Do single neuron models exhibit temporal interference stimulation?

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***Abstract*— Performing deep-brain stimulation (DBS) noninvasively can have a drastic impact on neuroscience and clinical care. A recent work suggests that such noninvasive DBS is feasible using "Temporal Interference" (TI) stimulation, where two interfering high-frequency sinusoidal currents produce electrical stimulation only when the amplitudes of the sinusoids are approximately equal. While electrical stimulation using TI has been studied for decades, the understanding of its fundamental neurobiological mechanisms is still poor. In order to establish a better understanding of TI stimulation, a theoretical and computational approach is needed. In this work, we adopt such an approach using a computational model that is a sea of single neurons inside a spherical head. We demonstrate that the classical Hodgkin-Huxley squid neurons and some mammalian cells do exhibit TI stimulation in this model. We also observe that some mammalian neurons do not exhibit TI stimulation, suggesting that deeper studies are needed to understand if TI stimulation works with all neuron-types, or if it is network mechanisms (instead of single neuron dynamics) that enable TI stimulation.**

***Index Terms*—Temporal Interference Stimulation, neuron models, computational models, noninvasive current stimulation.**

I. Introduction

Noninvasive stimulation of the nervous system can have significant impact on neuroscience, closed-loop brain-machine interfaces, and clinical treatments. In recent decades, noninvasive current stimulation has been proven to be effective using strategies such as Transcranial Direct Current Stimulation (tDCS) and Transcranial Alternating Current Stimulation (tACS). However, due to the dispersion of currents in biological tissues, it is challenging to achieve high spatial precision, and is particularly difficult to stimulate deep regions without engaging shallow neurons.

Towards addressing the latter problem, Grossman et al. [1] recently performed experiments in mice models which suggest that a strategy that they call "temporal interference" (TI) stimulation can stimulate deep regions inside the brain with no shallow stimulation. TI stimulation strategies have been applied to peripheral nerve stimulation as well as electroanesthesia in central nervous system for decades [2], [3], where they are called "Interferential Stimulation". The key observation that enables TI stimulation is as follows: two interfering high-frequency sinusoidal currents produce electrical stimulation only when the amplitudes of the sinusoids are approximately equal. The resulting stimulation is at "beat" frequencies, suggesting that an envelope demodulation-type operation is being performed. The way TI stimulation in [1] exploits this is by producing two different sinusoidal currents that have approximately equal and large amplitudes deep inside the brain, and closer to the electrodes (at shallow depths), only one sinusoid dominates. Thus, deep stimulation, with little or no shallow stimulation, is enabled.

Despite the long history of TI stimulation and its promising future in noninvasive deep-brain stimulation, the understanding of why TI stimulation works is limited. For instance, mere low-pass filtering, also called "neural resonant property" [4], does not explain TI stimulation because low-pass filtering of a sum of two high-frequency sinusoids will, ideally, yield a zero signal. It can be easily tested that integrate-and-fire neurons do not exhibit TI stimulation. Therefore, more sophisticated models are needed to explain TI stimulation. Can single neuron models explain TI stimulation? This is indicated by works showing that neural membranes exhibit rectification of inputs [5], which, with omnipresent capacitances and resistances, could explain a diode-based envelope demodulation. It is also possible that TI stimulation is a fundamentally network phenomenon, or arises from a mix of neuron-level and network-level phenomena.

In this work, our goal is to explore if the more sophisticated Hodgkin-Huxley (HH)-type neuron models exhibit TI stimulation on single-neuron level. Originally, such models were obtained by Hodgkin and Huxley in their celebrated works for the squid giant axon [6], that we call the classic HH neuron. This model can also be generalized by keeping the types of currents the same, but redefining their dynamics according to the specific neuron-types. We refer to such models, including the classic HH neuron, as HH-type neuron models. We limit our study to computational models that are a sea of neurons inside a spherical head model. The neuron-sea is constituted by single neuron models that describe the dynamics of neuron membrane potential as a function of the external current. We first show that the classic HH neuron exhibits TI stimulation. Next, we test whether HH-type *mammalian* neuron models exhibit TI stimulation. We observe that while some mammalian neurons do exhibit TI stimulation, there are others that do not. Further computational studies that incorporate network-level models, as well as in-vitro and in-vivo studies that leverage realistic networks, are needed to fully understand TI stimulation. This understanding can enable improved TI stimulation for human and other mammalian brains, provide alternative approaches, and also help understand when TI stimulation may not be applicable.

