

Applying Transcranial Alternating Current Stimulation to the Study of Spike Timing Dependent Plasticity in Neural Networks

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Abstract

In recent years transcranial alternating current stimulation (tACS) has emerged as a popular tool for the study of rhythmic brain activity. A great deal of focus has been directed toward applying tACS to modulate the spike timing dependent plasticity (STDP) of occipital neural networks for potential therapeutic purposes. While little clinical evidence has emerged supporting the efficacy of tACS as a treatment for cognitive and psychological disorders arising from the occipital lobe the ability of tACS to entrain and modulate the frequency, and consequent strength, of occipital network firing has been well documented in several EEG studies. However, little work has been done to develop robust models that can be used to study this effect *in silico*. In the present study we develop a micro-network of modified FitzHugh-Nagumo neurons to model of the effect of tACS on naturally oscillating neural networks. We conclude that while tACS modulates the resonant frequency of the network via the STDP of its constituent neurons, its effects are transient and that more work is necessary to accurately model the physiological dynamics of large scale neural network firing.

1 Introduction

The firing oscillations of occipital neural networks have been correlated to normal cognition and working memory [1]-[2]. A majority of these oscillations fall within the canonical alpha band frequencies. The 8-12Hz spectrum detected by occipital EEGs, and have become a hallmark of a healthy mental state. Deviations from the alpha rhythm have been implicated in a number of cognitive and psychological conditions ranging from reading-impairment to late stage Alzheimer's disease [3]-[4]. Yet despite these

implications little clinical attention has been given to treatment options that directly modulate the occipital alpha rhythm as their point of effect.

Transcranial electrical stimulation has emerged as one such treatment option. Specifically transcranial alternating current stimulation (tACS) has been shown to alter rhythmic brain activity and thus has the potential to alter cognition and perception [5]. tACS is thought to act by affecting the spike timing dependent plasticity (STDP) of neural networks. STDP explains the strengthening or weakening of a synapse in terms of the timing between presynaptic and postsynaptic action potentials. When the firing of a presynaptic neuron precedes that of a postsynaptic neuron a causal link is generated between the pair which is embodied by the strengthening of their shared synapse. Similarly, when the firing of a presynaptic neuron follows that of its postsynaptic partner an acausal relationship is created and the synapse is weakened. By entraining and modulating the resonant frequency at which neural networks fire tACS is able to alter the timing between pre and postsynaptic potentials and consequently alter network firing strength.

Despite growing interest in the use of tACS to manipulate neural networks there has been little effort to generate *in silico* models of its effects. The authors believe that an accurate digital simulation of tACS on a neural network with synaptic plasticity would be an invaluable tool for predicting outcomes of time consuming and costly clinical tests. The present study demonstrates the implementation of such a model using a micro-network of FitzHugh-Nagumo neurons.

2 Methods

2.1 Modified FitzHugh-Nagumo

To balance physiological realism with computational tractability we drew inspiration from the FitzHugh-Nagumo (FN) model. Although inherently less physiologically accurate than the similar, but more complex, Hodgkin Huxley model, the FN model's simplicity to implement and accurate mimicking of general neural spiking behavior make it an ideal first choice for the purposes of generating a neural micro-network. The specific FN model used here was originally developed by Kato [4] and is governed by the following:

$$\epsilon \frac{dv}{dt} = I_{ion} + I_{syn} + I_{ext} + tACS \quad (1)$$

$$\frac{dw}{dt} = v - w - b \quad (2)$$

$$I_{ion} = v(v - a)(1 - v) - w \quad (3)$$

Where v is the neuron voltage, w is the recovery variable, and I_{ion} is the ionic current impinging on the neuron. The I_{ext} term is the globally applied external current acting on the network and is meant to recreate the background stimulation a neural network receives as a part of conductive living tissue. Similarly, to simulate the indiscriminate effect of alternating current stimulation a tACS term is implemented affecting each neuron in the network.

The alterations to the canonically FN equations made by Kato allow for the addition of synaptic connections which are represented via synaptic currents (I_{syn}) between neurons and exponential synaptic conductances:

$$I_{syn} = g_{ij\ excite}(t)(V_{rev\ excite} - v_i(t)) + g_{ij\ inhib}(t)(V_{rev\ inhib} - v_i(t)) \quad (4)$$

$$\tau_{syn} \frac{dg_{ij}}{dt} = -g_{ij} \quad (5)$$

Where g_{ij} is the conductance of the synapse between neuron i and neuron j , V is the reversal potential, and τ_{syn} is the decay time for the synaptic conductance.

