Elena Rossi, Alberto Priori, Sara Marceglia

20 Modelization: Theoretical Aspects

Non-invasive cortical stimulation methods (TMS, tDCS) are known to have limitations, including the shunt of the current due to high impedance barriers (scalp and skull) and the difficulty in providing continuous therapies without interfering with normal daily activities, since the stimulating devices are not implanted in the patient (Priori and Lefaucheur 2007). Conversely, extradural cortex stimulation (ECS) and subdural cortex stimulation (SCS) use surgically implantable stimulation systems consisting of electrodes placed epidurally or subdurally and connected to a subcutaneous pulse generator. They have the potential to provide a continuous treatment without limiting patient's activities. In general, cortical stimulation consists of injecting electrical current or voltage through electrode(s) into the head or directly to the brain. The applied field can variously induce a modulated neuronal activation (neuronal firing), a synchronization of neuronal populations, or a change in neuronal excitability. The aim of modeling is to represent the spatial distribution and amplitude of the electrical field injected and to interpret its impact on target brain areas. These studies can improve ECS/SCS clinical outcomes by optimizing electrode design, device implantation and stimulation parameters selection, thus reducing side effects and improving outcomes.

20.1 Computational Modeling Principles

In physics, Maxwell's equation can represent the behavior of the electrical field within the head or brain and we can get, in a quasi-stationary condition, the following Laplace equation defined in the computational head model:

$$\nabla \cdot (\sigma \nabla \varphi) = 0 \text{ in } \Omega \quad (2.I)$$

where: scalar electric potential; ∇ : gradient vector; and σ : tissues' conductivity.

The quasi-static approximation is a valid assumption for typical neural stimulation parameters (Bossetti et al 2008).

This approximation cannot be accurately applied to cases involving Transcranial Magnetic Stimulation (TMS) because the magnetic field generated does not remain constant over time. With cases of TMS, it is necessary to consider the Maxwell-Faraday equation:

$$\nabla \times E = - \frac{\partial B}{\partial t} \quad (2.II)$$

where B is the magnetic field generated by the coil and E the electric field induced into the tissue.

The ideal solution for the Maxwell's equations is analytic, without approximations and continuous in time and space. Unfortunately, from a computational viewpoint, the solution to the purely analytical electromagnetic problem is too expensive and also the modelling of the sources and the transmission medium cannot be completely realistic. For these reasons, the numerical solution of the electromagnetic problem is usually implemented by a computational model. This solution is discrete in the time and in the frequency domains, and it is always affected by approximations. In fact, the numerical solution of differential equations requires the discretization of time and space in appropriate mesh grids consisting of a finite number of elements in which the partial derivatives are replaced by finite differences (that are their numerical approximation). Finite Element Method (FEM), Boundary Element Method (BEM), Finite Integration Technique (FIT) are examples of methods that can be used for the numerical solution of Maxwell's equations.

20.2 Head Model and Tissue Connectivity

The characterization of electrical properties of brain tissue is a fundamental issue for computational modelling methods. Within biological tissues, electric fields drive currents with ohmic (resistive) and displacement (capacitive) components. Ohmic currents are generated by the movement of free charges, such as unbound extracellular sodium and potassium ions, and are measured in terms of electrical conductivity of the medium. Displacement currents are generated by the polarization of paired charges, such as ionic double-layers that surround cellular membranes and/or macromolecules embedded in cellular membranes. *Electrical permittivity* is the measure of this polarization. Impedance measurements in ex-vivo tissues revealed that displacement currents are orders of magnitude smaller than ohmic (Wagner 2004, 2007). In-vivo recordings of the electromagnetic fields generated in brain tissues by TMS (Tay, 1992; Tay et al., 1989) and DBS (Miocinovic et al., 2009) suggest that the stimulatory fields are influenced by both tissue capacitance and resistance. This suggests that past theories of brain stimulation may not fully describe fundamental biophysical processes occurring in neural tissues, which could conversely influence the predicted response and the safety consideration that guide the clinical use of brain stimulation (Wagner et al., 2007). Furthermore, coupled displacement and ohmic mechanisms in the neural tissue could lead to frequency dependent filtering of the applied stimulatory fields, or endogenously generated fields, thus changing the expected distributions. Wagner et al (2014) recorded the in-vivo impedances of brain tissues during neurosurgical procedures and used these results to construct magnetic resonance image (MRI) guided computational models of TMS and DBS. Their results are relevant also to other CS techniques since they are all based on tissue conductivity parameters. They measured the conductivity, σ , and permittivity, ϵ , values of tissues, in the frequency range from 10 to 50000 Hz, in anesthetized animals that can be used

