Personalized Neuromodulation: A Computational Workflow to Guide Noninvasive Clinical Treatment of Neurological and Psychiatric Disorders

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Abstract*: Transcranial Electrical Stimulation (tES) is a noninvasive neuromodulation technique wherein low intensity electrical current is applied to the head via scalp-mounted electrodes. Transcranial Direct Current Stimulation (tDCS, a form of tES) is increasingly being used in the treatment of several neurological and psychiatric disorders such as stroke recovery, depression, and schizophrenia. However, tDCS-induced electrical current patterns in the brain show marked inter-individual variation due to underlying differences in brain morphology and choice of treatment protocol. It is therefore difficult to predict the clinical outcome of tDCS treatment in a particular subject. In the first part of this work, we develop a simulation workflow wherein high resolution patient-specific finite element models of the brain are used to determine the foci of tDCS-induced electric fields and thus predict the likely efficacy of the treatment.*

While tDCS can satisfactorily modulate neuronal activity in the cerebral cortex, it is less effective at stimulating deep brain regions implicated in movement and neuropsychiatric disorders such as Parkinson's disease, epilepsy, and obsessive-compulsive disorder (OCD). In patients that cannot be treated for these conditions with medications, a clinical alternative is deep brain stimulation (DBS), wherein electrodes are surgically implanted to modulate the neuronal activity in the affected deep brain region. However, DBS is highly invasive and carries many risks. In the second part of this work, we extend our workflow to incorporate transcranial Alternating Current Stimulation (tACS) using temporally interfering (TI) electric fields. By carefully selecting the current characteristics and electrode montage, it is possible to effectively stimulate specific deep brain targets while leaving the surrounding normal brain structures unaffected. It may therefore become possible to achieve the benefits of DBS in an entirely noninvasive manner. In this work, we demonstrate the clinical potential of computational modeling for tES treatment planning, including the ability for interactive real-time treatment protocol selection for a specific patient.

Keywords*: head, brain, neuromodulation, neurostimulation, neurophysiology, transcranial electrical stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, deep brain stimulation, tES, tDCS, tACS, DBS, temporal interference, schizophrenia, Parkinson's disease, neurological, psychiatric, movement disorders, clinical, personalized health, precision medicine, translational research, digital health, multiphysics*

1. Introduction

Neuromodulation, in a therapeutic context, refers to the clinically induced alteration of neural activity via an artificial stimulus such as an electrical current or a chemical agent. Neuromodulation may involve invasive approaches such as spinal cord stimulation or deep brain stimulation (DBS) wherein the stimulation electrodes are surgically implanted directly on the nerves to be stimulated. It may also be performed noninvasively using methods such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and transcranial electrical stimulation (tES) wherein external electrodes or magnets induce the required neural activity changes without the need for surgical implantation. Transcranial electrical stimulation (tES) is a noninvasive brain stimulation technique in which low intensity electrical currents (~1–2 mA) are applied to the head for several minutes (~5–30min) via scalp-mounted electrodes. The applied currents can be direct (transcranial Direct Current Stimulation, tDCS), alternating (transcranial Alternating Current Stimulation, tACS), or random noise (transcranial Random Noise Stimulation, tRNS) as shown in Figure 1 [Yavari 2017]. During tES, the subject is fully conscious and experiences minimal discomfort. TES in general and tDCS in particular are increasingly being used in the treatment of several neurological and psychiatric disorders such as depression, stroke recovery, and schizophrenia. Moreover, the simplicity, affordability, and portability of tES make it an ideal treatment in developing countries, such as India, which suffer from both a high prevalence of mental disease and low access to pharmacological therapy. However, efficacious personalized application of tES faces a number of challenges that the current work seeks to address.

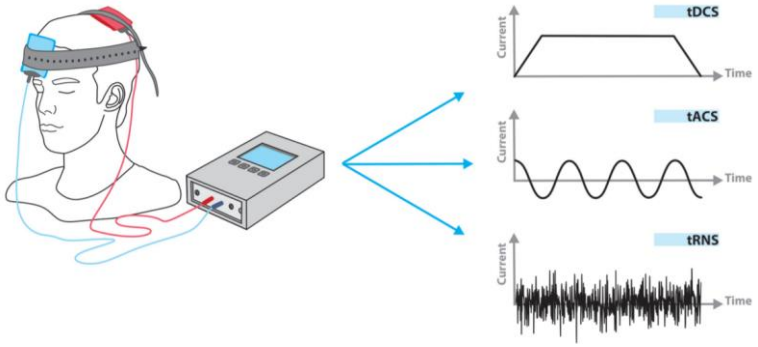


Figure 1. Schematic of tES modalities [Yavari 2017].

The primary challenge is that tES-induced electric current patterns in the brain show marked inter-subject variation due to underlying differences in brain morphology and tissue characteristics, including the relative size and shape of major head/brain regions, relative electrical conductivity of different regions, and the architecture of white matter tracts. In addition, the tES protocol itself involves the selection of several parameters such as the amplitude, polarity, and frequency of the applied current as well as the shape, size, number, and location of the electrodes. It is therefore

difficult to predict the distribution of electric current in the brain and consequently the likely efficacy of the treatment for a particular subject. Computational modeling and simulation of tES can potentially address this challenge. By computing the resulting electric field with high spatial resolution, we can observe exactly which brain regions are likely to have been stimulated and thus correlate input (treatment protocol) parameters with output (clinical or behavioral outcomes). Moreover, by virtually experimenting with different treatment protocols on a subject-specific simulation model, the clinician can determine the most efficacious treatment for a given individual rather than relying on conventional nonspecific guidelines as is typically the case today.

