineers.

The progress of non-invasive neuromodulation techniques is inconceivable without controlling the distribution of the induced electric field and efficient stimuli inside the human body, which is feasible only by accurate simulation; measurements *in vivo* are practically excluded. Numerical models could be successfully used to develop TMS strategies and therapeutic protocols, becoming valuable tools for optimizing equipment (especially applicators). Using simulation and improving the accuracy of models (detailed anatomy structure and realistic dielectric properties) would also help move forward with more accurate explanations and a deeper understanding of neuromodulation phenomena.

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