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Influence of Transcranial Electrical Stimulation (TES) waveforms on neural excitability of a realistic axon: a simulation study.

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***Abstract*— Neuromodulation caused by transcranial electrical stimulation (TES) has been used successfully to treat various neuro-degenerative diseases. Simulation models provide an essential tool to study brain and nerve stimulation. Simulation models of TES provide an opportunity to research personalization of therapy without extensive animal and human testing. A computer model of a realistic sensory axon was built by finding actual geometry of the trigeminal nerve through tractography. A finite element model of the head was solved to obtain electric potential distribution caused by TES. Different waveforms were defined to test transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) with varying amplitude and frequency. Neural activity patterns were observed. The strength-duration curve was plotted to verify the model.**

I. Introduction

Transcranial electrical stimulation (TES) methods are non-invasive, safe, low-cost techniques that have been used as therapy for conditions such as depression, epilepsy, Alzheimer's disease, and Parkinson's disease and prove effective in modulating brain function [1]. TES methods include transcranial direct current stimulation (tDCS) which uses weak direct currents targeting cortical neurons and transcranial alternating current stimulation (tACS) which use alternating currents targeting endogenous oscillations of the brain. Modulation effects vary from person to person due to differences in neuroanatomy and hence differences in induced electric field inside the brain [2]. Simulation models provide an effective platform to study neuromodulation and its repeatability without having to test on patients or animals. TES can also be used to target focal brain regions for personalized patient specific therapy.

A TES simulation study generally consist of two parts: 1. Using finite element modeling (FEM) to generate induced electric potential maps in a head model and 2. Applying those maps on an axon model to study neural activity. Recent studies have used realistic head models obtained by segmenting MRI data into individual tissue type and solving through finite-element methods. Software like SPM12 (fil.ion.ucl.ac.uk/spm) and FreeSurfer (surfer.nmr.mgh.harvard.edu) have been used to automate segmentation and processing pipelines like SimNIBS (simnibs.org) are now available to assist modeling current flow in realistic head models. Biophysical nerve models can be built using software like NEURON (neuron.yale.edu) and GENESIS (genesis-sim.org) which predict the effects of stimulation using methods presented by McNeal [3]. Such models assume quasi-static behavior and ignore the effects of ephaptic coupling.

The trigeminal nerve is a sensory motor nerve which provides tactile, proprioceptive, and nociceptive afference to the face and mouth. Neuromodulation of the trigeminal nerve can be achieved through TES. Most existing nerve simulation research use parallel axon geometries such as the double-cable axon model named MRG axon (McIntyre, Richardson, and Grill) [4]. However, nerve-fiber activation also depends on nerve orientation and trajectory relative to TES induced electric fields [5]. In previous work, excitability between a single straight axon and an axon with realistic 3D geometry was compared. The realistic axon model predicted lower thresholds than the straight axon model and showed different activation pattern [10]. This justified the use of a realistic axon instead of linear axon to study TES.

In this study, we have built a nerve fiber model with realistic geometry derived from MR tractography of the trigeminal nerve. Neural activation patterns were studied for temporal input waveforms simulating tDCS and tACS. The model was verified with data from Gaines et. al [4].

II. Methods

A. Mri Acquistion and Tractography

A high-resolution 3D T1-weighted structural image was acquired in a 3T MRI scanner (Philips Ingenia System, Barrow Neurological Institute, Phoenix, USA) with a 240 mm (FH) x 240 mm (AP) x 200 mm (RL) field-of-view (FOV) and 1 mm3 isotropic resolution. HARDI (high angular resolution diffusion imaging) protocol [6] was followed for diffusion weighted MR (DWI) data acquisition. All procedures were performed with approval from the Arizona State University Institutional Review Board. The ophthalmic branch of the trigeminal nerve was tracked using waypoint masks and probabilistic tractography methods discussed in previous research [9].

