Optimized Transcranial Brain Stimulation for Tumor Treating Fields

Dante C. Andrinolo O.[1[0009-0005-0560-1053]], Mariano Fernández-Corazza[1[0000-0002-9624-5023]], and Carlos H. Muravchik[1,2[0000-0003-2954-6675]]

[1] LEICI Instituto de Investigaciones en Electrónica, Control y Procesamiento de Señales (UNLP-CONICET)
[2] Comisión de Investigaciones Científicas, CICPBA, Provincia de Buenos Aires, Argentina
dante.andrinolo@alu.ing.unlp.edu.ar
{marianof.corazza,carlosm}@ing.unlp.edu.ar

Abstract. Transcranial electrical stimulation (TES) is a field that investigates the effects of applying low-intensity electrical currents to the human brain using electrodes placed on the scalp. Tumor Treating Fields (TTFields) is one application of TES, that consists of applying alternating electric fields (∼300KHz) to a tumoral region to arrest its growth. The physiological principle is that tumoral cells are killed during the mitosis if the fields are aligned with the cell subdivision direction. The conventional protocol involves switching between two ad-hoc and intuitive anterior-posterior and left-right stimulation patterns. This paper focuses on optimizing the current injection patterns to stimulate the tumoral region, maximizing the average electric field intensity inside the tumor along predefined electric field orientations. The reciprocity theorem is used to optimize the current injection using two electrode arrays: the conventional 36-electrode TTFields array and the 64-electrode 10-20 electroencephalography array. A realistic head model, including brain tissues and a tumor, is used to solve the forward problem of TES using the finite element method. The performance is evaluated based on the directionality and intensity metrics of the electric field within the tumor. The results show improved performance in terms of directionality and intensity for the optimized patterns compared to the conventional protocol. The proposed optimization approach has the potential to enhance the efficacy of TTFields.

Keywords: TTFields · Transcranial Electrical Stimulation (TES) · Optimal Electrical Stimulation · Reciprocity Theorem.

1 Introduction

Transcranial electrical stimulation (TES) is a rapidly evolving field in bioengineering and neuroscience that explores the effects of applying minimally-invasive 'low' intensity electrical currents to the human brain. TES relies on applying an electrical current through two or more electrodes (array of electrodes) placed on the scalp to modify or modulate cortical excitability and brain function. Alternate and direct current TES are known as tACS and tDCS respectively. Research has demonstrated that TES can be a valuable therapeutic tool for the treatment of epilepsy, Parkinson's disease, anxiety, and stroke rehabilitation [1]. They also proposed to enhance cognitive skills such as memory or learning [1]. In this work we focus on the application of TES for treating tumors.

In TES, the current injected by each electrode of the array, known as current injection pattern, produces an electric field (or current density) map on the brain [2, 3]. The computation of this map is known as the forward problem (FP), typically solved numerically using the finite element method (FEM) in a realistic human head model [4]. The electrical conductivity and the shape of the different head tissues determine the spatial distribution of the electric fields. [3]. The inverse problem (IP) is to determine the current injection pattern that stimulates a certain region of interest (ROI) in a desired way. Depending on the criteria, several optimization schemes have been proposed leading to different solutions.

Tumor treating fields (TTFields) therapy is a case of tACS applied to the treatment of glioblastoma multiforme (GBM). It consists in delivering intermediate-frequency electric fields to the tumoral region, arresting the growth of cancerous cells due the interference with mitosis and cytokinesis [2]. If an electric field of ∼100-300 KHz of frequency and 0.5-3 V/cm of intensity is applied to a GBM, the cellular growth can be disrupted [5, 6]. The electric field aligned to the cell-division preferred orientation is believed to affect metaphase by disrupting mitotic spindle formation, and anaphase, by dielectrophoretic dislocation of intracellular constituents, resulting in apoptosis [2]. Because the healthy cells of the brain do not divide frequently in comparison to the GBM cells, TTFields leaves the healthy cells relatively unaffected [6]. It was experimentally found in vitro that the technique is more efficient if more directions are covered [7].

The conventional protocol for TTFields use 4 arrays of 9 capacitive electrodes each, positioned on the right, left, anterior and posterior regions of the scalp (called here *TTFields array*) [5]. The injected current for this method is 100mA per electrode with a total current of 900mA. The injection pattern switches, between left to right (LR) and anterior to posterior (AP), expecting to generate electric fields inside the tumor along two orthogonal directions of the 3D space.