II. Methods

A. Review of TI Stimulation

It is well known that most neurons do not respond to high-frequency inputs [4]. TI stimulation is based on simultaneous application of two sinusoidal currents with slightly different high frequencies (e.g. 2000 and 2010 Hz in [1]). At locations where the two sinusoids have almost equal amplitudes, this creates an interference pattern in which a high-frequency carrier wave is modulated by a slow envelope at the "beat" frequency. The authors of [1] observed that in deep regions where the two sinusoids have similar amplitudes, neurons fire at the beat frequency, while in regions close to the electrodes where one of the frequencies is dominant, no firing was observed.

Defining when a neuron-type exhibits TI stimulation: We define a neuron-type to exhibit TI stimulation when it satisfies both of the following conditions in a 3D head model: a) there must exist a target region at a reasonably large depth in which there should be neural firing; and b) there must exist a small distance δ such that neurons farther from the target region by δ in any direction are not stimulated. We define a neuron-type to exhibit TI stimulation even when small regions of shallow neurons are stimulated, as long as such shallow regions are not connected with the target.

The rest of the paper tests which neuron-types exhibit TI stimulation in the computational head model described next.

B. 3D Computational Head Model

For simplicity, we assume that the brain is a "sea of neurons" (i.e., network models are not considered), and all neurons are of the same neuron-type, with their axonal directions all being along the z-axis in the Cartesian coordinates. The simplicity of this model helps us focus on understanding mechanisms of TI stimulation free of complications introduced by real brain models. Future work will test these results in real-brain template models and networks of neurons (e.g. those adapted from [7]) as well.

We examine TI stimulation with three different types of HH-type neurons, namely the classic HH (squid) neuron [6], the neocortical pyramidal neuron in [8], and the parvalbumin-expressing (PV) inhibitory neurons in [9] (with parameter corrections according to [10]).

For stimulation using external currents, we adopt a modified version of the well-known Hodgkin-Huxley equations that incorporates effects of external currents [11]. This modified version incorporates the "activating function" of neural membrane potential response to external currents, and is well-accepted in the neurostimulation community [12], [13]. The activating function is defined as $\frac{a}{2R}\frac{\partial^2 V}{\partial z^2}$, where a is the radius of the axon, R is the resistivity of intracellular fluid, V is the external potential induced by the input, and z is the axonal direction. Intuitively, the activating function is proportional to the first order spatial gradient of current density, because current densities are proportional to the first order gradient of voltages (in a medium with homogeneous resistivity).

We adopt a 3-sphere head model, consisting of brain, skull, and scalp layers. The outer radii of the layers are chosen to be 7.9 cm, 8.6 cm, and 9.2 cm [14]. Current dispersion in the spherical head is modeled through a finite-element method (FEM). We assume a purely resistive medium, which is accurate to at least a few hundred hertz [15]. The head model is discretized by intersecting a 3-layer unit sphere with a three-dimensional orthogonal lattice, whose spacings in x-, y-, and z-directions are all 0.04 (roughly 0.37 cm in the human brain). The unit sphere is constructed by normalizing all the radii in the spherical model by the outermost radius. The neighboring vertices are connected by resistors, whose values are based on which layer of the head model they are in. We denote the conductances of brain, skull, and scalp layers by σ_1, σ_2, and σ_3 respectively. According to [14], we assume $\sigma_1 = \sigma_3$, and $\sigma_2/\sigma_1 = 1/80$. We use current sources as input to the head model. Voltages and their second-order spatial derivatives at each node are then calculated using Kirchhoff's current law, with boundary conditions given by the current sources.

We define a "voxel" as a cube centered at a node in the lattice, whose faces bisect the lines connecting the node and its nearest neighbors, and are perpendicular to the lines. We assume the outermost layer of voxels of the brain sphere to be cerebrospinal fluid (CSF), which corresponds to a thickness of about 0.37 cm. This value is close to the actual thickness of CSF layer in the human brain [14].

C. Estimating Firing Events

A critical question in both computational and experimental studies is defining the firing event ([11, Ch. 1] has examples of some of the involved subtleties). Here, to estimate firing, following [1], the membrane potentials are first bandpass filtered (6th order Butterworth filter with passband 100-1000 Hz). After that, we adopt a simple "threshold-passing" criterion for deciding firing events. Specifically, we say that a neuron fires if its maximum filtered membrane potential reaches a chosen threshold, which is determined empirically for each neuron-type. To avoid boundary effects during differential equation solving, the first and last few milliseconds are omitted from firing determination.

