The Activation Function of TMS on a Finite Element Model of a Cortical Sulcus

Sofia Silva, Peter J. Basser, and Pedro C. Miranda

***Abstract*— TMS is a promising tool for the non-invasive stimulation of the cerebral cortex, with applications in Neurology and the Neurosciences. From cable theory, it is known that the activation function for neuronal stimulation in TMS may contain contributions from the electric field and the component of the electric field gradient along the direction of the nerve. Here we present a calculation of the spatial distribution of the induced electric field by TMS using a finite element model of the cerebral cortex and surrounding tissues. This distribution allows us to calculate the activation function for different experimental conditions, and is expected to provide new insight into the mechanisms of TMS in the cortex.**

I. INTRODUCTION

TRANSCRANIAL Magnetic Stimulation (TMS) is a non invasive tool to stimulate the cerebral cortex. It is based on the physical principle of electromagnetic induction, where a time varying magnetic field induces an electric field within the tissue. The electric field induced by the magnetic field pulse is given by

$$\nabla \times \vec{E} = -\frac{\partial \vec{B}}{\partial t} . \tag{1}$$

Since the magnetic field, $\vec{B}$, is given by the curl of the magnetic potential, $\vec{A}$,

$$\vec{B} = \nabla \times \vec{A} , \tag{2}$$

the resultant electric field can be written as

$$\vec{E} = -\frac{\partial \vec{A}}{\partial t} - \nabla \phi , \tag{3}$$

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where $\nabla \phi$ is the electric field due to charge accumulation on the volume conductor interfaces.

The electric (eddy) currents induced in the cortical tissues due to the electric field, $\vec{E}$, change the extracellular electric potentials. These changes can cause neuronal membranes to depolarize and, if this depolarization reaches a threshold, action potentials are fired.

TMS has applications in many fields, from Neurology (where it can be used to assess the conduction time of motor pathways, helping in the diagnosis of neurological pathologies of the motor system), to the Neurosciences, where TMS can temporarily disrupt local cortical function and, in that way, contributes to the understanding of the involvement of certain cortical areas in the execution of specific brain tasks.

It is known that the passive electrical behavior of the neuron (its passive response to changes in the extracellular electric potential) can be modeled by a Cable Equation, which in TMS is given by [1],

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} - V - \tau \frac{\partial V}{\partial t} = \lambda^2 \frac{\partial E_x}{\partial x} , \tag{4}$$

where V is the deviation of the electric potential of the membrane relative to its resting potential, when it is subjected to an external electric field. The parameters λ (space constant) and τ (time constant) are properties of the membrane. The term $\lambda^2 \partial E_x / \partial x$ is referred to as the activation function, where x is taken along the direction of the axon's axis.

For a long, straight axon, and assuming that V varies slowly with x, the cable equation reduces to $V = -\lambda^2 \partial E_x / \partial x$. In this case, the gradient of $\vec{E}$ along x, appropriately scaled by λ, is a good measure of the deviation V of the potential of the membrane. On the other hand, at a termination of an axon, the cable equation predicts that $V = -\lambda E_x(x_0)$, x_0 being the position of the axon's termination. So, at axonal terminations, λE_x gives us the amplitude of the potential V. For the TMS induced electric field, with an effective spatial extent of a few centimeters below the scalp, axonal terminations that can be depolarized are found inside the cortex only.

Another situation to consider is stimulation at points where axons bend. These bends have been shown to be plausible regions of membrane depolarization during TMS, and in this case it follows from the cable equation that λE_x is also the measure of the potential deviation, V, at the bending site.

Finally, it seems that the interface between cortical gray matter and white matter might also be a locus of membrane depolarization, due to the jump, ΔE_x, in the electric field along the axon's direction [2]. In this case, the cable equation yields $V = -\lambda(\Delta E_x / 2)$ for the deviation of membrane potential at an interface separating tissues with different electric conductivities.

The direction of the axons in the cortex is generally either normal to the cortical surface (as is the case for pyramidal neurons) or parallel to the cortical surface. For the case when the direction x of the axon is along the normal to the cortical surface, the derivative $\partial E_x / \partial x$ of E_x is substituted by its general expression $\vec{n}^T(\nabla \vec{E})\vec{n}$, the projection of the electric field gradient along $\vec{n}$, $\vec{n}$ being the normal to the cortical surface.