2. Simulation Workflow for tDCS in Schizophrenia

2.1 Neurophysiology of tDCS in Treatment of Schizophrenia

Schizophrenia is a serious mental disorder characterized by incoherent or illogical thoughts and bizarre behavior and speech. Positive symptoms include delusions and hallucinations, while negative symptoms include emotional withdrawal, difficulty in abstract thinking, and lack of spontaneity. Positive symptoms are associated with excessive neural activation in the temporo-parietal junction, while negative symptoms are associated with deficient neural activation in the prefrontal cortex (Figure 2). Since neuronal activation is positively correlated with membrane potential, tDCS works by applying an anodic stimulation to the underactivated brain regions to increase the local resting potential (i.e., depolarization) and applying a cathodic stimulation to the overactive brain regions to decrease the resting potential (i.e., hyperpolarization) in that neighborhood. Note that tDCS does not directly generate a neuronal action potential, rather, it increases or decreases neuronal excitability or the probability that an action potential will be spontaneously triggered by normal synaptic inputs. In a typical 2-electrode tDCS protocol, a current of 1-2mA is applied continually for 20 minutes, and a single treatment course involves 2 sessions daily for 5 days. A course of tDCS can significantly reduce auditory verbal hallucinations (the focus of our study) for up to 3 months [Bose 2017].

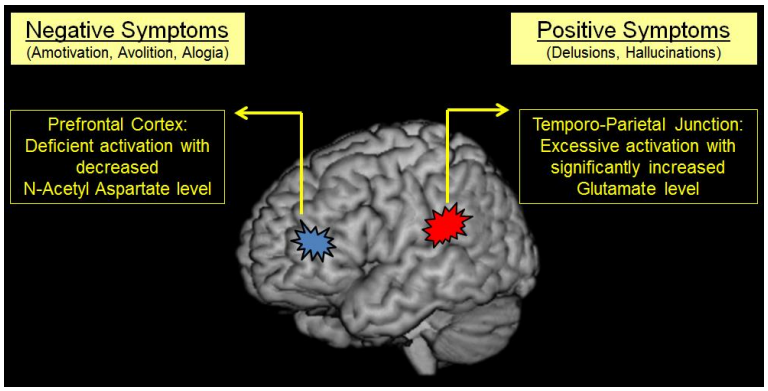


Figure 2. Brain Abnormalities associated with Schizophrenia [Venkatasubramanian 2005a and 2005b].

2.2 Personalized Model Generation

Since the primary goal of this project was to demonstrate the value of simulation for subject-specific tDCS outcome prediction, a post-hoc study was conducted to analyze the results of two patients with persistent auditory verbal hallucinations despite antipsychotic medication. One patient had responded favorably to tDCS while the other had not even though both were administered identical treatments (i.e., electrode positions, input currents, duration, etc.). The objective of the study was to examine if simulation could shed light on the difference in outcomes. To begin, T1 weighted MRI scans for the subjects were acquired using a Philips Ingenia 3T scanner with $1mm^3$ resolution. Each scan was then segmented using a probabilistic segmentation procedure with the Statistical Parametric Mapping (SPM) toolkit [Ashburner 2005] into 6 distinct non-overlapping tissue regions: grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), skin/flesh, skull, and sinus/air. Segmentation errors (e.g., non-smooth tissue surfaces and disconnected regions) were corrected using automated routines in MATLAB® [Huang 2012]. After a satisfactory 3D head/brain model was developed, electrode placement was performed with Simpleware® ScanIP (+ ScanCAD module) using the 10/10 international convention with the anode at AF3 and the cathode at CP5 (Figure 3). Finally a high resolution tetrahedral FE mesh (average element size = $1mm^3$) was generated using the ScanIP (+ ScanFE) module.

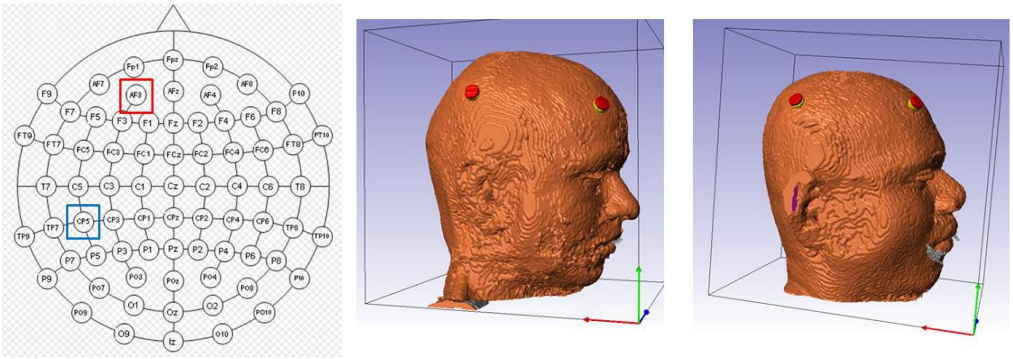
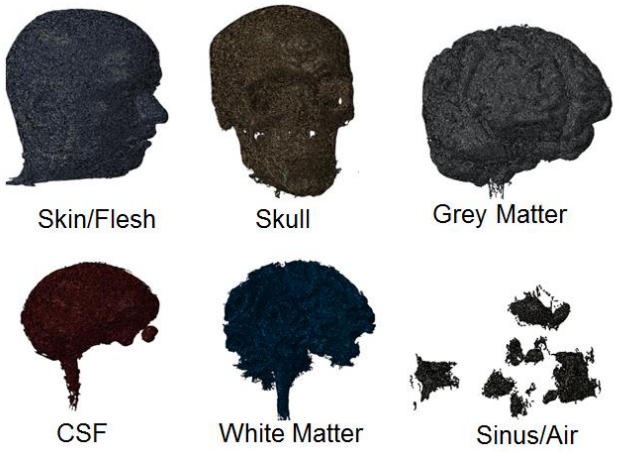


Figure 3. International 10/10 Convention showing Anode AF3 (red) and Cathode CP5 (blue); Subject-specific Models (Left: Responder; Right: Non-responder).

