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Effect of Variability of Tissue Dielectric Properties on Transcranial Alternating Current Stimulation Induced Electric Field

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ABSTRACT

Transcranial alternating current stimulation modeling is a common procedure to either predict the stimulation clinical effect or to design protocols with optimal parameters. Knowledge of dielectric properties of tissues, especially conductivity, is required to perform such modeling as prior information. However, the low-frequency values of dielectric properties of human tissues are still not well established, and vary between individuals. To address this, analysis of electric field variability due to conductivity variability was assessed recently in the literature. To date, no such analysis has been performed by including permittivity (or tissue capacity) and its own variability. The present study aims to fill this knowledge gap, test the hypothesis, and quantify whether the contribution of permittivity in the analysis of dielectric properties variability impacts the resulting variability of electric field estimation. Furthermore, we provide margins for the electric field and its focality using the extreme values of dielectric properties values reported in the literature. Our results suggest that electric field magnitude, and the component normal to the cortex, are sensitive to conductivity changes, but also to brain tissues permittivity, with an error of neglecting permittivity that can reach almost 40%. Overall, these results contribute to a better understanding of tACS computational modeling.

INTRODUCTION

Transcranial current stimulation (tCS) is a popular non-invasive brain stimulation (NIBS) method that has attracted growing interest in the last two decades, especially since its ability to increase neural response was demonstrated in [1]. Transcranial alternating current stimulation (tACS), using sinusoidal current, has been shown to entrain the neural activity to the stimulation frequency [2]. Since then, it has been shown to be a safe NIBS technique [3], however with variable outcomes depending on protocol design and inter-individual variability [4]. Predictions of tCS effects on neural activity require precise knowledge of the *in situ* electric field (EF), even at the single neuron level. Numerical methods, especially finite element methods, are commonly used to assess the EF in brain tissues using either simplified [5] or realistic head models [6–8]. To compute the EF induced by tACS on these models, dielectric properties values have to be attributed to each tissue region as required by Maxwell equations. A common assumption is to consider conductivity only, since the relative permittivity is often neglected by using the quasi-static approximation (QSA) [9]. However, the assumption of negligible effect of permittivity is the weakest, and this formulation of QSA, which differs from the definition in physics

and electromagnetics, can be relaxed to consider the contribution of the capacitive effect of tissues [10]. The error due to this approximation was quantified for tACS [10,11] and transcranial temporal interference stimulation [11,12] for one set of dielectric properties or on 2D models. Multiple measurements of tissues' conductivity, either direct or indirect, have been reported with strong variations among studies [13]. The relative permittivity has been less investigated at low frequencies, since the QSA assumption is commonly used. One study characterized both relative permittivity and conductivity in a broad spectrum range, with a minimal frequency of 10 Hz [14]. The results showed high values of relative permittivity for several tissue types at low-frequency, which highlights that neglecting permittivity can lead to reduced modeling accuracy. However, the conductivities associated with these measurements deviate from literature findings at low frequency, and the authors highlight that these results should be taken with caution. Nevertheless, another study reported the same range of relative permittivity at low frequency [15]. This should be contrasted with [16], which points out that these high relative permittivity values could result from under-corrected electrode polarization and therefore increase the measured values from the true sample value.

The uncertainty on dielectric properties values then propagates on the uncertainty on the EF induced by simulation, even from one subject with an accurate individual anatomical model. This could explain, at least in part, the variability in stimulation outcomes, along with anatomic variability [17] and inter-individual variation in neural states and susceptibility. Recent efforts focused on assessing EF uncertainty at the brain level using chaotic polynomial expansion with probabilistic distribution of conductivities [18], which showed that the EF induced by tACS is strongly sensitive to gray matter (GM), scalp, and skull conductivity variations. However, to the best of our knowledge, how these variations, in combination with relative permittivity variations, could induce uncertainty on EF estimation, has not been assessed so far.

In this study, we investigated uncertainties due to both conductivity and permittivity on EF magnitude and focality. The objective was to determine the range of variation for these metrics. To achieve this objective, we used extreme values for dielectric properties for a specific electrode montage. We also compared the results with and without considering permittivity to evaluate the impact of capacitive effects on modeling uncertainty.