Here we present a calculation of the spatial distribution of E_n, $\vec{n}^T(\nabla \vec{E})\vec{n}$ and $\Delta E_n / 2$ in a region simulating a cortical *sulcus*. This information is expected to help shed light on the mechanisms of TMS.

II. Methods

A. The FEM Model

The electric field induced within the cerebral cortex by a current within a figure-eight coil was calculated using the Electromagnetics Quasi-statics Module of Comsol Multiphysics software. The model of the coil is based on the Magstim 70 mm (P/N 9790), as described in [3] and [4]. In our model, the coil windings are one-dimensional, but the radii of the turns were kept the same as in those references. The current in the coil is modelled as sinusoidal and its maximum rate of change is 67 A/µs. The coil lies 1 cm above the surface of the volume conductor. The volume conductor has 3 layers, representing CSF, cortical gray matter and white matter (WM), respectively. The cortex layer has one *sulcus*, 3 mm wide and lying 2 cm below the upper surface of the volume conductor, as can be seen in Figs. 1 and 2. The *sulcus* extends along the diameter of the volume conductor, parallel to the y-axis. The centre of the coil (the point between the two wings) is placed at (x,y,z) = (0,0,0.01) m. As a first approximation, brain regions were modelled as isotropic, with conductivities σ_{CSF} = 1.79 S/m, σ_{cortex} = 0.33 S/m and σ_{WM} = 0.15 S/m. The space (air) surrounding the conductor has a conductivity given by σ_{Air} = 0.002 S/m.

The global mesh has 402520 elements. The average dimension of the finite elements inside the region of interest (a parallelepiped centred at y = 0 and surrounding the *sulcus*) is about 3 mm. Close to the *sulcus* and within it, the average dimension of the elements is 0.5 mm.

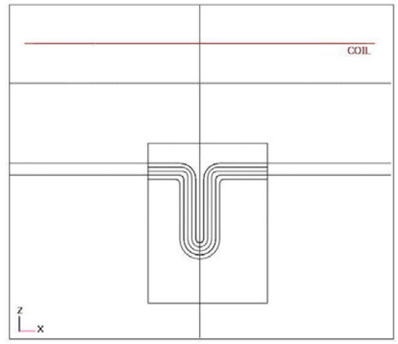

Fig. 1. Geometry of the volume conductor, detail of the side view. The coil is placed 1 cm above the volume conductor surface and parallel to it. The region of interest of the volume conductor can be seen here as the rectangle around the *sulcus*.

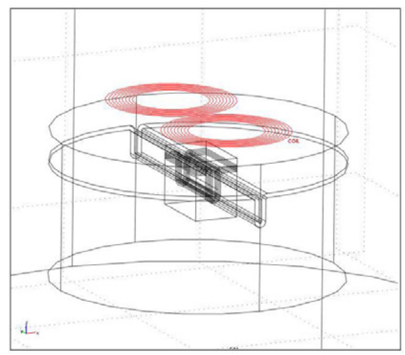

Fig. 2. Geometry of the volume conductor.

The FEM software solves Maxwell's equations for the potentials $\vec{A}$ and ϕ, using vector elements of first order for $\vec{A}$ and Lagrange elements of first order for ϕ. The solution obtained was post-processed in MATLAB, in order to obtain the gradient of $\vec{E}$.

B. Data Post-Processing

The gradient of the electric field along the normal $\vec{n}$ to the cortical surface is given by

$$\vec{n}^T(\nabla \vec{E})\vec{n} = \\ = n_x^2 \frac{\partial E_x}{\partial x} + n_y^2 \frac{\partial E_y}{\partial y} + n_z^2 \frac{\partial E_z}{\partial z} + n_x n_y \left(\frac{\partial E_x}{\partial y} + \frac{\partial E_y}{\partial x} \right) + \\ + n_x n_z \left(\frac{\partial E_x}{\partial z} + \frac{\partial E_z}{\partial x} \right) + n_y n_z \left(\frac{\partial E_y}{\partial z} + \frac{\partial E_z}{\partial y} \right). \quad (5)$$

Since the normal to the cortical surface in our volume conductor model has only two components (n_x, n_z), the normal component of the electric field gradient reduces to

$$\vec{n}^T\left(\nabla\vec{E}\right)\vec{n} = n_x^2\frac{\partial E_x}{\partial x} + n_z^2\frac{\partial E_z}{\partial z} + n_x n_z\left(\frac{\partial E_x}{\partial z} + \frac{\partial E_z}{\partial x}\right). \qquad (6)$$