2.3 FE Analysis: Scenario

Each FE model (responder and non-responder) was meshed with about 3M nodes and 17M DC3D4E electrical conduction elements. The different brain regions were assigned appropriate isotropic electrical conductivity values taken from the literature (shown in Figure 4). A thin layer of gel was also included in the model between the scalp and the electrodes to better mimic the experimental set-up. At the anode, an inward current of 2mA was applied while at the cathode an outward current of 2mA was applied; the rest of the exterior surface of the model was insulated. At an arbitrary node of the model in the chin region (away from the electrodes), the electric

potential was set to zero to eliminate possible rigid body solutions. A single-step single-increment electrical analysis was performed in Abaqus/Standard version R2017x to determine the electrical potential gradient (EPG) distribution (which is identical to the electric current density distribution) in the brain. The different tissue regions and material properties used are shown in Figure 4.



Region	Electrical Conductivity (KS/mm)
Skin/Flesh	4.65E-07
Skull	1.00E-08
CSF	1.65E-06
White Matter	1.26E-07
Grey Matter	2.76E-07
Sinus/Air	1.00E-21
Gel	3.00E-07
Electrode	5.90E07

Figure 4. FE Model Regions (Responder) and Conductivities (both Subjects).

2.4 FE Analysis: Results

By examining the distribution of electric current at steady state, we can see that overall head shape and tissue morphology play an important role in determining the focus of neurostimulation in a specific subject. Careful comparison of the EPG distribution on the exterior surface of the grey matter (GM) (Figure 5) shows a higher electric current density in the parietal lobe of the responder, while in the non-responder, we see current more evenly distributed across the parietal and frontal lobes. This can be explained by the fact that the responder's grey matter contains deeper sulci in the parietal lobe when compared with those seen in the non-responder. As the sulci are filled with CSF, which is a better conductor than grey matter, we can expect the current density to be higher in this region for the responder than for the non-responder. Since the total current in the brain is the same in both cases (2mA), this could imply that the parietal regions, implicated in auditory hallucinations, are being insufficiently stimulated in the case of the non-responder rendering his treatment less efficacious. Possible solutions include increasing the amplitude of the current, repositioning the electrodes, or using multiple electrodes to focus the current more effectively at the temporo-parietal junction. We also see very low (physiologically insignificant) electric current density in regions below the WM/GM boundary as expected. From this simple retrospective analysis, we can see how subject-specific 3D electric current distribution information can explain (at least partially) the difference in response between subjects. More

importantly, by virtually experimenting with various electrode configurations and current characteristics, the clinician can optimize the treatment protocol for a given individual.

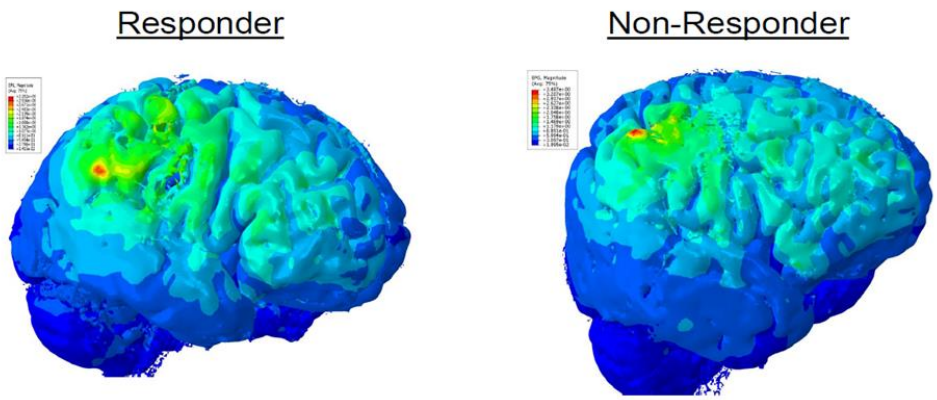
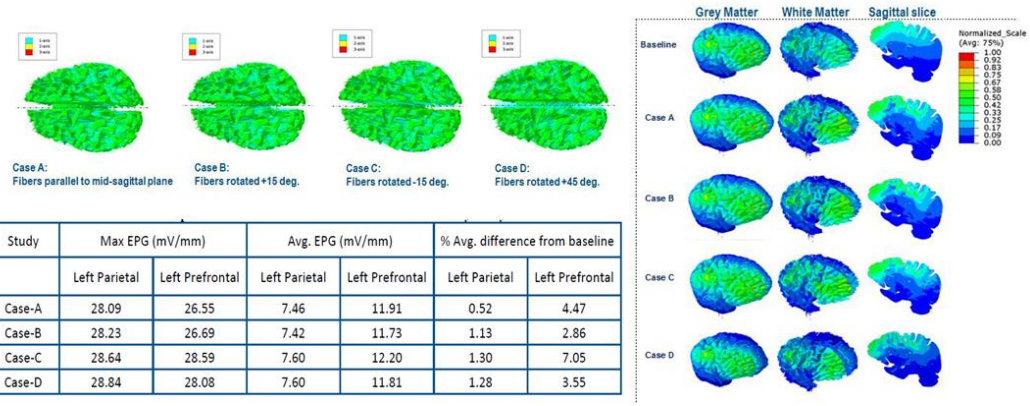