METHODS

Model Geometry:

We used the ICBM152 anatomy [19], which is a standard template representing an average of anatomical head and brain geometries. The model was obtained from the SimNIBS exemplar dataset [20], and contains 6 segmented tissues, namely GM, white matter (WM), cerebrospinal fluid (CSF), skull, skin, and eyes. All tissue boundaries, consisting of surface mesh, were imported into COMSOL Multiphysics (COMSOL Inc, MA, USA). A bipolar montage with two circular electrodes of 2 cm diameters was used with the two electrodes positioned in the F8 and Cz positions of the 10-10 electrode position system [21]. This montage was chosen to target the right inferior frontal gyrus. Stimulation of this area is under investigation in clinical trials to improve inhibition-related disorders. Therefore, any results here would be applicable to the clinical results. Numerically, the two electrodes consisted of the outer boundaries of 2-mm thick cylindrical domains representing contact gel. Boolean operations were performed to obtain a match between the surface meshes of the skin and contact gel domains. Finally, the resulting surface mesh was combined with the remaining set of surface meshes, and volumetrically meshed with 6.25M tetrahedron elements. The average element quality of the tetrahedral mesh was 0.65. The resulting numerical head model is depicted Figure 1(a).

Electric Field Calculations:

To compute the electric field generated by a 10-Hz tACS stimulation over the full numerical head model, the Laplace equation on the electric potential needs to be solved over the mesh assuming QSA [10]. The Laplace equation relaxed to include the capacitive effect of tissues can be written as:

$$\nabla \cdot (\sigma + j\omega\varepsilon_r\varepsilon_0)\nabla V = 0 \quad (1)$$

where V denotes the electric potential, related to the EF by $\mathbf{E} = -\nabla V$, σ the conductivity, and ε_r the relative medium permittivity, ω the angular frequency, and ε_0 the vacuum permittivity. The Laplace equation commonly solved using QSA in the neuromodulation community can be obtained when $\sigma \gg j\omega\varepsilon_r\varepsilon_0$ and therefore neglecting the complex term. This equation can be numerically solved over a numerical mesh, provided with the boundary conditions. Here, the boundary corresponding to the anode was set to a modified Dirichlet boundary condition known as the Terminal boundary condition on COMSOL Multiphysics ($\iint \mathbf{J} \cdot d\mathbf{S} = I, V = V_{terminal}, \mathbf{J}$ being the current density, S the anode surface and I the total stimulation current, here 1mA). At the cathode boundary, the Dirichlet boundary condition $V = 0$ was set as a ground boundary to be the return current electrode. Finally, in the remaining boundaries, an insulation boundary condition was set ($\mathbf{J} \cdot \mathbf{n} = 0, \mathbf{n}$ being the surface normal vector). The resulting linear system was solved using the BiCStab solver with a relative tolerance of 10^{-6} .

Variation of Dielectric Properties:

To solve equations on the electric potential – and therefore EF – prior knowledge of dielectric properties is required as aforementioned. Commonly, the conductivity of the 6 tissues is set according to admitted conductivity values found in the literature. However, we sought to test the impact of relative permittivity and its variations coupled with the conductivity variation. Therefore, we assessed the extreme variations reported in the literature to estimate the related limits of EF variation. This approach enables less parameters sampling, and thereby less computations since only two values for each pair of dielectric properties were tested. Since CSF conductivity variability does not induce significant changes in EF [18] and the measurement data are considered accurate, we decided not to include its values into the analysis to further reduce the amount of calculation, setting its conductivity to 1.654 S/m and its relative permittivity to 10^2 . For GM, WM, skull, and skin, the set of min-max conductivity was taken from [13], but the relative permittivity measurement being less investigated, few values were available in the Hz range. We therefore decided to use a reasonable range based on the reported values in [14,15] and on a recent study pointing to the possible electrode polarisation during experiments, which led to overestimation [16]. The corresponding values are depicted in the table Figure 1, which resulted in 256 combinations and EF maps for further analysis.