B. TES Modeling

Structural MR images were segmented into different tissue types using SPM12 and Simpleware ScanIP (Synopsys Inc.) to construct a labeled volume model with FOV 256 x 256 x 256 mm3, using methods outlined in [6], [7]. The trigeminal nerve tract obtained from tractography was added to the segmented model as an additional compartment. The segmentation model also included electrodes placed at right supraorbital (RS) and mastoid process locations for TES stimulation and electrical properties of tissues were assigned from the literature [8]. The

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segmented labeled volume was then meshed and imported into COMSOL Multiphysics (Burlington, MA, USA), and was solved using the Laplace equation with 1 mA current injection applied to the RS electrode, and the other electrode grounded. The flow process for obtaining a solution from a realistic head model is represented in Fig 1.

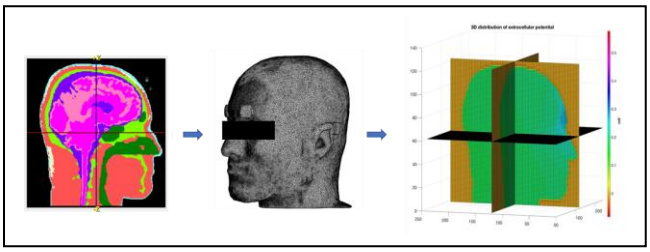

Figure 1. Steps involved in modeling electric potential distribution.

C. NEURON Modeling

The extracellular voltage input for NEURON modelling was found by mapping along the geometry of trigeminal nerve from FEM generated voltage distribution. Physiological ion channel properties of a sensory nerve were assigned to the axon model following the specification used by Gaines et al. [4]. The NEURON model consisted of 51 nodes and 50 inter-nodal compartments with a total length of 63.75 mm. The model was tested for tDCS and tACS waveforms. Following quasi-static assumption, the extracellular medium is purely resistive and hence a time-dependent waveform can be multiplied to the corresponding extracellular potential value at each node. The cable equation [3] was solved for the NEURON model in each waveform condition to obtain transmembrane potentials.

III. RESULTS AND DISCUSSION

A. tDCS

A square waveform was multiplied with the extracellular voltage and applied for 100ms after a delay of 10ms. At lower amplitudes (multiplication factor <105) no significant increase in neural activity was observed. This is consistent with tDCS experimental literature [1] which show that tDCS works through neuroplasticity over a long period of time. Action potentials (AP) are observed only at higher amplitude multiplication factors. The shape of AP (Fig. 2) is consistent with that obtained by Gaines et. al for a sensory axon having a longer refractory period after AP. After the threshold is crossed, for a higher multiplication factor of 106, AP is reached faster than for factor 105.

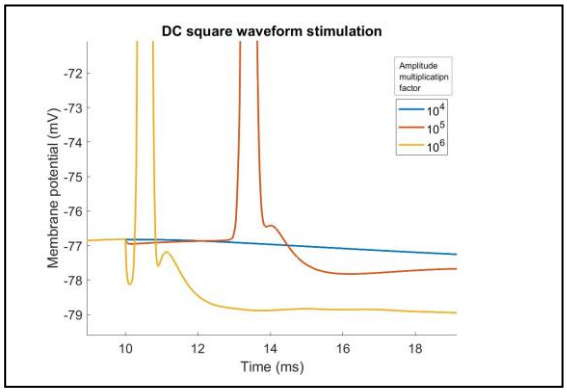

Figure 2. Membrane potential patterns seen from tDCS over varying amplitude.

The strength-duration curve was studied to verify the model. The shape of the curve (Fig. 3) is consistent with the Gaines et. al model [4] with a rheobase of 14.05kV.