Figure 5. EPG Magnitude on Exterior Surface of GM for Both Subjects

2.5 Influence of White Matter (WM) Tract Anisotropy

In the above study, the brain was assumed to have isotropic electrical conductivity. While WM fiber tracts exhibit complex topology and spatially varying fractional anisotropy, it is unclear to what extent their complexity impacts tDCS. To explore the sensitivity of tDCS to WM tract orientation, a series of models was created with 4 different (but spatially invariant in each model) WM fiber tract orientations (rotated about the mid-sagittal plane at angles of 0^o, $+15^o$, -15^o, and $+45^o$), as shown in the top left of Figure 6. While physiologically unrealistic, these arbitrary orientations were mainly intended to quantify the anisotropy-induced change in maximum and average EPG distribution from the baseline (isotropic) case. In all cases, electrical conductivity along the fiber direction was set identical to the isotropic value used earlier, while transverse conductivities were set to 10% of the isotropic value. Each model was run with identical constraints as the baseline analysis. Figure 6 also shows the results of the WM anisotropy study in both tabular and graphical form. It is clear that WM tract orientations affect tDCS-induced current distribution in the brain in a non-uniform manner (e.g., the frontal lobe appears more sensitive to anisotropy than the parietal lobe). In all 4 cases, the change in peak and average EPG magnitude from baseline was less than 10% and a small shift in peak location was noted. At this time, it is unclear if the changes in EPG distribution are of clinical significance; further studies with more realistic WM topologies as well as experimental data are needed to answer this question. If future work affirms the importance of WM anisotropy on clinical outcome of tDCS, then the FE models will need to incorporate anisotropy by using either idealized fiber topologies (that can simply be scaled and positioned appropriately in a subject-specific FE model) or by using subject-specific topologies derived from diffusion tensor (DT-MRI) data.



Study	Max EPG (mV/mm)		Avg. EPG (mV/mm)		% Avg. difference from baseline	
	Left Parietal	Left Prefrontal	Left Parietal	Left Prefrontal	Left Parietal	Left Prefrontal
Case-A	28.09	26.55	7.46	11.91	0.52	4.47
Case-B	28.23	26.69	7.42	11.73	1.13	2.86
Case-C	28.64	28.59	7.60	12.20	1.30	7.05
Case-D	28.84	28.08	7.60	11.81	1.28	3.55

Figure 6. Models and Results from WM Anisotropy study.

3. Noninvasive Deep Brain Stimulation

3.1 Limitations of tDCS for Deep Brain Stimulation

While tDCS is increasingly being used in clinical settings, its applicability is predominantly limited to disorders that originate in malfunctions of the higher regions of the brain, primarily in the cortex. This is because tDCS uses low intensity currents that are unable to penetrate into the deeper regions of the brain (although deep brain regions may be indirectly modulated due to neural network connectivity). Increasing current amplitude will allow deeper regions to be stimulated but may be undesirable for two reasons. First, greater current strength will also stimulate normally functioning overlying areas and may even cause unintended neuronal firing. Second, prolonged exposure to higher current can cause discomfort or injury to the scalp. The conventional treatment for deep brain disorders therefore uses deep brain stimulation (DBS) wherein stimulation electrodes are surgically implanted directly into the malfunctioning areas so that neuromodulation can be limited to a small area with minimal disruption of the surrounding tissue. However, DBS is a highly invasive procedure with potential adverse effects including electrode displacement and erosion, infection, stroke, and seizures. Moreover, the high cost of DBS surgery and recovery, and the high level of clinical expertise necessary to ensure positive outcomes typically render this treatment infeasible for routine public health in developing countries such as India. Recent research suggests that tES may be a viable alternative to conventional DBS, at least for some mental disorders. The second part of our work describes how tES can be used for subject-specific noninvasive DBS and extends our computational workflow to facilitate clinical use of this new technology.

3.2 Transcranial Alternating Current Stimulation (tACS)

While some mental disorders involve abnormal (and polarity-specific) neuronal excitability and can therefore be treated by the application of direct current, others, such as Parkinson's disease,

Alzheimer's and epilepsy are correlated with abnormal brain rhythms (which typically range from 0.05Hz to 500Hz) [Reato 2013]. Treatments for these conditions may therefore involve attempts to restore normal brain wave activity in the affected area using alternating current. AC stimulation can improve brain rhythm either by entrainment (where brain oscillation frequency is aligned with the forcing frequency) or by modulation (where brain oscillation amplitude is scaled by the external signal) as shown in Figure 7 [Reato 2013].

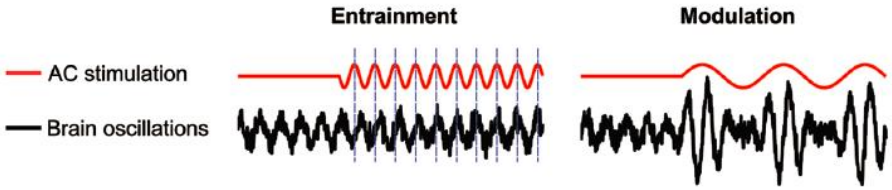


Figure 7. Effects of AC stimulation on Brain Oscillation [Reato 2013].