To incorporate synaptic plasticity while maintaining the simplicity of the network the canonical additive model of STDP was applied solely to excitatory synapses while inhibitory synapses were left static. The plasticity of the excitatory synapses is given by:

$$g_{ij} \rightarrow g_{ij} + \Delta g_{ij} \quad (6)$$

$$\Delta g_{ij} = F(\Delta t_{ij}) \quad (7)$$

$$F(t_{pre} - t_{post}) = \begin{cases} A_+ e^{(t_{pre} - t_{post})/\tau_+} & \text{if } t_{pre} < t_{post} \\ A_- e^{-(t_{pre} - t_{post})/\tau_-} & \text{if } t_{pre} > t_{post} \end{cases} \quad (8)$$

Kato was also referenced for initial parameter values: $\varepsilon = 0.005$, $a = 0.5$, $b = 0.12$, $I_{ext} = 0.2$, $V_{rev\ excite} = 0.7$, $V_{rev\ inhib} = 0$, $\tau_{syn} = 0.2$, $\tau_+ = 2.0$, $\tau_- = 1.0$, $A_+ = 0.01$, $A_- = 0.006$.

2.2 Neural Network Design

To efficiently study the effects of tACS on an oscillating neural network, we designed a simple three-neuron closed network connected by three excitatory and three inhibitory synapses. Excitatory and inhibitory connections connected the neurons in a clockwise and counterclockwise ring respectively (Figure 1). The excitatory synapses were made plastic and followed equations (6-8) while the inhibitory synapses were made static. This asymmetry in the plasticity of the synapses was designed to ensure the relative stability afforded by the ring of inhibitory synapses would not be affected by tACS and confound its effect on the excitatory synaptic weights.

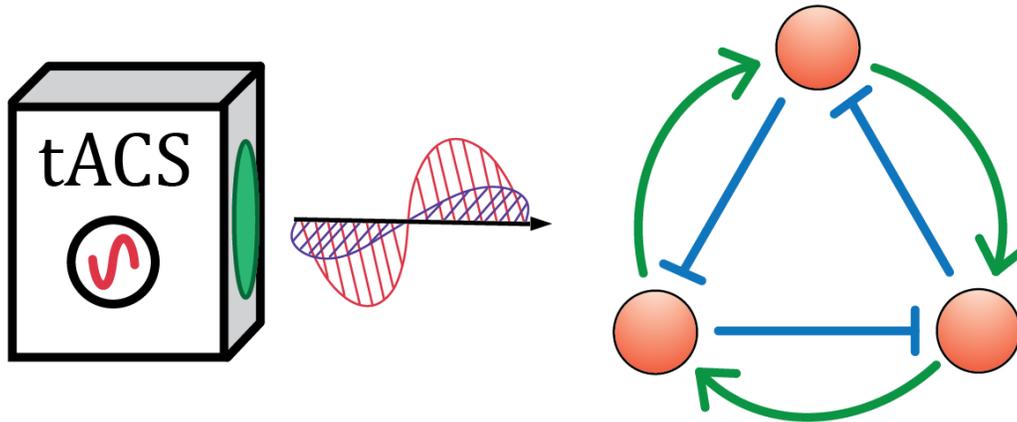


Figure 1: Neural Network Design.

Three neurons connected clockwise by excitatory STDP synapses (arrows) and counterclockwise by static synapses (T's) are stimulated by an oscillating tACS.

2.3 Simulations

To gauge the fidelity of the model to the physiological effects of tACS observed by Zaelhe a suite of tACS frequencies was applied to the neural micro-network [3]. This suite consisted of frequencies both above and below the resting firing frequency(f_o): 0 , $0.3f_o$, f_o , and $1.1f_o$. At each applied frequency the network was analyzed from time 0 to 200 . This time window was divided into 3 regions: from time 0 to 45 during which the network was allowed to settle at f_o , time 45 to 180 during which tACS was applied, and time 180 to 200 during which no tACS was present.