Metrics and errors:

The impact of dielectric properties on the variability in different metrics was evaluated to compare the 256 cases. The EF norm or magnitude was computed on grey matter. The 98th quantile of the highest EF magnitude was then computed as well as focality, being the volume of GM where the EF magnitude was higher than half its maximum value. Based on the hypothesis that pyramidal cells are the most sensitive to the EF and, particularly, when the EF is aligned with their somatodendritic axis, we computed the EF normal component to the GM surface (sometimes called the radial EF). Finally, we computed the error between considering relative permittivity (capacity) or only conductivity (purely ohmic) as $\eta = \left| \left| \mathbf{E}_{ohmic} - \mathbf{E}_{capa} \right| \right| / \left| \left| \mathbf{E}_{capa} \right| \right|$.

RESULTS

The 98th highest EF norm and radial magnitude shared the same trends as depicted in Figure 2 (a) and (b) despite their difference in value. This was mostly due to the fact that EF was not perfectly aligned with the cortex. The EF norm was therefore higher than the radial EF normal magnitude. GM, skin, and skull conductivities showed the largest differences in these metrics (the distributions between maximal and minimal values differed), which is consistent with [18]. WM conductivity induced little changes in EF, consistently with [18] and highlighting a small, but non-zero EF sensitivity to WM conductivity changes. Finally, the distributions for minimal and maximal permittivity differed only in the case of GM with less variation than the aforementioned parameters. The EF norm ranged from 0.025 V/m to 0.91 V/m across all used dielectric parameters, while the normal component ranged from 0.019 V/m to 0.64 V/m. The associated maximal and minimal values were obtained using the same dielectric properties set. The maxima were obtained when both relative permittivity and conductivity were minimal for GM and skin and maximal for WM, but, remarkably, when the smallest relative permittivity and the highest conductivity were set for the skull. The minima were obtained when both relative permittivity and conductivity were maximal for WM, GM, and skin and minimal for the skull.

The distributions for each focality fixed parameters strongly differed between GM conductivity maxima and minima but also differed for WM but to a lesser extent for skull, skin, or GM permittivity. It ranged from 25.862 mm³ (highly focal, 0.01% of the GM) to 1766.25 mm³ (less focal, still 0.88% of the brain). The best focality occurred when conductivity and permittivity were the lowest for GM, WM, and skull as well as for the smallest permittivity and highest conductivity for the skin.

The relative error between the solutions with and without considering permittivity (η) varied from 0.095% to 39.42% at the cortical level. Distributions obtained for each fixed parameter are depicted in Figure 3. The highest errors were obtained when the maximal permittivities were used in all tissues, as can be expected, while conductivities were at their lowest values except for WM. The distributions which strongly differed between min-max parameters values were for GM relative permittivities and conductivities. It is important to note that WM distributions for both relative permittivity and conductivity also differed even if less substantially.

DISCUSSION

This study aimed to quantify the EF variations due to both conductivity and permittivity uncertainty, and also to demonstrate if permittivity should be considered for tACS numerical modeling. Our results provided a range of the EF norm and normal magnitude with a max/min ratio of 36 and 33, respectively. We also highlight that EF magnitude is most sensitive to GM, skin and skull conductivity, and GM relative permittivity. Focality was also found to vary among tested values, with the best focality for low GM conductivity.

The results of the comparisons between EF with and without relative permittivity consideration showed an error that mainly depended on GM and WM relative permittivity values. This could be explained by the high values of relative permittivity reported for brain tissues [14,15]. The term $\omega \epsilon_r \epsilon_0$ in equation 1 becomes non-negligible and induced changes in EF distribution in GM. These results are consistent with previous reports [10], showing that neglecting conductivity can induce significant error depending on the ratio between conductivity and permittivity.

Among the limitations of our study, let us mention a lack of precise knowledge of EF sensitivity to each pair of dielectric properties. Uncertainty propagation methods could improve this lack of details, but would require substantial computational resources, since it involves an 8-dimensional parametric space to sample. Also, CSF uncertainty was not included here. If included, this would result in a 10-

dimensional space, which would require even more samples to study. Finally, more reliable measurements of low-frequency relative permittivity of tissues are required for accurate prior knowledge of the uncertainties that have to be considered in the computational modeling of tACS.