However, the conventional protocol relies on pure intuition and hence, is not optimal. LR or AP stimulation on the scalp does not guarantee the largest, most orthogonal or most directional electric fields within the tumor. To improve the orthogonality and intensity of the fields, the current injection patterns require optimization.

This work uses the reciprocity theorem optimization methodology to maximize the electric field intensity inside the tumor along the three canonical orientations (LR, AP and bottom-up or BU), with the TTFields array (36 electrodes) and with the standard 10-20 electroencephalography (EEG) 64-electrode system (considering 18 active electrodes in all cases).

2 Methods

2.1 Head model

We used a realistic head model based on the ICBM-152 atlas with five tissues: brain (BR), cerebrospinal fluid (CSF), skull (SK), scalp (SC), and the tumor. We extracted, meshed and generated the 3D surfaces, to produce a tetrahedral volumetric mesh from these surfaces, with the Iso2mesh library. The final tetrahedral mesh has around of 950.000 elements and 160.000 nodes (N). The proposed tumor was modeled as a sphere of 0.5 cm radius, placed at 1.8cm under the central sulcus, biased 1.2 cm towards the right hemisphere. Each tissue was assumed to be homogeneous and isotropic conductivity with values 0.25, 1.79, 0.01, 0.25 and 0.24 S/m assigned to BR, CSF, SK, SC and tumor respectively [2]. The model considers two pointwise electrode arrays, the TTFields 4×9 electrode array [5], and the standard 10-20 EEG 64 electrode array, shown in Fig. 1. We manually determined the TTFields array electrode locations based on anatomical landmarks and visual inspection. The 10-20 standard array was projected to the scalp surface from the standard spherical coordinates.

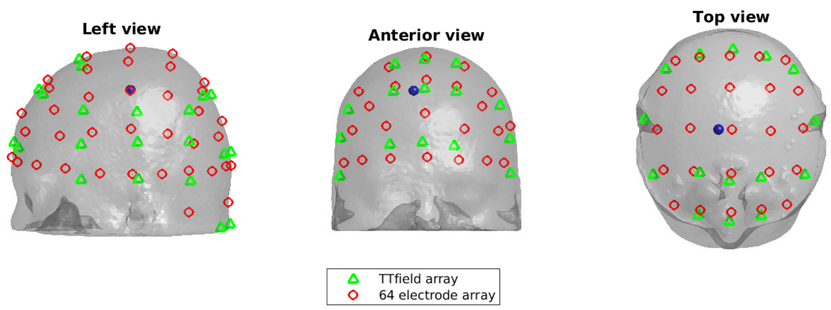

Fig. 1. Plot of the scalp surface and the tumor (in blue). TTFields electrodes and 10-20 EEG 64 electrodes are plotted as green triangles and red circles respectively.

2.2 TES Forward problem

The solution of the FP requires solving the electromagnetic physical (Maxwell's) equations. Given the frequency range of the problem, the quasi-static approximation is applicable [8, 9]. Assuming a pointwise electrode model, the mathematical formulation is established as:

$$\begin{cases} \vec{\nabla} \cdot (\boldsymbol{\sigma}(\vec{x}) \vec{\nabla} \Phi(\vec{x})) = 0, & \text{in } \Omega \\ \boldsymbol{\sigma}(\vec{x})(\vec{\nabla} \Phi(\vec{x})) \cdot \hat{n} = \jmath(\vec{x}), & \text{in } \delta\Omega \end{cases} \tag{1}$$

where Ω is the head solid, $\delta\Omega$ is its boundary, $\vec{x}$ is an arbitrary location in space, Φ is the electric potential, $\boldsymbol{\sigma}$ is the tensor conductivity, j is the normal component of the current density on the external surface, and $\hat{n}$ is the normal to the boundary vector.

This equation system is solved using the first order FEM with the Galerkin approach, that converts the FP (1) into a linear system of equations $\boldsymbol{K}\boldsymbol{v} = \boldsymbol{f}$, where $\boldsymbol{K}$ is the $N \times N$*stiffness* matrix computed using the geometry and conductivity map of each tissue, $\boldsymbol{v}$ is the $N \times 1$ unknown vector of electric potential and $\boldsymbol{f}$ is the $N \times 1$ vector of injected current [10, 3]. An arbitrary electrode is used as a reference for the electric potential and thus, the range of $\boldsymbol{K}$ is $N - 1$ implying that K is not an invertible matrix. The algorithm used to solve this linear system is the preconditioned conjugated gradient algorithm with the LU factorization as preconditioner [11]. After $\boldsymbol{v}$ is determined, the numerical gradient operator is calculated in order to get the electric field at the ROI.