The spike trains and excitatory synaptic weights of each neuron in the network under all conditions were recorded. Under no applied tACS the network will oscillate at f_o and the synaptic weights should remain stable. When the applied tACS is not equal to f_o the excitatory synaptic weights should decrease in agreement with the observation of Zaelhe [3]. When the applied tACS is equal to f_o the synaptic weights should increase. These effects should be seen both during and after tACS application if the system is physiologically sound.

3 Results

3.1 STDP

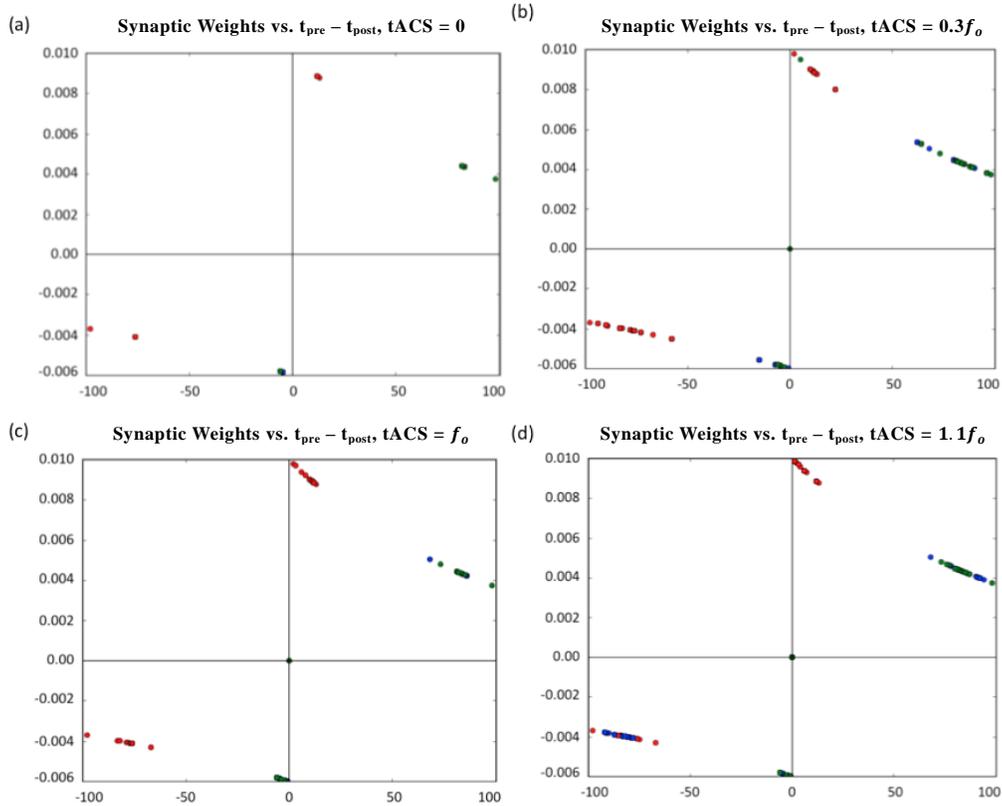


Figure 2: STDP Windows

Asymmetric STDP windows as seen at (a) $tACS = 0$, (b) $tACS = 0.3f_0$,
(c) $tACS = f_0$, (d) $tACS = 1.1f_0$

To ensure that the applied tACS did not interfere with the plasticity of the excitatory synapses the STDP windows for each synapse was recorded under each tACS frequency (Figure 2). Excitatory synapses exhibited the behavior predicted by the canonical asymmetric STDP window under all conditions [5]. It is interesting to note that although the profile of each STDP window matches that found in the literature there are significant data gaps in the range $t_{pre} - t_{post} = \pm(10 - 50)$. This is likely an artifact of the parameter values establishing an inherent reaction time to pre and postsynaptic neurons.