CONCLUSION

The uncertainty analysis on both conductivity and permittivity in tACS modeling was performed in this study, using extreme values reported in the literature. Our results provide the range of EF variation, which is broad and mainly depends on the conductivity of GM, skin, and skull and less on WM conductivity and GM permittivity. The relative error on EF prediction by neglecting relative permittivity in such analysis was quantified and can reach up to 40%. The main take-home message is that relative permittivity can become sufficiently high in tissues to cause changes in the results, depending on the associated conductivities. We argue for the need for new relative permittivity measurements of head tissues at low frequency, to finally settle which parameters to include in numerical analysis for accurate neural effect prediction of tCS effects.

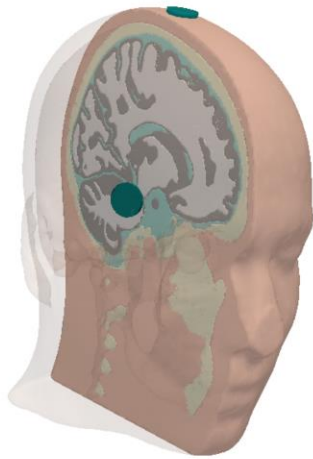
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White matter	$\sigma \in \{0.0646, 0.81\}$ S/m	$\epsilon_r \in \{10^5, 5.10^7\}$
Grey matter	$\sigma \in \{0.06, 2.47\}$ S/m	$\epsilon_r \in \{5.10^5, 10^8\}$
CSF	$\sigma = 1.654$ S/m	$\epsilon_r = 10^2$
Skull	$\sigma \in \{0.0182, 0.28\}$ S/m	$\epsilon_r \in \{10^3, 10^5\}$
Skin	$\sigma \in \{0.137, 2.1\}$ S/m	$\epsilon_r \in \{10^2, 10^4\}$
Contact gel	$\sigma = 4.0$ S/m	$\epsilon_r = 80$

Figure 1: Problem formulation. Head model geometry with the five main tissues (left) and associated dielectric properties values (right).