The solution of the FEM problem (E_x, E_z, $\partial\phi/\partial x$, $\partial\phi/\partial z$ and σ) was exported to MATLAB on regular grids of $81\times 61\times 101$ points, corresponding to the (*z,x,y*) coordinates. The data matrices E_x and E_z were fitted (along the lines and along the columns) using least-square algorithms written for the purpose. The electric field has a continuous and slowly varying component, $-\partial\vec{A}/\partial t$, which is independent of the heterogeneities of the volume conductor, and can be fitted with polynomials of low degree, n. We fitted $-\partial A_x/\partial t$ with polynomials of degree n = 2 and n = 4. On the other hand, across each interface, the component of the electric field due to charge accumulation ($-\nabla\phi$) experiences a "boost" in its intensity, which is positive where σ is lower and negative where σ is higher. This boost is predicted to decay exponentially with the distance from the interface [2], and therefore we used exponential functions as a default when fitting curves for the "heterogeneous" part of the electric field components. The stimulating coil is positioned parallel to the surface of the volume conductor. Therefore, $-\partial A_z/\partial t \equiv 0$, and E_z reduces to $-\partial\phi/\partial z$. Fig. 3 illustrates the fitting results.

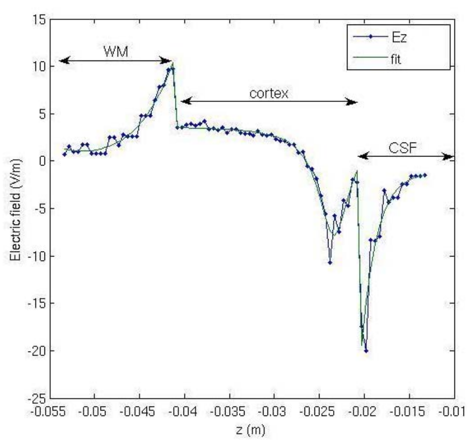

Fig. 3. Fit to Ez along z. Each segment of the data (corresponding to a specific brain tissue – WM, CSF or cortex) is fitted separately from the others.

After passing the data matrices to the curve fitting algorithms, goodness-of-fit was assessed by calculating the z-score of a Wald-Wolfowitz runs test [5].

The Wald-Wolfowitz runs test determines if the residuals of the fit are random. In our curve fitting procedure, if the residuals of one fit are not random, the algorithm substitutes the default fitting curve for another, more appropriate curve. We chose a Lorentzian with an offset and a polyfunctional, given by

$$y(x) = \frac{a}{x} + bx^2 + ce^x + d\ ,$$

as alternative fitting curves. These curves were suggested by examination of some data sets, representative of the variation of the electric field in the regions where the exponential function does not perform well, to online curve fitting software (www.zunzun.com) that finds, for specific data, the best fitting curve from a large set of functions.

The partial derivatives of E_x and E_z were then obtained through analytic differentiation of the curves fitted to the data.

III. Results

The activation function has been calculated in the region of interest (ROI) of the volume conductor. In Figs. 4, 5 and 6, we display the functions λE_n, $\lambda^2\left(\vec{n}^T\left(\nabla\vec{E}\right)\vec{n}\right)$ and $\lambda\left(\Delta E_n/2\right)$, the first two on a surface inside the cortex, and the other on the interface between the cortex and white matter. We used λ = 0.002 m for the space constant. The gradient $\lambda^2\left(\vec{n}^T\left(\nabla\vec{E}\right)\vec{n}\right)$ will be referred here simply as the activation function. The results suggest that the spatial distribution of the activation function is focal, located along the lip of the *gyrus*, as can be seen in Fig. 4. This gradient might produce activation of the initial segment of pyramidal axons located along the lip of the *gyrus*. The maximum expected membrane potential deviation due to $\lambda^2\left(\vec{n}^T\left(\nabla\vec{E}\right)\vec{n}\right)$ on the surface of Fig. 4 is 41 mV and this value is thought to be higher than the average threshold for action potential firing, which is thought to be of about 20 mV [6].

Concerning λE_n (Fig. 5), its distribution is broad and its maximum value (124 mV) occurs just beneath the lip of the *gyrus*, in the plane y = 0. This function might be responsible for the stimulation of pyramidal axons at the bends, outside of gray matter.