3.2 No tACS

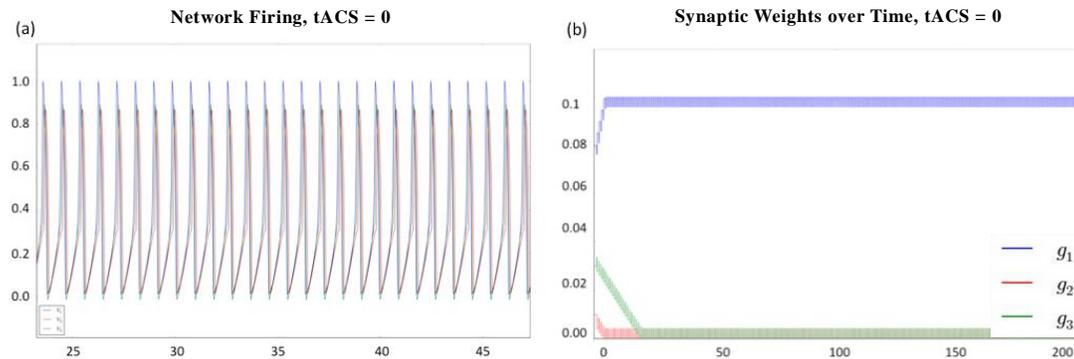


Figure 3 Neural Network at tACS = 0

Without tACS the network settled at a regular firing rate f_o (Figure 3). The synaptic weight of the first synapse increases until reaching the imposed limit while the second and third synaptic weights become zero. This is a result of the structure of the excitatory ring which causes neuron 1 to fire first, followed by neuron 3, followed lastly by neuron 2. With the synapses constructed such that neuron 1 leads to 2, 2 leads to 3 and 3 leads to 1 this firing order causes the postsynaptic neurons for both synapses 2 and 3 to fire first thus lowering the synaptic weights of neurons 2 and 3.

3.2 tACS = $0.3f_o$

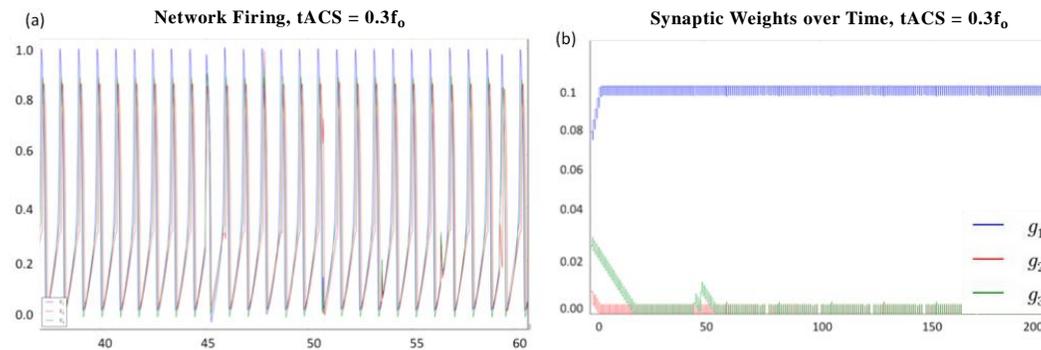


Figure 4: Neural Network at tACS = $0.3f_o$.

After establishing the steady state behavior of the network a tACS of $0.3f_o$ was applied (Figure 3). Under these conditions the network did not react as predicted [1]-[2]. Rather than each synaptic weight decreasing over time, the network behavior closely resembled that of steady state. An upward spike in the synaptic updates of the synapse between neuron 2 and 3 can be seen at time 50; this is likely an artifact resulting from the onset of the tACS. However after every 35 time units following time 50 a decrease in the synaptic weights can be seen. This corresponds to the frequency with which

tACS pulses and influences the network. This indicates that in order for the effects of tACS to be prominent stimulation must be more frequent.

3.3 tACS = f_0

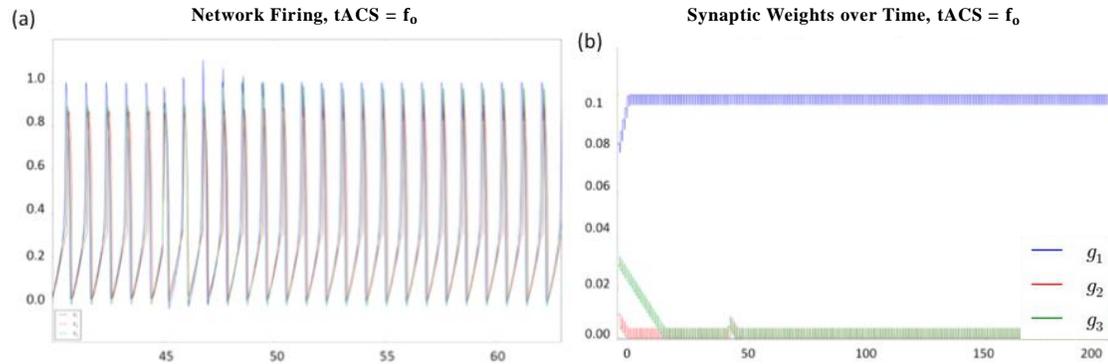


Figure 5: Neural Network at tACS = f_0 .