3.3 Temporal Interference in tACS

If the malfunctioning neurons are located in deep brain structures, then "conventional" application of tACS via scalp electrodes will suffer from the same limitations as those outlined for tDCS. However, as demonstrated by Grossman et al [Grossman 2017], if we use two frequencies instead of one, it becomes possible to selectively stimulate the deep brain without affecting the surrounding tissue by exploiting the phenomenon of wave interference. Consider two electric fields $\bar{\mathbf{E}}_1$ and $\bar{\mathbf{E}}_2$ of equal magnitude that coexist at the same point in space. If the two fields oscillate at slightly different frequencies ($f1$ and $f2 = f1+\Delta f$), the resultant linearly superposed field will oscillate at the average frequency ($f1+ f2)/2$ but its amplitude will be modulated at the difference or 'beat' frequency Δf. Moreover, the beat amplitude will depend on the degree of alignment of the two fields $\bar{\mathbf{E}}_1$ and $\bar{\mathbf{E}}_2$. This is illustrated in Figure 8 – on the left side, we see that the envelope of the y-component of resultant modulated field $\bar{\mathbf{E}}_{AM} = \bar{\mathbf{E}}_1 + \bar{\mathbf{E}}_2$ has a high amplitude if the y-components of $\bar{\mathbf{E}}_1$ and $\bar{\mathbf{E}}_2$ have similar magnitudes, whereas the reverse is true if their y-components have dissimilar magnitudes. The net amplitude of the modulated signal $\bar{\mathbf{E}}_{AM}$ at any point in space is the vector sum of the amplitudes of the x-, y-, and z-components of $\bar{\mathbf{E}}_{AM}$.

The main point of this discussion is that if it were possible to specify $\bar{\mathbf{E}}_1$ and $\bar{\mathbf{E}}_2$ at every point in some closed domain, we would be able to control the amplitude of the resultant linearly superposed field throughout the domain. In regions where a high amplitude envelope was desired, we would need to ensure close alignment in the magnitude and direction of the individual fields $\bar{\mathbf{E}}_1$ and $\bar{\mathbf{E}}_2$, whereas in regions where minimal or no modulation was desired, we could have one field be much stronger than the other. For the simple 2D case of a closed circular domain, this concept is illustrated on the right side of Figure 8 where we can see that $\bar{\mathbf{E}}_1$ and $\bar{\mathbf{E}}_2$ are aligned and of equal magnitude in the central region of the domain. Therefore the beat amplitude would be highest in this region and would gradually decrease as we move away from it. This concept of linearly superposing two oscillating electric fields (also known as temporal interference) suggests a technique to stimulate specific structures of the brain with minimal impact on other structures.

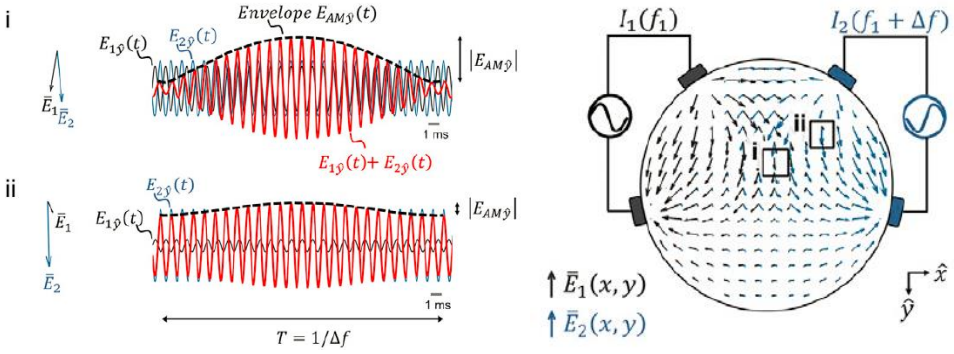


Figure 8. Temporal Interference in tACS [Grossman 2017].

3.4 Neurophysiology of Temporal Interference in tACS

Temporal Interference tACS (TI-tACS) relies on two important neurophysiological characteristics. The first is that neurons respond to low frequency external fields but their response decreases significantly at high frequencies. In essence, the neuron acts as a low-pass filter that is effectively insensitive to frequencies above some threshold (typically ~1kHz). Moreover, greater the amplitude of the local excitation, greater is the neuronal response. In Figure 9 [Reato 2013], we see that membrane polarization (i.e., the response of the neuron) decreases as the frequency of the applied AC signal increases and increases with increasing AC signal amplitude. Therefore, if we set the frequency of both signals ($\bar{\mathbf{E}}_1$ and $\bar{\mathbf{E}}_2$) above the threshold, we will stimulate only those regions in the brain where the two fields result in a modulated signal of appreciable amplitude. In other regions, the modulated amplitude will be too low and the average frequency too high to effect any change in the neurons. As such, we can selectively stimulate the brain using TI-tACS.

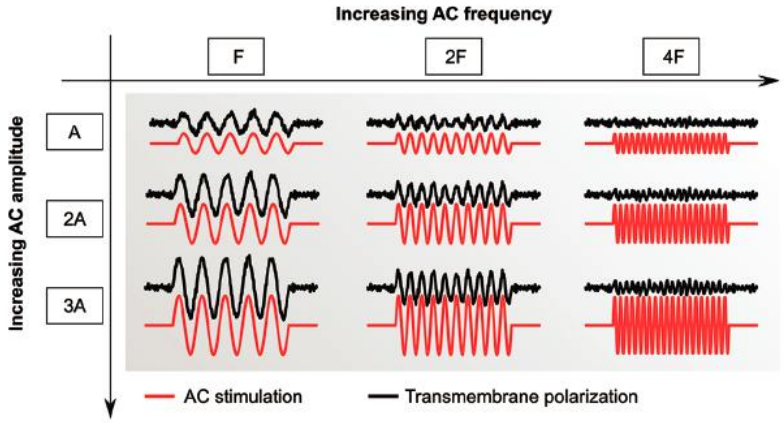


Figure 9. Effects of AC stimulation on Single Neurons [Reato 2013].