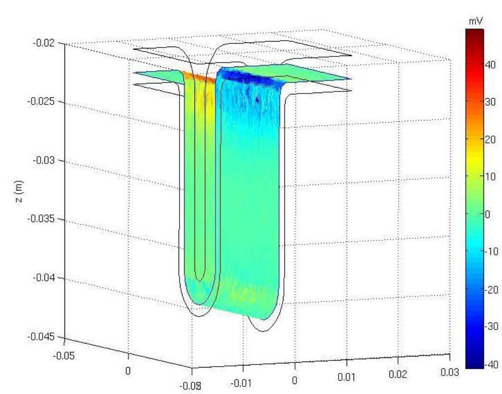

Fig. 4. The activation function inside the cortex. The maximum value on this surface is 49 mV; the minimum value is -41 mV.

As for $\lambda\left(\Delta E_n/2\right)$ on the interface cortex-WM (Fig. 6), the maximum expected membrane potential deviation due to this function is 52 mV and occurs on the wall of the *sulcus*. The function $\lambda(\Delta E_n / 2)$ is expected to be responsible for the depolarization of pyramidal axons, at the axonal segment crossing the cortex-WM interface.

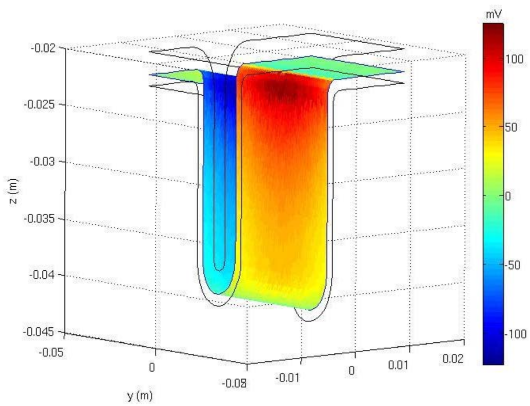

Fig. 5. λE_n inside the cortex. The maximum value on this surface is 124 mV and the minimum value is -123 mV.

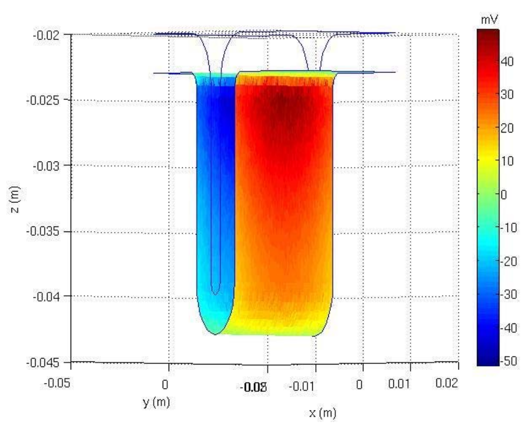

Fig. 6. $\lambda(\Delta E_n/2)$ on the cortex-WM interface. The maximum value on this surface is 49 mV and the minimum value is -52 mV.

IV. DISCUSSION

We calculated the spatial distribution of the activation function of TMS using an FEM model of the cerebral cortex.

The results obtained here represent an improvement in the prediction of the intensity of the electric field induced by TMS on a target region of the cortex. Furthermore, these results help us to understand the importance of the geometry of the cortex in the distribution of the induced electric field and electric field gradient. In particular, the high amplitude of $\lambda^2\left(\vec{n}^T\left(\nabla\vec{E}\right)\vec{n}\right)$ comparable to that of λE_n is a consequence of the curved geometry of the cortex.

For the stimulation of motor cortex, which is the gold standard of TMS, the predominant cortical responses to TMS are I waves and it is thought that these waves are primarily generated by intracortical interneurons and corticocortical association fibers [7]. Concerning intracortical interneurons, these cells have their axons parallel to the cortical surface. Therefore, in order to study the stimulation of these fibers by TMS, it will be necessary to calculate the projection of $\vec{E}$ along the tangential direction to the cortical surface, which was not done here.

The constraint of boundaries from nearby *gyri* is expected to distort the electric field even more, so for a complete knowledge of the distribution of the activation function of TMS, it will be necessary to calculate this distribution on models with a more realistic description of the cortical geometry. Such information could be obtained from MRI and/or CT data acquired during routine brain scanning procedures.

V. CONCLUSION

We calculated the spatial distribution of the activation function of TMS on a finite element model of a cortical *sulcus*. The results obtained here are expected to improve our understanding of the mechanisms of neuronal stimulation by TMS.

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