When the network is driven with a tACS at f_0 , its spike train and synaptic weights resemble the steady state. Again there is a small upward spike in the synaptic weights of neuron 3, but this is likely an artifact of the tACS initiation. Contrary to our predictions and clinical results our network does not experience any increase in synaptic weights due to a tACS applied at the network resting frequency.

3.3 tACS = $1.1f_0$

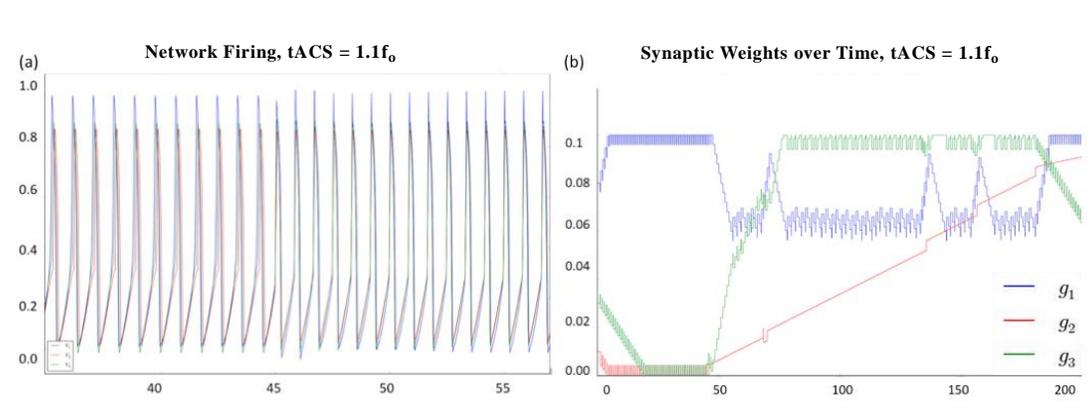


Figure 6: Neural Network at tACS = $1.1f_0$.

At a tACS frequency of $1.1f_0$, just above the resting frequency of the network, the synaptic weights of neuron 2 increase linearly once tACS application begins. However when tACS is turned off at time 180, the synaptic weights do not begin to trend toward their steady state values but rather continues to increase. This behavior aligns with what we have seen

physiologically from entire neural networks [1]. However the synaptic weights of neurons 1 and 3 do not exhibit the same linear behavior, instead they oscillate until tACS is turned off at which time they trend back to their steady state values.

4 Discussion

It has been seen clinically that tACS applied at the resting frequency of a neural system causes an increase in synaptic weights and synchrony between the neurons: an effect that remains for approximately an hour after tACS ceases [1]. If the effects of tACS could be made to be semi-permanent it has the potential to become a novel and effective therapy for a variety of cognitive disorders stemming from pathologically active or inactive neural networks. Developing *in silico* neural networks with which to test the efficacy of tACS stands to reduce the cost and time associated with the research needed to translate this therapy from the lab to the clinic. The present study created such a micro-network composed of modified FitzHugh-Nagumo neurons implementing additive STDP and attempted to recapitulate results found from *in vivo* studies. Although the plasticity of the neurons behaved as expected the simulation output did not match what has been clinically observed: synaptic weights did not diminish as the frequency of tACS deviated from the resting frequency of the network and the effects of tACS did not persist following its removal. This could be due to network size, the FitzHugh-Nagumo implementation, or the connectivity of the network. It is possible that more than three neurons are required for the effects of tACS to propagate. It could also be that the FitzHugh-Nagumo neuron is not a suitable physiological representation of a neuron for the purposes of studying the effects of tACS. A model in which hundreds of Hodgkin-Huxley neurons are connected via a random assortment of synapses may better reflect the effects of tACS *in vivo* and warrants further study.

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