for comparison to the current ex-vivo estimated values. Then they evaluated how these tissue properties affected TMS and DBS stimulatory fields: they constructed MRI guided FEMs of the human head based on the individual tissue impedance properties recorded in-vivo and compared their results with FEMs based on classical ex-vivo impedance values. The recorded impedance properties of the skin, skull, gray matter, and white matter differed substantially compared to past tissue impedance values used for characterizing the fields of neurostimulation. Conductivities were generally within the range of past reported magnitudes used for brain stimulation studies, with a slightly greater frequency response, but permittivities differed greatly in magnitude and frequency response to values typically implemented in neurostimulation modeling ((IFAP), 2007; Foster and Schwan, 1996; Gabriel et al., 1996; Wagner et al., 2004, 2007). Such sizeable differences in the overall permittivity values can be due to the alteration of tissue impedance properties in ex-vivo models where cell are degenerated and/or death. Overall, Wagner et al. (2014) demonstrated that the living tissue carries currents through both dipole and ionic mechanisms, in a frequency-dependent manner. They found also significant alterations of the TMS and DBS field distributions in the brain when comparing the solutions from the in-vivo tissue impedance recordings with those from past ex-vivo values commonly used for modeling brain stimulation. Predicted stimulation thresholds were consistently higher for the in-vivo models compared to those resulting from the ex-vivo tissue systems. The in-vivo systems higher thresholds were due to the increased tissue impedance attenuation of the stimulatory electric fields. The application of these parameters estimated in-vivo may change the results obtained in modeling the effects in other CS techniques and should be considered in future modeling studies.

20.3 Models of Implantable Cortical Stimulation (ICS)

ICS systems consist of epidurally or subdurally placed electrodes connected to an implantable pulse generator. The main difference between epidural cortical stimulation (ECS) and subdural cortical stimulation (SCS) is the electrode placement, right above the dura mater (ECS) and right beneath the dura mater (SCS) respectively. Compared to SCS, ECS is less invasive and safer in inducing seizures (Bezard et al. 1999). However, SCS has more focality and less loss of current, yielding higher efficiency. Conversely, ECS is strongly influenced by the thickness or conductivity of the dura mater (Wongsarnpigoon and Grill 2008). Subdural stimulation is more focused with lower current intensities compared to ECS; SCS however has a higher complication rate due to epileptic seizures, intracerebral hemorrhages and wound infections. In general, stimulation devices can deliver the output current in two different ways: current controlled or voltage controlled stimulation. In current-controlled devices, the user specifies the device output in units of Amperes and the current output will be kept constant while the voltage will be adjusted to keep the current intensity at the

desired level. Conversely, in voltage-controlled devices, the user specifies the device output in units of Volts, and the output voltage will be kept constant while the output current will change according to the tissue impedance. Whereas non-invasive cortical stimulation methods (tDCS and TMS) have been extensively investigated using computational models, there is a lack of reports studying SCS likely due to difficulties in model generation. As explained in Kim et al (2011), the current density distribution (CDD) in invasive CS can be estimated by solving the Laplace equation (2.I) with the following assumptions:

- the Neumann boundary condition is applied to the upper boundary on skull because the electric flux through skull is negligibly small:

$$\mathbf{n} \cdot \mathbf{J} = 0 \text{ on } \partial \Omega_{\text{upper}} \quad (4.I)$$

where $\mathbf{n}$ is the normal vector to the boundary

- The Dirichlet boundary condition is applied to the remaining outer boundaries in the model and the upper boundary on electrode (s) surface:

$$V = 0 \text{ on } \partial \Omega_{\text{other}} \quad (4.II)$$

$$V = V_0 \text{ on } \partial \Psi_{\text{upper}} \quad (4.III)$$

where V_0 is considered as an input value.