III. Results

We use both Cartesian (x, y, z) coordinates and spherical coordinates (r, θ, ϕ), where r is the radius, θ is the polar angle, and ϕ is the azimuthal angle. For simplicity, each electrode-pair is placed such that the line joining the two electrodes is parallel to the z-axis (i.e. the axis along which neurons are aligned). For all results below, two electrode-pairs are placed at $\phi = 0$ and $\phi = \pi$ respectively, and the electrodes in the upper hemisphere both have a polar angle of $\theta = \pi/6$. We aim to stimulate a disk on the xy-plane with a diameter of 0.2 (corresponding to about 1.8 cm in the human brain) centered at point [0,0,0.4] (in Cartesian coordinates). We aim to stimulate a disk rather than a single point because the results obtained for a single-point stimulation can be unrealistically optimistic, and the obtained strategies may fail in practice because of

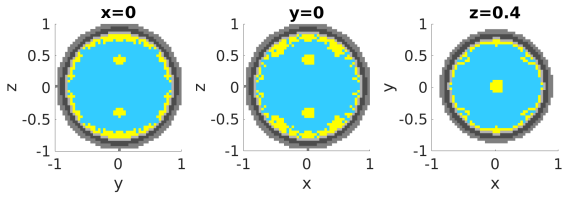


Fig. 1. TI stimulation is observed with the classic HH neurons [6]. Despite some engagement of shallow neurons, the deep target site ([0,0,0.4]) is stimulated without stimulation of neurons nearby. Yellow: firing; Blue: no firing; Gray from outside to inside: scalp, skull, and CSF.

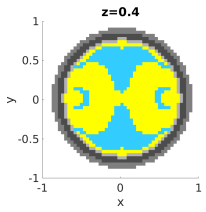


Fig. 2. Classic HH neurons in [6] do not exhibit TI stimulation when base frequency is not high enough. Frequencies are chosen to be 1200 and 1215 Hz. Farther away from the target towards electrodes, the neurons are still stimulated. Yellow: firing; Blue: no firing; Gray from outside to inside: scalp, skull, and CSF.

small variations, e.g. in electrode placement, tissue parameters, etc. The target [0,0,0.4] is still deeper than half of the brain, and is therefore sufficient to demonstrate DBS. The choice of current frequencies and amplitudes are different depending on the different neuron-types. These are chosen by sweeping across possibilities to find the best values so that TI stimulation is observed. In real brains, where a mixture of neuron-types is present, one would be forced to choose one set of values of currents, and further optimization will be needed to stimulate only the desired type(s).

A. Do classic HH neurons exhibit TI stimulation?

We attempted several frequency combinations, and observed that if the frequencies of the two sinusoids are chosen to be 2000 and 2050 Hz respectively, the HH neuron exhibits TI stimulation. Specifically, we tailor the currents to both generate an activating function of 170 $\mu A/cm^2$ at the target [0,0,0.4] (just above the minimum current to generate stimulation in the target region). The threshold for deciding firing events is chosen to be 30 mV. The results are shown in Fig. 1 along different planes. In the target region, the two sinusoids have similar amplitudes, and neurons are stimulated. Away from the target in any direction, firing does not happen. We also observe some shallow engagement (see Sec. IV for a possible explanation), which suggests that careful monitoring of shallow neurons may be needed in human experiments, and more sophisticated techniques might be needed to avoid this.

We further observe that the base frequency (i.e. the lower of the two) of the applied currents must be sufficiently high in order for the classic HH neuron to exhibit TI stimulation. Fig. 2 illustrates this for f_1=1200 Hz and f_2=1215 Hz. The neuron does not show TI stimulation, potentially because it can still follow the oscillations of the underlying sinusoids.

One must note that the HH squid neuron is large in size, and its electrophysical properties are also very different from those of mammalian central-nervous-system neurons.

B. Do mammalian neurons exhibit TI stimulation?

We consider two neurons to illustrate the diversity, an excitatory pyramidal neuron that exhibits TI stimulation, and an inhibitory neuron that does not exhibit TI stimulation.

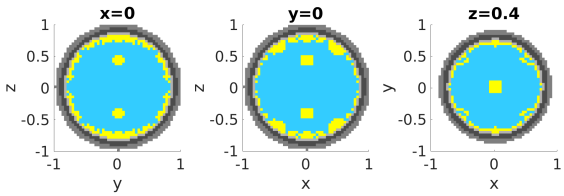


Fig. 3. TI stimulation for the excitatory pyramidal neuron in [8]. Similar to the classic HH neurons, the target region is stimulated and stimulation is not observed in regions far from the target, and closer to the electrodes. Yellow: firing; Blue: no firing; Gray from outside to inside: scalp, skull, and CSF.

1) Neocortical pyramidal neuron: We first observe that a neocortical pyramidal neuron (parameters taken from [8]) exhibits TI stimulation. We also observe that when the base frequency is low (e.g. 100 Hz), similarly to the classic HH neuron, the pyramidal neuron does not exhibit TI stimulation.