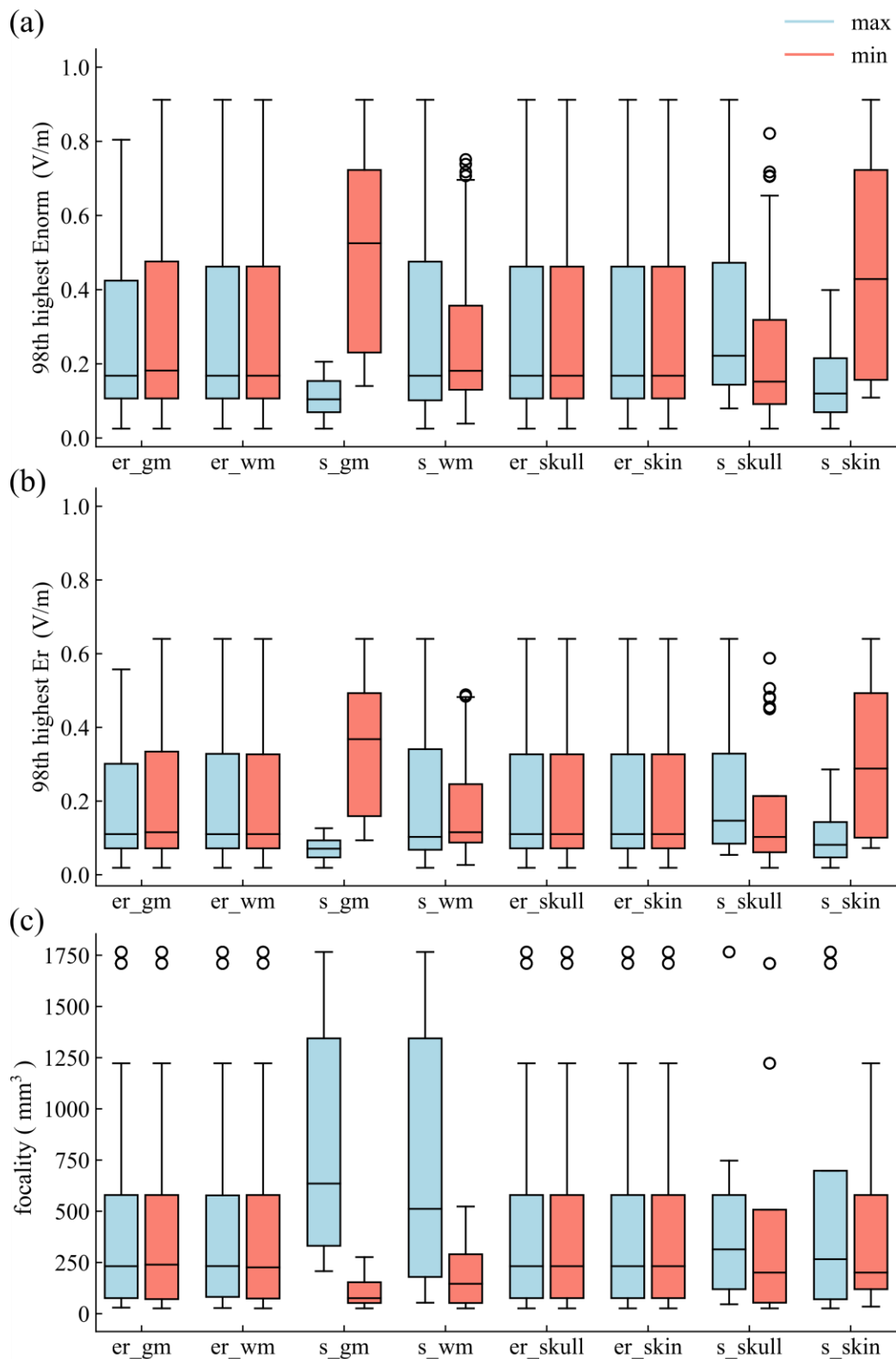


Figure 2: (a): 98th highest EF norm magnitude distribution as box plot for each parameters fixed values with other varying. Boxes are blue for maximum values of the dielectric parameter and red for minimum values. The same applies for (b) and (c) for 98th highest radial field magnitude and focality.

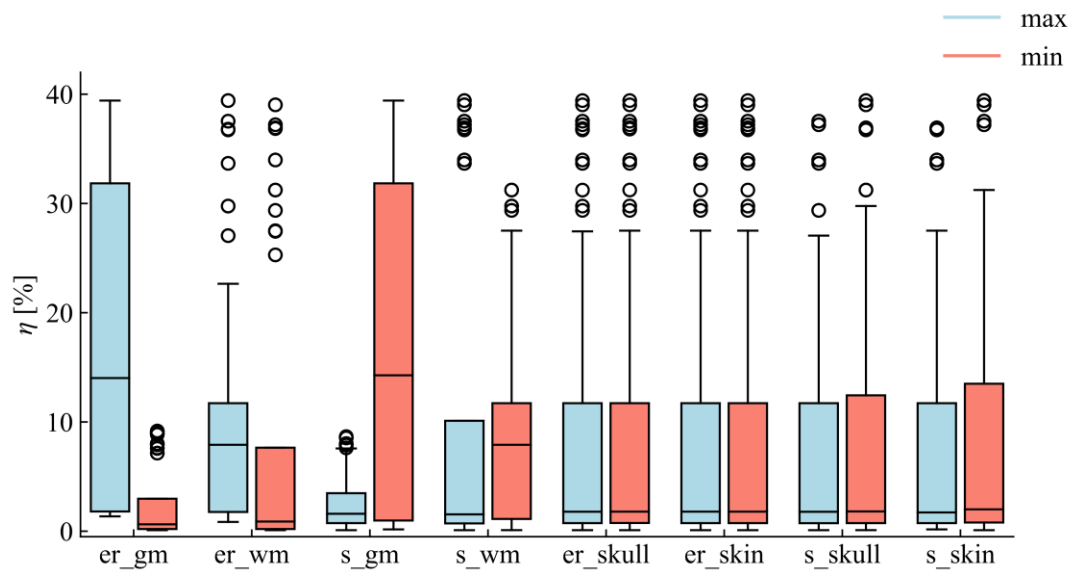


Figure 3: Relative error between the solution with and without relative permittivity (η) distribution as box plot for each parameters fixed values with other varying. Boxes are blue for maximum values of the dielectric parameter and red for minimum values.