In the case of voltage controlled stimulation, when voltage is injected through the electrode and kept constant, the corresponding total current induced over the model can be estimated with the following equation:

$$\begin{aligned} 0 &= \int_{\Omega} \nabla \cdot (\sigma \nabla V) d\mathbf{r} = \int_{\partial \Omega} (\sigma \nabla V) \cdot \mathbf{n} dS \\ &= \int_{\partial \Omega_{\text{upper}}} (\sigma \nabla V) \cdot \mathbf{n} dS + \int_{\partial \Omega_{\text{other}}} (\sigma \nabla V) \cdot \mathbf{n} dS - \int_{\partial \Psi_{\text{upper}}} (\sigma \nabla V) \cdot \mathbf{n} dS \end{aligned}$$

where $\mathbf{n}$ is outward normal vector on the boundary. Since in invasive CS the vector $\mathbf{n}$ is directed inward, the third term changes in sign. Hence, considering the boundary conditions, the current induced by voltage input to the electrodes (output current) is estimated by:

$$I_{\text{output}} = \int_{\partial \Psi_{\text{upper}}} \sigma \frac{dV}{dn} dS = \int_{\partial \Omega_{\text{other}}} \sigma \frac{dV}{dn} dS \quad (4.IV)$$

The total output current is the sum of all currents flowing out of the model's boundaries below the electrode.

20.3.1 Extradural ICS Models

Different studies using human motor cortex finite element models (including detailed anatomical structures such as gyrus and sulci) estimated the spatial distribution of

the stimulation potential in the cortical tissue, that, combined with compartmental neuron models for the simulation, could also be used to estimate the subsequent response of neural elements. These studies demonstrated that many factors can influence the neurons excitability during ECS. The combination of conductor volume models with compartmental neuronal models allowed researchers to evaluate the effects of ECS on neuronal excitation.

20.3.1.1 Electrode Design

Electrode design is a crucial factor that influences the power supplied by the implanted pulse generator (IPG). In order to avoid frequent surgical replacement of battery-depleted IPGs, the electrode design has to reduce power usage. Surgical leads used for ECS have heterogeneous geometry: FEMs can be useful to better understand the impact of electrode's material, geometry, shape and lead's location on device efficiency.

According to Ohm's Law the power consumed by electrode and tissue is equal to

$$i^2 \times Z_{\text{load}}$$

where i is the stimulation current and Z_{load} is the load impedance (series combination of tissue resistance, interface impedance of the working and the return electrodes). Different materials can be used to reduce the electrode impedance. Moreover, by suppressing tissue encapsulation of the implanted electrode during the inflammation process, also the stimulation thresholds can be reduced. The electrode geometry can influence the efficiency of the stimulation by decreasing the power necessary to achieve the same level of cortical excitability. In fact the activation function f of neurons can be considered (Rattay, 1989) proportional to the second spatial derivate of the extracellular potential V_e :

$$f_x \propto \frac{\Delta^2 V_e}{\Delta x^2} = \frac{\Delta J_x}{-\sigma \Delta x}$$

this means that the activating function in the x direction is proportional to the derivative of the current density (J). Wei and Grill (2009) investigated the effects on stimulation efficiency of different electrode geometries. In order to increase the spatial non-uniformity of J , they increased the electrode perimeter (using a serpentine shape) without changing the electrode area. They created FEM models of different electrodes and, to quantify stimulation efficiency, each resulting potential was coupled with cable models of a population of axons. They demonstrated that increasing the perimeter of the electrode results in an increase of the activation function of neurons underneath. Thus, the stimulation efficiency of planar disk electrodes can be improved by high-perimeter designs. However, before this new electrode geometry can be introduced for clinical use, safety aspects have to be considered, as higher current densities on the electrode surface may induce tissue damage (Kronberg and Bikson, 2012). In the specific case of ECS, changing electrode geometry could also

mean varying the distance between contacts of the same epidural lead, the diameter of each electrode or the width of the substrate. The inter-electrode spacing (ISI) can influence not only the spread of stimulation but also the stimulation thresholds: a reduction of the distance between electrodes increases the threshold in motor cortex during bipolar stimulation and decreases it during equipolar stimulation. Also, the diameter of each electrode can influence the threshold amplitude in the underlying gyri. Substrate width has little influence on the threshold of the neurons around the edge of the substrate (Wongsarnpigoon et Grill, 2012).