Due to the linear nature of the electric fields, any current injection pattern can be obtained as a linear combination of a complete set of independent elementary patterns. Then, if there are L electrodes, $L - 1$ independent injection patterns are needed to form a complete set. Each independent pattern was modeled as an L-dimensional vector p_i, with I_{max} at the i-th electrode and $-I_{max}$ at the reference electrode, where I_{max} is the maximum current allowed per electrode.

Then, the electric field was computed for all ROI tetrahedrons and for each elementary current injection pattern leading to a $3T \times (L-1)$ dimension matrix $\boldsymbol{T_M}$ known as *transfer matrix* (T is the number of ROI tetrahedrons). The resulting electric field for an arbitrary current injection pattern $\boldsymbol{c}$ is obtained as $\boldsymbol{E} = \boldsymbol{T_M}\boldsymbol{c}$.

2.3 Inverse problem

We solved the IP applying the reciprocity theorem for TES and EEG, that maximizes the average electric field intensity at the ROI along a predefined direction [3].

Reciprocity theorem as an optimization method. The reciprocity theorem coupling between TES and EEG is formulated as:

$$\boldsymbol{\Phi}(a) - \boldsymbol{\Phi}(b) = \frac{\vec{d} \cdot \vec{\nabla}\boldsymbol{\psi}_{ab}(\vec{x})}{I_{ab}} \tag{2}$$

where $\boldsymbol{\Phi}(p)$ is the electric potential at an arbitrary point of the boundary p produced by a dipolar electrical source $\vec{d}$ in $\vec{x}$, and $\vec{\nabla}\boldsymbol{\psi}_{ab}(\vec{x})$ is the gradient of the impressed potential (or minus the electric field) at $\vec{x}$ when a current is injected between locations a and b. Assuming that $\vec{d}$ is the desired direction for the impressed electric field, to maximize the dot product of $\vec{d}$ and the electric field at $\vec{x}$, $\boldsymbol{\Phi}(a) - \boldsymbol{\Phi}(b)$ should be maximized, therefore, $a = A$ and $b = B$

should be the points where $\boldsymbol{\Phi}(A)$ and $\boldsymbol{\Phi}(B)$ are the maximum and minimum of $\boldsymbol{\Phi}$ respectively [3].

$$A, B = \text{argmax}_{a,b}\{\boldsymbol{\Phi}(a) - \boldsymbol{\Phi}(b)\} = \text{argmax}_{a,b}\left\{\frac{\vec{d} \cdot \vec{\nabla}\boldsymbol{\psi}_{ab}(\vec{x})}{I_{ab}}\right\} \tag{3}$$

$$\Leftrightarrow \vec{d} \cdot \vec{\nabla}\boldsymbol{\psi}_{AB}(\vec{x}) \text{ is maximal}$$

Ideally, solution points A and B could be at any location on the scalp. In our head model, these points can be only specific electrode locations. Reciprocity optimization was applied three times to the two electrode arrays, optimizing the electric field in the canonical set of axes, x (LR), y (AP) and z (BU).

2.4 Measures of performance

The method performance is measured with 2 metrics: directionality and intensity. The directionality metric quantifies the average orientation of the electric field with respect to a specific orientation and the intensity quantifies the average intensity along a specific orientation. Both were calculated for all three canonical orientations. Intensity measure was defined as:

$$Int_{\hat{p}} = \frac{\sum_{i \in ROI}^{T} vol(i)|\vec{E}_i \cdot \hat{p}|}{\sum_{i \in ROI}^{T} vol(i)} \tag{4}$$

where $\hat{p} = \hat{\imath}, \hat{\jmath}, \hat{k}$ for x, y, z respectively, $vol(i)$ is the volume of the i-th ROI tetrahedron, and $\vec{E}_i$ is the electric field vector at the i-th ROI tetrahedron. Similarly, directionality was given by

$$Dir_{\hat{p}} = \frac{\sum_{i \in ROI}^{T} vol(i)\frac{|\vec{E}_i \cdot \hat{p}|^2}{|\vec{E}_i|^2}}{\sum_{i \in ROI}^{T} vol(i)} \tag{5}$$

3 Results

Fig. 2 shows the two conventional and the six optimized current injection patterns. Tables 1 and 2 show that the conventional injection patterns do not stimulate well in the BU direction, but the optimized pattern for the same array, gains almost 4 and 10 times in intensity and directionality respectively. For the rest of the axes, the performances of the optimized patterns using the TTFields array are better in intensity (around 10% for both axes), and in directionality (around 7% for y). An interesting finding is that even when using the TTFields electrode positions, the optimized for x and for y patterns slightly differ from the intuitive ones, as seen on Fig. 2 (first column versus second column).