3.5 Verification of TI-tACS Simulation in Abaqus

We began our tACS project by replicating the computational tests of Grossman et al [Grossman 2017]. On the left side of Figure 10, we show the Grossman model, a cylinder of 50mm diameter and 10mm height. The grey electrode pair at the bottom applies a 1kHz signal while the black electrode pair on the top applies a 1.02kHz frequency signal. The contour plot show the normalized magnitude of the modulated resultant field oscillating at Δf = 20Hz throughout the domain with yellow representing high amplitude regions and dark blue representing low amplitude regions. On the right, we show the equivalent Abaqus model – we see that our model (high amplitude in red, low amplitude in blue) is able to replicate the spatial characteristics of the Grossman model; in particular, it generates the same spatial contrast in amplitude computed by the Grossman model. We also verified our results against the Grossman model for different electrode configurations and current ratios. Since the electrical procedure in Abaqus does not permit frequency domain analysis (and since a time domain simulation would be unnecessarily computationally expensive), we used the following methodology. For each electrode pair, a single DC analysis (1-step 1-increment) was conducted to determine the non-oscillating electric field vector at every point in space for a unit amplitude input signal. The results of both analyses were then vectorially superposed using a Python script that enabled scaling of individual signal amplitudes (and frequencies) as needed. The resultant modulated field is taken to oscillate at the beat frequency and the contours indicate the magnitude of the modulation.

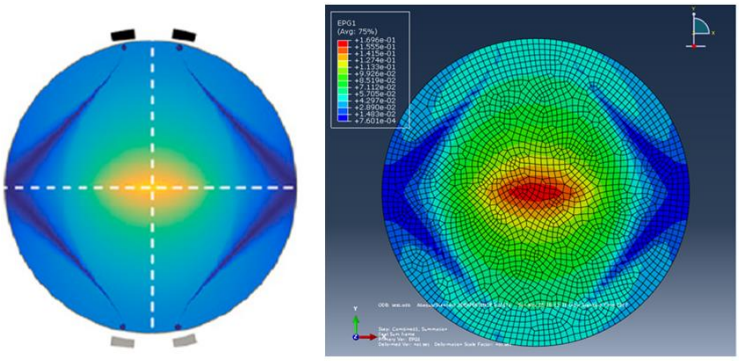


Figure 10. Comparison of Grossman Model (left) and Abaqus Model (right).

3.6 High Definition TI-tACS Simulation in Abaqus

Having verified the concept of TI-tACS with Abaqus for a simple geometry, we then began using an MRI-derived subject-specific FE model to assess the clinical feasibility of this technique. Initial simulation runs were conducted with simple bipolar electrode configurations for each frequency. For instance, one frequency might be applied via an electrode pair located at F9 and F10 while the other frequency applied via another pair located at the coronally symmetric regions PO9 and PO10. It was observed that the resulting modulated field was quite diffuse (i.e., it was difficult to

generate focused amplification of the modulated signal). Moreover, in some cases, we observed constructive interference in multiple disconnected regions (i.e., off-target locations were being stimulated as effectively as the target location). Both issues can be seen in Figure 11 for the configuration mentioned above. To circumvent these problems, we decided to deploy multipolar electrode configurations, also known as High Definition tACS (HD-tACS) in which more than 2 electrodes are used for each frequency. We used a 4x1 multipolar configuration as shown in Figure 12. For both frequencies (1kHz and 1.02kHz), the polarity of the center electrode (highlighted in yellow) is opposite to that of the four surrounding electrodes and the applied currents are scaled accordingly (e.g., +1mA for the central electrode, -0.25mA for each of the surrounding electrodes in the Abaqus DC analysis).

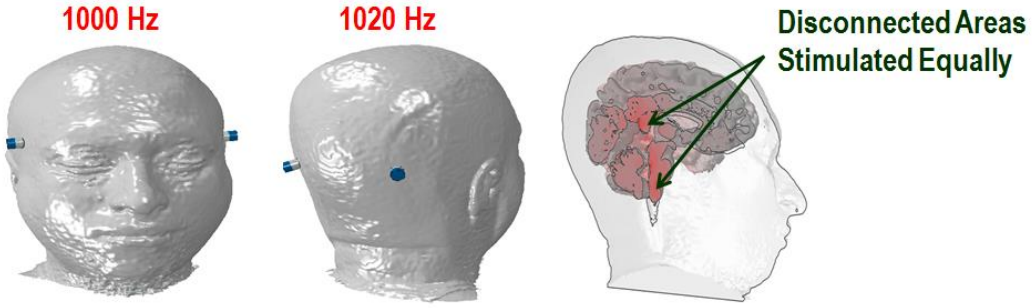


Figure 11. TI-tACS Simulation using an Electrode Pair for each Frequency.