20.3.1.2 Electrode Position

MEP recording experiments (Wongsarnpigoon et Grill, 2011) showed that the excitability threshold of neurons are lower in primary sites as compared to secondary sites, so that the electrode location over the primary area can reduce the stimulation intensity necessary for cortical excitation (with a consequent reduction of battery consumption). Efficiency of ECS depends not only on the distance of the neuronal populations from the electrode (Wei and Grill 2009), but also on the relative position between the electrode and the underlying sulci or gyri, because deep neurons within sulci have larger stimulation thresholds than those on the crown and lips of the gyri. In general, stimulation thresholds are lowest on the crown or lip of the precentral gyrus beneath the active electrode (Wongsarnpigoon et Grill, 2012). Also the rotation of the lead placed over the central sulcus can alter the stimulation threshold in adjacent gyri (Wongsarnpigoon et Grill, 2012). Wongsarnpigoon and Grill (2008) additionally carried out different simulations varying the thickness of tissues in an extruded slab model of the precentral gyrus, characterized by an anisotropic conductivity in the white matter. Their results showed that, by placing the ECS electrode directly above the gyrus, about half of the stimulus current flowed through the crown of the gyrus while the current density was lower along the banks deep in the sulci.

20.3.1.3 Electrode Polarity

In order to investigate the effect of polarity on the stimulation threshold during ECS, a 3D model of the motor cortex was developed (Wongsarnpigoon et Grill, 2012) and the electric potentials within the cortex were calculated. Since the polarity was expected to affect the responses depending on the neuron orientations, the model was characterized by an anisotropic conductivity: inside the white matter the electrical conductivity was higher in the axial direction because the orientation of the fibers in this tissue is mostly perpendicular to the skull. In order to determine the excitation thresholds, the estimated potentials were applied to a compartmental model of cortical neurons: pyramidal cells (PCs) of layer 3 (L3) and 5 (L5) and thalamocortical axons (TCAs). Anodal and cathodal stimulations had opposite effects. For cathodal stimulation of L3 PCs, thresholds were lower on the bank of the precentral gyrus

than on the crown. Anodal thresholds were lower than cathodal ones on the crown of the precentral gyrus for L3 and L5 PCs, and higher for TCAs. Neurons could be activated by opposite stimulation polarity, according to the orientation of their axons relative to the electrode, as the site of action potential generation is the terminal of the axon. The results of this study demonstrated that thresholds were affected more by neuron orientation than by the reciprocal position between neurons and electrodes. Wongsarnpigoon and Grill (2008, 2012)'s data confirm previous computer modeling studies (Manola et al. 2005) that described a polarity-conditioned excitation of nerve fibers arranged parallel or perpendicular to the electrode surface. These fibers were excitable only by cathodal (parallel) or anodal (perpendicular) stimulation respectively. The same results were obtained using a more detailed compartmental neuron model including the axon, soma and dendritic trunk (Manola et al. in 2007). In general, the introduction of a soma-dendritic model reduced the estimated excitation threshold compared to the simulation results using the simpler axonal model. They however confirmed that anodal stimulation excited neural elements perpendicular to the electrode surface and cathodal stimulation neural element parallel to the electrode surface. Despite different models, the two approaches were consistent in describing the effects of anodal and cathodal stimulation. These models however were made only with separate and independent neurons: a more detailed model with interneurons would be useful to better understand the communication between neurons during anodal and cathodal ECS. Other useful information about the effects of stimulation polarity comes from MEP recording experiments in animals, as done by Wongsarnpigoon and Grill (2011): excitation thresholds for anodal and cathodal ECS were equal when the stimulation electrode was placed over the primary site, whereas over the secondary site cathodal thresholds were significantly lower than anodal thresholds for evoking a response in primary muscle. These result suggest that, *during therapeutic ECS, the polarity and amplitude that are most effective at one location of the cortex may be less effective a few millimeters away.*

20.3.1.4 Monopolar and Bipolar Stimulation

Even though available ECS devices do not yet allow clinicians to fully control the montage (monopolar, bipolar or equipolar), FEM studies reveal that the choice of montage can influence ECS outcomes. During monopolar stimulation, all the electrodes have the same polarity, whereas during bipolar stimulation some electrodes act as anodes (positive polarity) and others as cathodes (negative polarity). Bipolar ECS, employed in most clinical applications, is believed to induce a more focal stimulation over a specific cortical area due to the proximity of the anode and the cathode. Indeed, results from FEM simulations (Wongsarnpigoon et Grill, 2011, 2012) evince that bipolar stimulation increases neuronal threshold compared to monopolar stimulation for neurons beyond the electrodes. The lowest thresholds were identified in the region beneath the electrodes. The non-passive return electrode may be responsible for the

different outcomes observed using bipolar and monopolar stimulations. This result was observed in studies where monopolar ECS of human motor cortex induced larger EMG responses than during bipolar stimulation (Holsheimer et al. 2007). Moreover bipolar or equipolar stimulation produces a confounding effect because the two electrodes stimulate different populations of neurons. During bipolar and equipolar stimulation, one of the two electrodes is sometimes placed on an adjacent gyrus in order to minimize interaction between neurons. However, this configuration is characterized by a lower threshold in the adjacent gyrus compared to the stimulation with the leads parallel to the pre-central gyrus, thus leading to possible ECS side effects. For these reasons, modeling suggests that *the simplest method of stimulation is monopolar or equipolar over the target*.