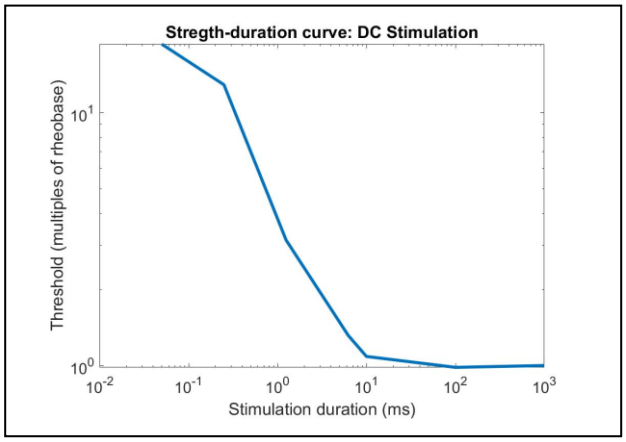

Figure 3: Strength-Duration curve for a sensory axon of 12µm diameter.

B. tACS

Alternating sine waveforms of different frequency were multiplied with the extracellular voltage and applied for 100ms after a delay of 10ms. Amplitude multiplication factor of 1 and 10 were studied. For amplitude 1 (Fig. 4), AP was seen at frequency 100Hz and more, whereas, for amplitude 10, AP was seen at frequency 20Hz and more. In each case, higher frequencies reached AP faster. A constant change in membrane potential above resting potential (-79mV) was seen for the duration of AC stimulation, more notable in amplitude 10. APs were also seen after AC stimulation was removed indicating continued neural activity after tACS admistration.

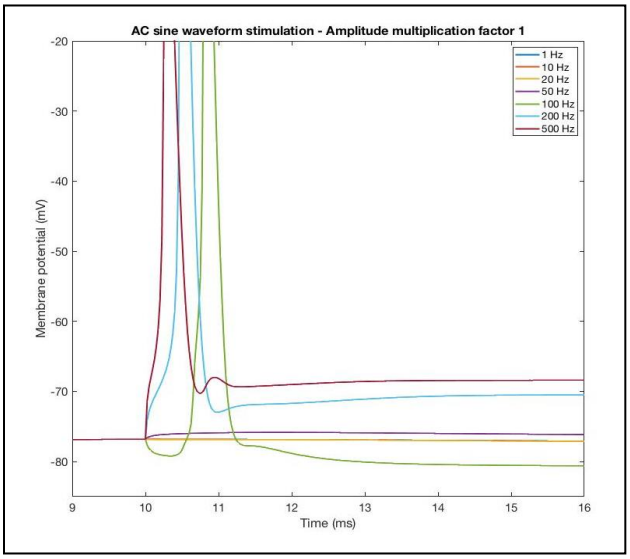

Figure 4: Membrane potential patterns seen from tACS over varying frequency and amplitude multiplication factor 1.

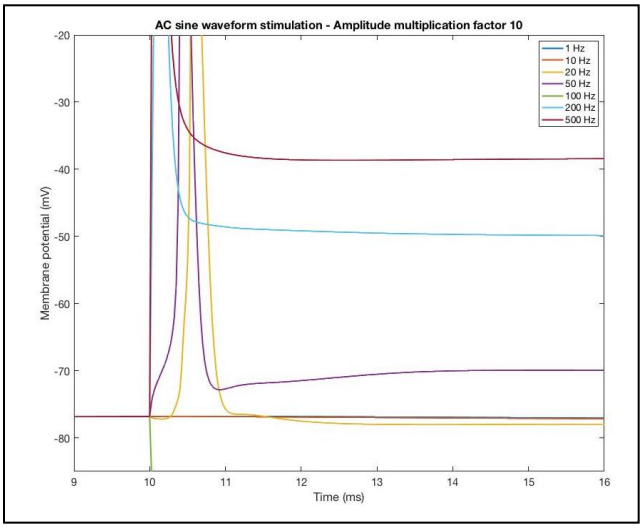

Figure 5: Membrane potential patterns seen from tACS over varying frequency and amplitude multiplication factor 10.

IV. FUTURE WORK

This model has ignored the effects of tissue capacitance and ephaptic coupling due to TES. These effects need be investigated further. This study will be further developed to investigate a realistic nerve fascicle with varying axon diameter distribution similar to the trigeminal nerve.

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