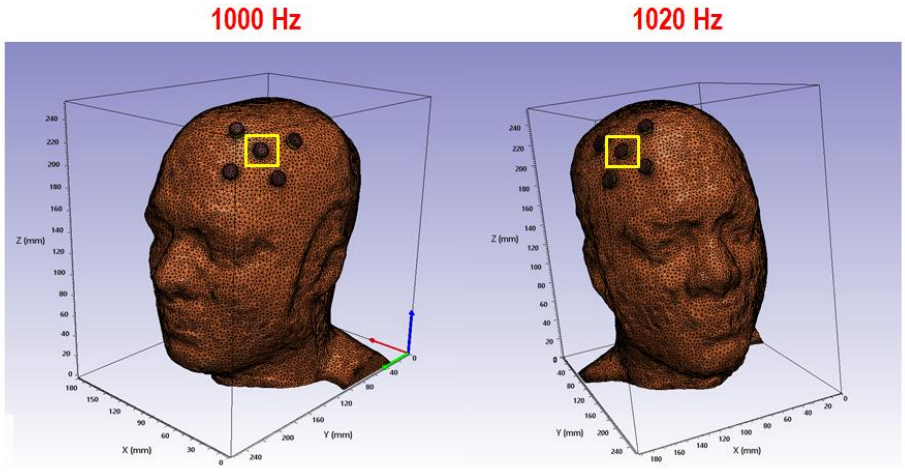


Figure 12. High Definition 4x1 Montage used for TI-tACS Simulations.

Subject-specific HD TI-tACS simulations were conducted for 16 unique electrode montages. Contour plots of the resultant modulated field amplitude on the mid-sagittal plane are shown in Figure 13 for 4 different scenarios, where the locations listed correspond to the position of the central electrode. It is clear that by selecting the appropriate electrode montage, we can control both the focus and the extent of effective neurostimulation. While F3/F4 is able to stimulate only the cortical region, the other 3 configurations are able to selectively stimulate deep brain regions with little impact on the rest of the brain. In fact, if we use more sophisticated electrode montages (M_1xN_1 electrodes for frequency f_1 and M_2xN_2 electrodes for frequency f_2), it is possible to achieve high levels of spatial concentration and amplitude of neurostimulation. Thus, we have demonstrated that clinicians can use our computational workflow to devise optimal subject-specific TI-tACS treatment protocols for noninvasive deep brain stimulation.

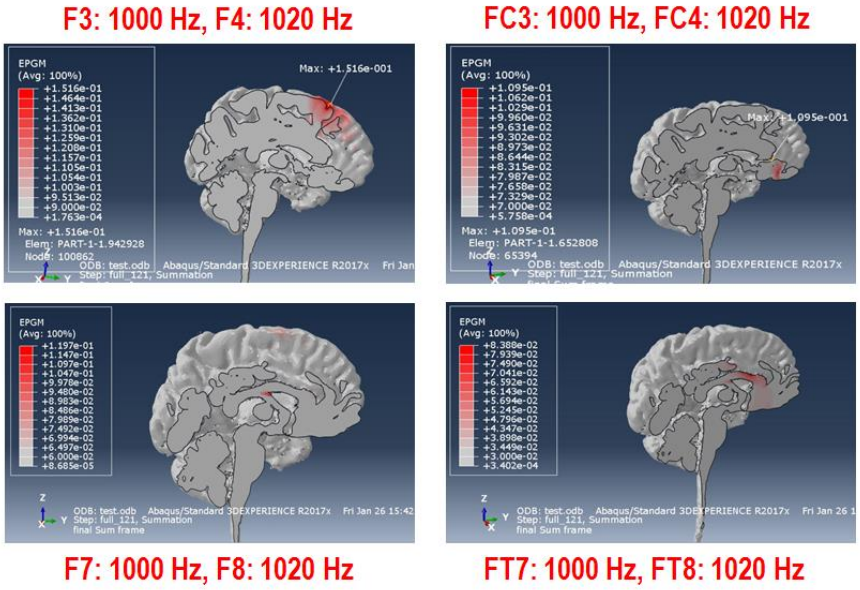


Figure 13. Selected Results of Subject-specific HD TI-tACS Simulations.

4. Clinical Usability of Personalized Neuromodulation Workflow

4.1 Clinical Visualization of Simulation Results

While FE mesh-based contour plots are useful to engineers, they may not be ideal for clinicians who are typically unfamiliar with such visualization modalities. To facilitate clinical analysis of the simulated results, the SPM toolkit was used to overlay Abaqus EPG results on standard MNI ICBM 152 template. In Figure 14, we show two ways in which simulation results can be visualized in MRI space. In the tACS image on the left, we plot the modulated resultant amplitude for the F7-F8 pair discussed above with the crosshairs indicating points of maximum amplitude. It

is clear that MRI-based presentation of the result allows easier identification of the anatomic structures likely to be stimulated. In the tDCS image on the right, we show the difference in tDCS-induced EPG distribution for the responder versus the non-responder. Areas in red correspond to regions where EPG magnitude was higher for the responder while those in blue indicate where EPG was higher for the non-responder. We see that the responder shows more localized activation in the inferior parietal lobule while the non-responder shows more diffuse activation. These results are in accordance with our earlier observations; however, by examining the responder and non-responder results overlaid on each other, clinicians can more readily connect the differences in stimulated neuroanatomical regions to the differences in response to tDCS. As such, we can combine the benefits of patient-specific modeling with standardized clinical visualization practice.

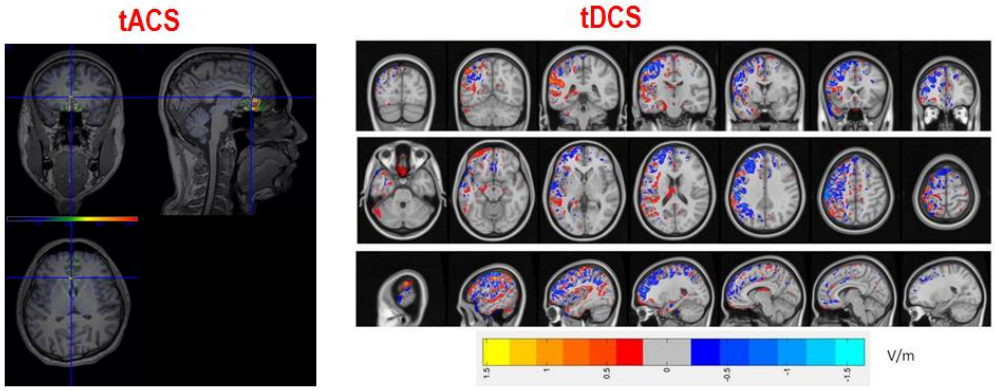


Figure 14. Simulation Results projected on Standard MRI template.