20.3.1.5 Stimulation Waveform

The stimulation waveform delivered to the tissue depends on the stimulation type (voltage- or current- controlled), the stimulation frequency, and the number of pulses delivered per time unit. The effects of stimulation type were investigated by Wongsarnpigoon and Grill (2008). The neuronal activating function was found to be inversely proportional to the thickness of CSF and dura during voltage controlled stimulation. In case of current controlled stimulation, instead, they found influences only from the thickness of cerebrospinal fluid (CSF) and not from the dura. This means that in *current controlled ECS, treatment outcomes are less affected by individual anatomical features*. However, the thickness of the CSF layer between the dura mater and the cortex beneath the electrode always influences the distribution of the electrical field and the excitation threshold due to its highest electrical conductivity (Manola et al. 2005). A possible explanation of the different level of activation obtained with current controlled or voltage controlled stimulation could be the difference in shape of voltage and current waveforms, due to the capacitive behavior of tissues and the electrode-tissue interface (Merrill et al. 2005). ECS was delivered in anesthetized animal (Wongsarnpigoon et Grill, 2011) in order to investigate the effect of two stimulation parameters (stimulation frequency and number of pulses per train) on the threshold for evoking motor responses. Thresholds were measured for monopolar anodal and cathodal ECS over the primary site and were defined as the amplitude necessary to evoke EMG responses. The result was that the threshold for evoking EMG responses is inversely related to both the parameters analyzed.

20.3.2 Subdural SCS Models

Whereas selective stimulation of neurons located deep within sulci is very difficult with ECS, subdural stimulation (SCS) may allow more localized stimulation of deep neurons in sulci: the location of the electrodes on the cerebral surface and beneath

the dura mater reduces the loss of current in the cerebral spinal fluid (CSF). SCS is generally less frequently used than ECS even though it is more focal. Again, FEM studies can be useful to investigate the effect of different factors on SCS efficiency.

20.3.2.1 The Electrode Factor: Design, Position and Polarity

Kim et al (2012) investigated the effects of three SCS electrode types (disc, ring, and covered-disc) and the stimulation condition (voltage controlled vs current controlled stimulation) in bipolar subdural cortical stimulation (SCS). In the covered-disc, all the sides of the electrode were covered by a substrate; only a metal internal disc on the bottom face of the cylinder was in contact with the cortex. This electrode model is more realistic because the SCS devices used in clinic include an array of electrodes characterized by metal contacts insulated with silicone membranes in order to avoid current leakage into the CSF. Using a MRI-derived 3D realistic head FEM model, the authors proposed three efficiency measures to compare the effectiveness of the stimulation between different stimulation conditions:

- effective depth of penetration: diameter of the region having current density above the effective threshold (for the motor cortex is 2.5A/m^2 at frequency 50Hz, Kowalski et al. 2002).
- effective volume: the volume of the region with current density exceeding the effective threshold
- amount of CSF leakage current: amount of current that flows out to cerebrospinal fluid. CSF leakage current can be computed by the following equation:

$$\iiint_{\Omega} J_{\text{norm}} dV$$

where Ω is the cerebrospinal fluid domain and J_{norm} is the magnitude of the current density. If CSF leakage current is high, much of the current flows to cerebrospinal fluid but not the cortex. Therefore, cerebrospinal fluid leakage current should be reduced in order to have an effective stimulation.