For the 64 electrode array, the optimized injection patterns result in the largest intensity metrics among the three simulations, gaining about 154%, 125%,

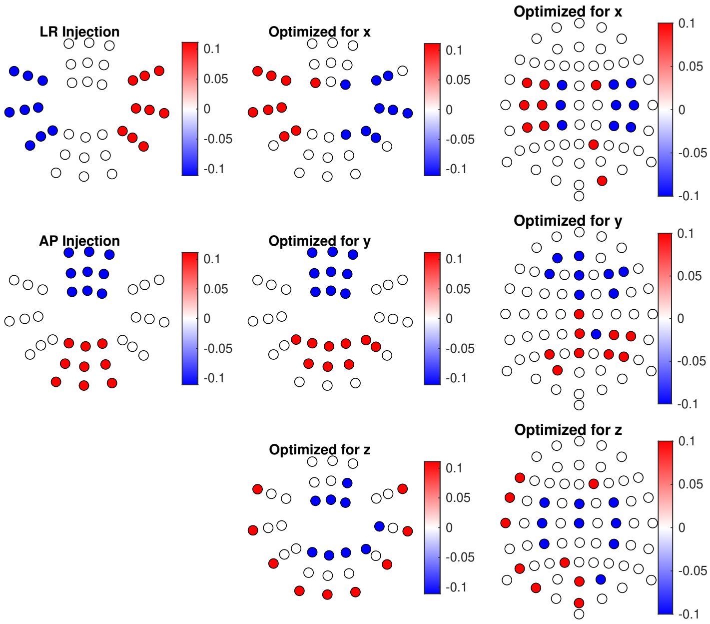

Fig. 2. Conventional stimulation using TTFields array (first column), optimized stimulation using TTFields array (second column) and optimized stimulation using 10-20 EEG array (third column). The sources and sinks of each current injection pattern are colored in red and blue respectively. Each row represents the targeting in the AP (first row), LR (second row) and BU (third row) directions. Note that for the intuitive patterns of the first column, there is no BU pattern simply because the currently used TTFields protocol does not include it. The colorbar is in [A].

and 370% times the intensity for the conventional injection pattern and 141%, 116%, and 180% times respect to the optimized pattern for the TTFields array.

Regarding the directionality metric, there is not a big difference between the 3 injection patterns for x and y axes. For the z axis, the conventional pattern does not produce a significant electric field along that direction (<0.1) while the directionality of the optimized patterns is >0.8. Note that the optimized patterns might not be visually intuitive, particularly for the 64 electrode array.

4 Discussion

It can be observed that, as intuitively designed, the LR pattern has more intensity and directionality on the x-axis and similarly with the AP pattern for the y-axis. However, the optimized patterns are better in terms of intensity and

Table 1. Intensity of the electric field, decomposed in the three canonical directions x, y and z for the conventional and optimized current injection patterns.

Mean electric field [V/cm]									
	LR/Opt in x			AP/Opt in y			Opt in z		
	x	y	z	x	y	z	x	y	z
TTFields array Conventional patterns	**0.60**	0.04	0.04	0.05	**0.64**	0.2	-	-	-
TTFields array Optimized patterns	**0.65**	0.08	0.09	0.03	**0.70**	0.12	0.19	0.04	**0.41**
64 electrodes 10-20 system Optimized patterns	**0.92**	0.06	0.15	0.13	**0.81**	0.09	0.24	0.07	**0.73**

Table 2. Directionality of the electric field along the three canonical directions x, y and z for the conventional and optimized current injection patterns.

