‘Intelligent’ Current Source And Computational Modeling for Personalized Temporal Interference Brain Stimulation From DC–100 kHz

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Temporal interference (TI) stimulation enables 3D focal non-invasive electrical neural stimulation of both superficial and deep regions in the brain [1]. The technology is based on two or multiple electric fields that are applied at slightly different frequencies (e.g., 2.01 kHz and 2.00 kHz) to drive neural dynamics at the difference frequency (i.e., 10 Hz) at locations where the corresponding currents intersect. Experimental research, however, is still limited due to the lack of adequate hardware and treatment planning solutions currently available. Here we report on the development a novel TI investigational device that enables the safe application of arbitrary, customizable, and fully differential current waveforms in the DC to 100 kHz range with exceptional performance. The device consists of an 8-channel, battery-powered ‘intelligent’ current source that includes output currents up to 10 mA (suitable for both animal and human experiments), very low mixing product (harmonic and intermodulation distortion) between channels and very low distortion. It is magnetic resonance imaging compatible, supplied with multiple synchronization inputs and outputs to allow triggering and/or synchronization with for example electroencephalographic (EEG) or electrocardiographic signals, and is remotely connected via optical links to a PC for setup and control. In addition to the device, a computational framework for *in silico* TI stimulation modelling is being developed to (i) support the planning of human and animal experiments, (ii) permit the formulation of testable hypotheses about mechanisms of stimulation; (iii) improve targeting of clinically relevant targets by optimizing electrode placement and stimulation parameter; (iv) ascertain safety (e.g., avoidance of off-target stimulation) and treatment performances. The framework relies on low frequency electromagnetic (EM) finite element method simulations executed on high resolution reference anatomical whole-body animal and human head models – such as the MIDA [2] – as well as on personalized, image-based human and animal head models. The framework allows the importing/creation/editing and placement of electrode geometries (either user-defined or pre-localized e.g., according to the 10-10 International EEG system) via interactive graphical user interface or Python scripts. Full automation of model setup and the execution of EM simulations is provided by Python scripts and customizable, shareable, pipelines. Post-processing analysis functionalities to quantify standard TI exposure (e.g., maximum total or directional amplitude modulation), TI dose (i.e., whole brain and regional cumulative dose-volume histograms, isopercentiles), targeting (focality, accuracy), and safety (dose on sensitive non-target regions) relevant metrics are provided that can be used as goal functionals for treatment optimization. The software allows optimization of TI strategies requiring the exploration of large parameter spaces such as the selection of treatment electrode locations or the use of multiple electrode pairs. For these applications, field optimization is accelerated through the use of the superposition principle on *N-1* precomputed E-field maps (*N* being the number electrodes in the head models largely reducing the computational burden). The software will also allow the execution of coupled EM-neuronal dynamics modeling enabling to study the impact of TI exposure on neuroelectric activity using electrophysiological models of neurons and axons and functionalities to quantify treatment uncertainty.
Validation experiments conducted at state-of-the-art facilities, including the Massachusetts Institute of Technology and Harvard Medical School in the US, Imperial College London, UK, the Edmond & Lily Safra Center for Brain Sciences, IL, and the Swiss Federal Institute of Technology, CH, to target a range of deep brain structures (insula, hippocampus, etc.) are ongoing and provide experimental validation. Applications related to TI stimulation using existing implants (such as deep brain stimulators) to achieve a degree of stimulation adjustment and steering (e.g., to compensate for non-optimal electrode placement) are being investigated.

References

[1] Grossman N et al. “Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields”, *Cell*. **1**; 169(6): 1029–1041 (2017)
[2] Iacono MI et al. “MIDA: A Multimodal Imaging-Based Detailed Anatomical Model of the Human Head and Neck” PLoS One. **10**(4): e0124126 (2015)