With voltage-controlled stimulation, there was no difference in effectiveness between the disc and ring electrodes. However the minimum leakage current in CSF was obtained with covered-disk electrodes. At the same time this electrode type reduced the volume and the depth of penetration compared to uncovered electrodes, because the substrate layer increased the electrode impedance and consequently reduced the output current. On the contrary, during current-controlled stimulation, the current from the covered-disc did not diffuse in the CSF and penetrated deeper into the cortex, reaching larger stimulation areas. So this study demonstrated that *the optimal SCS condition is a current-controlled stimulation using covered electrodes in order to reduce the current shunt effect into the cerebral spinal fluid and to maximize the efficiency of the stimulation*. For subdural cortical stimulation optimization,

substrate design seems to be a crucial factor, because it can avoid leakage current into the cerebrospinal fluid, but it can also manipulate the amount of output current and the effects of stimulation, especially during voltage controlled stimulation. Both electrode grid location and the activated electrode pair influence the current distribution inside the cortex. Modeled bipolar stimulation with various electrode pairs active inside the subdural electrode grids demonstrated that each current density distribution generated was unique and highly dependent on the distance of the active pair from a gyrus or sulcus (Agarwal et al. 1994).

20.3.2.2 Stimulation Type and Waveform

Seo et al (2013) investigated the effects of monopolar and bipolar SCS on neurons' activation thresholds using a pyramidal neuronal model coupled with a realistic 3D head model (FEM model based on MRI data). Two electrodes were disposed over the gray matter beneath the dura mater and covered with a substrate (conductivity equal to $0.1 \times 10^{-9} \text{ S/m}$); their polarity during monopolar simulation was positive (anodic). This study demonstrated that during monopolar stimulation the neuron excitation threshold was the same underneath both the electrodes, the threshold being lower in the crown. During bipolar simulation, neurons underlying the anode revealed comparable thresholds to the monopolar case, whereas, in the other location, neurons' excitation threshold was higher due to the cathodic influence. In accordance with previous studies (Manola et al. 2005, Manola et al. 2007, Wongsarnpigoon et Grill, 2012) cathodal stimulation preferably excited neurons parallel to the electrode surface. Compared to the extruded slab model (where the thickness of gray matter and depth of sulci were uniform), the estimated thresholds were higher in the realistic head model. According to MRI data, the distance between each electrode and the bottom of the sulcus was not equal and this could be the reason of the difference in estimating the excitability thresholds. Experiments in animals with subdural stimulation of the motor cortex demonstrated that thresholds for visually observed evoked movements were inversely related to the number of pulse per train (NP) and stimulation frequency with thresholds plateaued at 200 Hz (Lilly et al 1952). These results are consistent with ECS experiments.

20.3.3 Comparing ECS and SCS

The first comparison between ECS and SCS was conducted by Kim et al (2011). They developed 3D computational models for respectively epidural and subdural stimulation of the precentral gyrus. For each model, two types of electrode, a disc and a ring electrode, were used and the current density distributions (CDD) were analyzed to compare ECS and SCS. They simulated voltage controlled stimulations so the corresponding current induced could be estimated as I_{output} . The total output current

(I_{output}) in ECS was the sum of currents flowing through the boundaries of the dura mater, CSF, gray matter, and white matter. I_{output} in SCS was the sum of currents flowing out of the boundaries of CSF, gray matter, and white matter, since SCS electrodes were located below the dura mater. Exploring the extent of current density distribution for each CS over various input voltages (1 V, 1.5 V, 2 V, 2.5 V, 3 V), Kim et al showed that SCS produced total output currents about four times larger than those of ECS when the input was 1 V. SCS had effective volumes that were about 6 times larger on average than those of ECS. The difference between effective volumes in the gray and white matter increased with the increase of injected current. *SCS therefore penetrated deeper into the brain than ECS on voltage controlled stimulation.* In terms of current penetration, SCS yielded an average penetration about 3.4 times higher than ECS. The overall difference between the disc and ring electrodes was negligible. This suggested that the ring type can be an advantageous alternative to the disc electrode without significantly reducing effectiveness, since the area available in the middle of the ring can be used for a pH sensor or a sensor for monitoring neural responses to stimuli. *SCS seems hence more effective than ECS for the amount of current both entering the brain cortex and penetrating in depth.* However, SCS requires implanting an electrode beneath the dura mater, while ECS is less invasive. Seo et al (2012) compared ECS and SCS during both monopolar and bipolar stimulation. In this case too, a simple geometrical model restricted to the precentral gyrus was used, but the authors did not find significant differences in the current density distribution between ECS and SCS. The authors described a deeper and wider penetration of the stimulation current during unipolar CS with respect to bipolar CS, in both the epidural and subdural cases. Therefore unipolar stimulation could to be more effective for functional recovery than bipolar. Results from these two studies are opposite, because Seo et al (2012) simulated a constant current condition, whereas Kim et al (2011) compared ECS and SCS under constant voltage condition: this corresponds to different output currents due to different tissue conductivities under the electrode. Hence, *the advantages in terms of penetration and effective volumes of SCS compared to ECS are consistently reduced when using current-controlled stimulation. Current-controlled stimulation can be used in ECS to maximize its effects while keeping the benefits of lower complications and easier electrode positioning.*