Directionality Metric									
	LR/Opt in x			AP/Opt in y			Opt in z		
	x	y	z	x	y	z	x	y	z
TTFields array Conventional patterns	**0.99**	0.01	0	0	**0.90**	0.09	-	-	-
TTFields array Optimized patterns	**0.96**	0.02	0.02	0	**0.97**	0.03	0.18	0.01	**0.80**
64 electrodes 10-20 system Optimized patterns	**0.97**	0.01	0.02	0.03	**0.96**	0.01	0.1	0.01	**0.89**

directionality in almost all cases. Only the AP pattern slightly outperforms the optimized patterns in directionality (0.99 versus 0.96 and 0.97), but the gain is negligible. Furthermore, the optimal patterns achieve intensity and directionality metrics for the z-axis in the same order of those obtained for the x and y axis. This is a major finding of this work, because the z-axis is not targeted in the intuitive conventional protocol, presumably because it is not possible to place non-invasive electrodes at the bottom of the brain. Here we show that optimization in the BU direction is indeed possible with scalp electrodes.

5 Conclusions

We showed that the conventional TTFields method can be easily strongly improved by using an optimization method such as the one based on the reciprocity theorem, for either obtaining more electric field intensity or the same actual intensity using less power. In the former case, this can improve the efficacy of the therapy and in the latter case, it could reduce the irritation skin side effects due to the high surface current. Moreover, we showed that stimulation along the BU direction is possible using optimized patterns, which should also increase the efficacy of the treatment. If a standard EEG 64 electrode array is used, both the intensity and directionality metrics can be further improved.

We will expand this work replacing the point source model with the complete electrode model, that will allow us to model the contact impedance, the different shape and layers of the electrode and the current density distribution on the scalp. We will also consider another optimization method, an iterative 'linearly constrained minimum variance method', that forces electric field directionality. Finally, we will simulate the whole problem by assuming stochastic cell division orientations and analyze how the temporal switching of the different patterns affects the efficacy of the optimized versus not-optimized patterns.

Acknowledgments This work was supported by the ANPCyT PICT 2019-0701, UNLP I-257, CONICET PIP 11220200101515CO, BENTRE23 and Becas Manuel Belgrano.

References

1. Obeso, I., Oliviero, A., Jahanshahi, M.: Editorial: Non-invasive brain stimulation in neurology and psychiatry. Front. Neurosci. **10** (December 2016) 574
2. Miranda, P.C., Mekonnen, A., Salvador, R., Basser, P.J.: Predicting the electric field distribution in the brain for the treatment of glioblastoma. Physics in Medicine & Biology **59**(15) (jul 2014) 4137
3. Fernández-Corazza, M., Turovets, S., Luu, P., Anderson, E., Tucker, D.: Transcranial electrical neuromodulation based on the reciprocity principle. Frontiers in Psychiatry **7** (2016)
4. Windhoff, M., Opitz, A., Thielscher, A.: Electric field calculations in brain stimulation based on finite elements: an optimized processing pipeline for the generation and usage of accurate individual head models. Hum. Brain Mapp. **34**(4) (April 2013) 923–935
5. Swanson, K.D., Lok, E., Wong, E.T.: An overview of alternating electric fields therapy (NovoTTF therapy) for the treatment of malignant glioma. Curr. Neurol. Neurosci. Rep. **16**(1) (January 2016) 8
6. Davies, A.M., Weinberg, U., Palti, Y.: Tumor treating fields: a new frontier in cancer therapy. Annals of the New York Academy of Sciences **1291**(1) (2013) 86–95
7. Kirson, E.D., Dbalý, V., Tovarys, F., Vymazal, J., Soustiel, J.F., Itzhaki, A., Mordechovich, D., Steinberg-Shapira, S., Gurvich, Z., Schneiderman, R., Wasserman, Y., Salzberg, M., Ryffel, B., Goldsher, D., Dekel, E., Palti, Y.: Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc. Natl. Acad. Sci. U. S. A. **104**(24) (June 2007) 10152–10157
8. Malmivuo, J., Plonsey, R.: Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields. Oxford University Press (10 1995)
9. Jackson, J.D.: Classical electrodynamics. 3rd ed. edn. Wiley, New York, NY (1999)
10. Kwon, Y.W., Bang, H.: The finite element method using MATLAB. CRC press (2018)
11. Barrett, R., Berry, M., Chan, T.F., Demmel, J., Donato, J., Dongarra, J., Eijkhout, V., Pozo, R., Romine, C., der Vorst, H.V.: Templates for the Solution of Linear Systems: Building Blocks for Iterative Methods, 2nd Edition. SIAM, Philadelphia, PA (1994)