4.2 Subject-specific Optimization of tACS Treatment Protocol

A typical subject-specific FE model runs to completion in under 30 minutes on 128 cores. It is therefore possible to sequentially assess about 25-50 different treatment configurations within a 24-hour period from the subject's arrival for MRI scanning in an effort of select the best approach for a particular subject. This can be done in two ways. In the simple case, treatment configurations can be standardized such that the same set of electrode configurations is run for all subjects to identify the one best suited for the specific subject. Obviously, this approach is limited by the computational resources available. Alternatively, by using an intelligent parametric optimization tool such as Isight, the clinician can specify the brain region to be stimulated and let the optimization code determine the optimal choice of montage parameters (number and position of electrodes) to achieve the desired objective for that specific subject. While this approach is also ultimately constrained by the available computational resources, it is certainly more effective at devising optimal treatment protocols than the simple approach, given the same HPC capacity. Once the optimal electrode configuration has been identified, the superposition theorem for linear electric circuits allows us to further optimize the current characteristics in an interactive manner. Since the normalized magnitudes of the precomputed DC solutions are invariant with respect to

changes in amplitude or frequency, we can modify these parameters for each field individually and examine the resultant current distribution in real time. This allows the clinician to fine tune the current characteristics to achieve more focused neurostimulation. For instance, by retaining the optimal electrode positions but modifying the amplitude ratio of the two input frequencies, the clinician can shift the focal point in real time (using visual feedback for guidance). This two-step optimization of subject-specific tACS treatment protocols is illustrated in Figure 15.

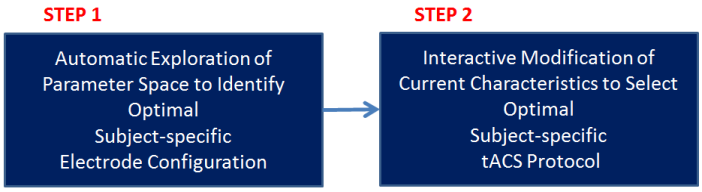


Figure 15. Two-step Methodology to Optimize Subject-specific tACS Treatment.

5. Conclusion

In this paper, we have described a computational workflow to guide the clinical application of subject-specific tES for the treatment of neurological and psychiatric disorders. In Figure 16, we show the key components of the workflow. Beginning with a high resolution FE mesh derived from subject-specific structural MRI data, we can automate the number and location of electrodes for tDCS and tACS given the desired region of maximal neurostimulation. We can then map the simulation results on MRI space to facilitate clinical analysis and collaboration. Finally, we can support real time interactive modification of current characteristics to decide on the best treatment protocol for a specific subject. Using this workflow, clinicians can devise optimal patient-specific treatment plans in a practical timeframe.

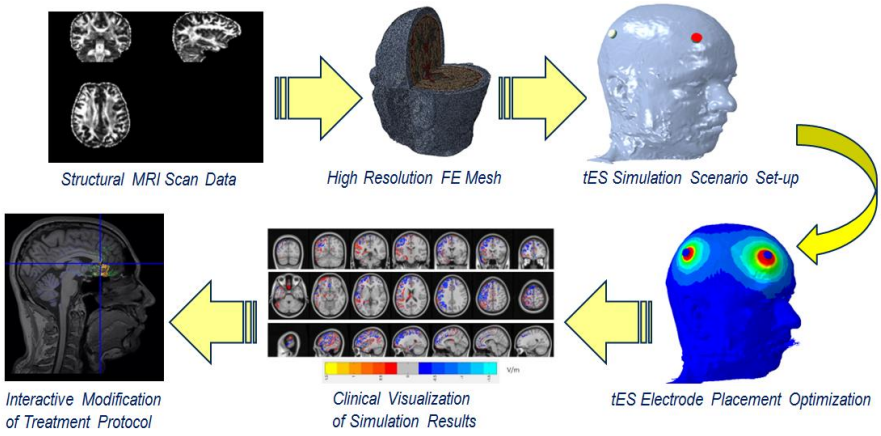


Figure 16. Computational Workflow for Personalized Neuromodulation.

Future work on this project will include both scientific and practical components. To deploy this workflow at scale in a clinical setting, the Image->Mesh process needs to be robust and fully automated. More research needs to be done on TI-tACS, HD electrode configurations, and the effects of electrical anisotropy of the brain. We are currently developing a multiscale methodology to couple single neuron biophysics (systems) models to 3D whole brain (FE) models to elucidate the neurophysiological changes induced by tES. We are also using machine learning to develop a more holistic predictive framework based on 3D imaging and physics-based simulation as well as on subject-specific genetic, clinical, biometric, behavioral, and environmental information to better guide the diagnosis and treatment of neurological and psychiatric disorders.

6. Acknowledgments

This work was supported by the Swarnajayanti Fellowship Research Grant (DST/SJF/LSA-02/2014-15) awarded by the Department of Science and Technology (Government of India) to Dr. Ganesan Venkatasubramanian. UberCloud, Advania, Hewlett Packard Enterprise, and Intel provided cloud-based HPC resources for verification of subject-specific TI-tACS optimization.

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