20.4 Comparison with Models of Non-Invasive Cortical Stimulation

During both invasive and non-invasive cortical stimulations (CS) there are two critical factors influencing the activation of the target brain tissue: the induced electric field strength and its spatiotemporal distribution. Accurate methods for estimating the brain volumes activated by CS and modeling the interaction between the electric field and the neurons are essential for the optimization of stimulation parameters and for

the repeatability of electrode positions. In the last decade several FEM studies of non-invasive CS were conducted in order to analyze which mechanisms lead to activation of neurons using different stimulation parameters and montages for transcranial Direct Current Stimulation (tDCS) or Transcranial Magnetic Stimulation (TMS). This is the same unsolved issue as for epidural and subdural cortical stimulation. Yet, comparing FEM results in the case of invasive and non-invasive CS, it is possible to extract some common behaviors. One is the impact of gyral geometry on the induced electrical field inside the cortex (Datta et al. 2012). Thielscher et al (2011) used FEM characterized by a high-resolution volume mesh, constructed from T1-weighted structural MR images, in order to obtain an anatomically accurate modeling of the gyrification pattern. Their results demonstrated that the field strength induced by TMS in the gray matter increased up to 51% when the induced currents were perpendicular to local gyrus orientation. This effect was mainly restricted to the gyral crowns and lips, and did not extend into the sulcal walls. This enhancement effect might in part underlie the dependency of stimulation thresholds on coil orientation, as commonly observed in TMS motor cortex studies. In contrast to the clear-cut effects of the gyrification pattern on the induced field strength, current directions were predominantly influenced by the CSF-skull boundary. This latter result has to be considered with caution because charge accumulation and conductivity differences in tissues borders (for instance skin/skull, skull/cerebrospinal fluid, cerebrospinal fluid/gray matter, and gray matter/white matter interfaces) were shown to introduce significant distortions to electric fields generated by TMS in the brain (Chen and Mogul 2010). Another commonality with ECS modeling studies (Wongsarnpigoon and Grill 2012) was the identification of the action potentials initialization area: neurons were especially excitable at the white matter - gray matter boundary. This low threshold zone can be caused by the discontinuity of electrical conductivities, so future studies are necessary to avoid incorrect interpretation of FEM results due to distortions, as in the case of TMS studies. The demonstration that the origin of the low threshold zone is not caused by electrical field distortions injected into the model suggests the development of models characterized by pathological alteration of tissue conductivity (such as ischemic tissue damage) for further improving surgical CS outcomes. FEM results can be validated by performing neurophysiological recordings during motor mapping experiments or analyzing subject behaviors during task performance. In case of non-invasive CS, FEM results were compared with both MEPs and working memory tasks. Opitz et al (2013) measured motor evoked potentials (MEPs) elicited by single-pulse TMS over the motor cortex with different coil orientations and in different locations. Results of neurophysiological recordings and those of personalized modeling (MRI-based FEM simulations) were correlated, thus validating this new approach. Kim et al. (2013) investigated the relationship between the behavioral outcomes of a simple working memory (WM) task and the current density value at the dorsolateral prefrontal cortex (DLPFC) induced by tDCS and simulated using FEM models from individual MRI data. Their results showed that participants with