Using a base frequency of higher than 300 Hz, however, neurons do not fire when points far from the target region are chosen. The results are shown in Fig. 3. The frequencies are chosen to be 2000 and 2040 Hz respectively, and both electrode-pairs generate an activating function of 300 $\mu A/cm^2$ at the target point [0,0,0.4] (chosen, again, by finding the minimum current that stimulates the target).

For the pyramidal neuron, the threshold for deciding firing events is chosen to be 3 mV.

2) PV interneuron: An inhibitory mammalian cell that does not exhibit TI stimulation: We now examine parvalbumin-expressing (PV) interneurons found in the mammalian cortex (both neocortex and allocortex). We swept across base frequencies and frequency differences to test if the neuron exhibits TI stimulation. In Fig. 4, we illustrate the case of frequencies of 4000 Hz and 4015 Hz, where both sinusoids generate an activating function of 307 $\mu A/cm^2$ at the same target (chosen analogously to the other two neuron-types). The threshold for deciding firing is chosen to be 30 mV. Although no firing is observed in regions that are very close to the electrodes, neurons next to these regions fire. This neuron-type, therefore, does not exhibit TI stimulation.

The activating functions and their resulting filtered membrane potentials at different locations are shown in Fig. 5. This figure is included to illustrate what we mean by the neuron not exhibiting TI stimulation. At the off-center location where

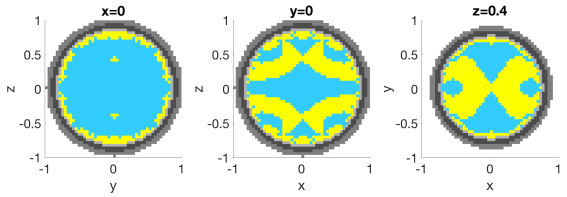
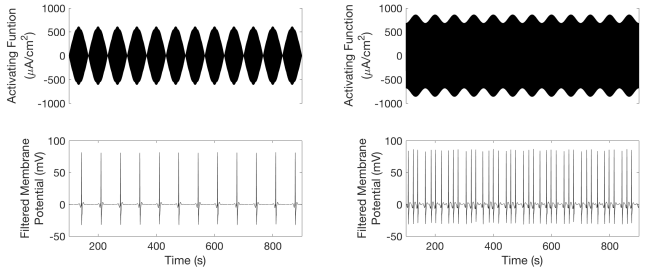


Fig. 4. PV neurons do not exhibit TI stimulation. Even when higher frequencies of 4000 and 4015 Hz are used, voxels not at the target are also stimulated. Yellow: firing; Blue: no firing; Gray from outside to inside: scalp, skull, and CSF.



(a) (b)

Fig. 5. Activating functions and the resulting filtered membrane potentials for a PV neuron [9] that does not exhibit TI stimulation. (a) At the target the PV neuron is stimulated. (b) A PV neuron slightly away from the target ([0.16,0,0.4]) can still be stimulated by an envelope with less modulation depth. Note that the firing rate away from the target is, in fact, higher.

the envelope has less modulation depth, a neuron can still be stimulated, at an even higher firing rate.

IV. Discussion

This paper takes the first step in understanding and explaining the mechanisms behind TI stimulation. In [1], the authors hypothesize that neurons perform envelope demodulation when responding to temporally interfering waves. Here, we get a more refined understanding of that hypothesis: our observation that neurons do not exhibit TI unless the base frequencies are higher than a threshold (Section III-B1) suggests that the neurons do not perform an *ideal* envelope detection (i.e. via a Hilbert transform) because they do not respond *only* to the envelope. Instead, the nonideal (and more commonly understood) diode-based demodulation [16] may be a better approximation. A minimalist model that still captures the essence of TI stimulation will be a goal of future work. The fact that some neuron-types (e.g. PV neurons) do not exhibit TI stimulation suggests that understanding the mechanisms of TI stimulation is of vital importance for optimizing TI stimulation in human participants.

We do notice some amount of shallow engagement even for the neurons that exhibit TI stimulation. This may be caused by the boundary effect of current dispersion: at the boundary between two media with different conductances, a sharp change of current density happens (similar to the dispersion of EEG signal when traveling out of the brain [17]), resulting in a large magnitude of activating function. While the phenomenon of shallow engagement needs to be tested further, both experimentally and computationally, it may suggest a limitation of TI stimulation, especially in larger brains. Our parallel work [18] explores extensions of TI stimulation, proposing both multielectrode TI (more than 2 electrode-pairs) and spatial interference techniques, that improve the accuracy of stimulation and reduce shallow firing.

An important limitation of this work is that we test TI stimulation using a "sea-of-neurons" model, where the network connectivity effects are ignored. It is possible that TI stimulation has second-order network-level effects which determine its strength or efficacy. More theoretical, computational, and experimental studies are therefore needed to improve the understanding of the underlying mechanisms.

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