enhanced WM task performance after tDCS had a significantly larger current density on DLPFC. This outcome suggests that the inconsistent behavioral outcomes of tDCS might be *partially due to the anatomical differences among subjects*. This might also apply to ICS, but further studies must yet be conducted. More realistic human head models should be developed that include tissue anisotropy and individual anatomical differences. In case of non-invasive CS, simulations demonstrated that personalized FEM can improve the spatial targeting accuracy of stimulation. Indeed, both heterogeneity and anisotropy of the conductive medium influence the spatial distribution of the electric field, thus affecting the stimulation site (Miranda et al. 2003). Individual FEM model can be based on subject's structural MRI and DTI image data, describing both anatomical and anisotropic conductivity properties (Opitz et al. 2013). Inter-individual neuroanatomical characteristics can alter CS outcomes, even if the same stimulation protocol (electrode montage and stimulator setting) is used over different subjects. The stimulation montage and parameters defined by the operator and by the subject-specific anatomy can both influence the amount of electrical current that reaches the target area in the brain and the responsiveness of the subject to the treatment. Currently, there is still limited knowledge for the optimization of the "dose" which can be controlled by the operator (Bikson et al., 2008; Peterchev et al., 2012). However, the distribution of current flow in the brain depends not only on the stimulation dose, but also on the underlying anatomy/tissue properties. The same dose applied to different subjects may result in different brain current flow patterns (Chaieb et al., 2008). Furthermore, if one of the subjects has compromised anatomy (i.e., lesions or skull defects), this may lead to activation of other various brain regions and thus to inconsistent clinical outcomes (Wagner et al. 2007, Datta et al. 2010). In the case of non-invasive CS, the use of personalized FEM was crucial for the estimation of the amount of stimulation current that penetrates over the scalp and skull barriers: inter-individual variation of the amount of hairs on the scalp, of the thickness of the skull and of the shape of the head has to be considered during the optimization of non-invasive CS. For ICS, personalized FEM could be useful to improve the modeling of neurons' population localization and orientation or connectivity based on individual MRI data. This new approach may be essential for the investigation of the effects of cortical pathological lesions on surgical CS outcomes. Finally, in case of tDCS, FEM studies provided a quantitative comparison between different electrode montages described in the literature. Since the exact mechanisms through which tDCS acts are still unclear (Creutzfeldt et al 1962, Purpura et al 1965), the electrode montage can vary consistently also for the treatment of the same pathology. In particular, the position of the return electrode influences the treatment outcomes because it is not passive. For this reason, there are two categories of tDCS montages using respectively intra or extra-cephalic references (Parazzini et al. 2013a, 2013b). Similarly, the effect of the return electrode has to be considered for bipolar ICS: future simulations with highly detailed FEM of the cortex, including synaptic connections, beneath the electrode pair could be useful to better

describe the behavioral connection of the two populations of neurons activated respectively by the anode and by the cathode.

20.5 Conclusions

FEM models are an essential tool for the optimization of both invasive and non-invasive CS and suggest future FEM studies for ICS, in order to better describe the shunt effect of the stimulation current inside the cerebrospinal fluid (CSF) and to reduce CSF leakage currents. In case of tDCS, this effect was demonstrated using FEM: a large amount of stimulation current spreads inside the scalp making the stimulation less focal. In order to assist the surgeon in his choice of monopolar or bipolar ICS, further FEM studies investigating the effect of the return electrode location are necessary for the optimization of the montage. FEM simulations demonstrated that outcomes of non-invasive CS are inconsistent among subjects, even if identical protocols are applied, due to inter-individual anatomic variation at the scalp and skull level. In the case of invasive CS the anatomical variation is less, but the electrode position and orientation are more crucial factors for the efficiency of the treatment.

FEM studies for ECS and SCS have revealed important information about the effect of various factors on the treatment outcomes. First of all, the orientation of the neurons can have a greater influence on neurons activation threshold than the location of neurons with respect to the electrode. This result suggests that during therapeutic ECS, the polarity and amplitude that are most effective at one location of the cortex may be less effective a few millimeters away. Moreover the level of activation obtained with current controlled or voltage controlled stimulator settings differ. Since FEM studies demonstrated that all the considered factors (electrode design, location, polarity and stimulator setting) can influence neuronal excitability during ICS, this investigational technique can be used for the research of optimal parameters combinations, in order to reduce the side effect and increase the efficiency of implantable device. However FEM results have to be validated by performing neurophysiological recordings during motor mapping experiments or analyzing the behavior of the subjects during task performance.

Most computational studies for the optimization of CS parameters have used very simple geometrical models, such as extrusion slab partial head models, in order to estimate the distribution of current density and potential induced in the cortex at the level of the precentral gyrus. Their combination with compartmental neuronal models allowed the estimation of stimulation thresholds of neurons during CS. Future simulations with more realistic human head models, characterized by anisotropic tissue conductivities and based on individual MRI data, coupled with neuronal models are needed to confirm the estimated thresholds. Finally, FEM models could also include simulations of synaptic connections between the several neurons represented, which would allow not only the investigation of the mechanisms that

determine the stimulation of an individual neuron, but also the prediction of the response due to synaptic interactions between neurons in the network (Salvador et al. 2011).

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