Controlling synchronization of spiking neuronal networks by harnessing synaptic plasticity

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Disrupting the pathological synchronous firing patterns of neurons in the subthalamic nucleus of the Basal Ganglia circuit is a common treatment for Parkinsonian symptoms. In this paper, our goal is to design a desynchronization strategy for large networks of spiking neurons such that the neuronal activity of the network remains in the desynchronized regime for a long period of time after the removal of the stimulation. We develop a novel “Forced Temporal-Spike Time Stimulation” (FTSTS) stimulation strategy that harness the spike-timing dependent plasticity to control the synchronization of neural activity in the network by forcing the neurons in the network to artificially fire in a specific temporal pattern. Our strategy modulates the synaptic strengths of selective synapses to achieve a desired synchrony of neural activity in the network. Our simulation results show that the FTSTS strategy can effectively synchronize or desynchronize neural activity in large spiking neuron networks and keep them in the desired state for a long period of time after the removal of the external stimulation. Using simulations, we demonstrate the robustness of our strategy in desynchronizing neural activity of networks against uncertainties in the designed stimulation pulses and network parameters. Additionally, we show in simulation, how our strategy could be incorporated within the existing desynchronization strategies to improve their overall efficacy in desynchronizing large networks. Our proposed strategy provides a complete control over the synchronization of neurons in large networks and can be used to either synchronize or desynchronize neural activity based on specific applications. Moreover, it can be incorporated within other desynchronization strategies to improve the efficacy of existing therapies for numerous neurological and psychiatric disorders associated with pathological synchronization.
1. Introduction

Most of the existing therapies for neurological disorders focus on behavioral recovery and ignore the dynamical aspects of the underlying network. Therapies that purely focus on behavioral recovery instead of addressing aberrant dynamic characteristics of the network could fail to achieve a long term behavioral recovery [1]. One such example is deep brain stimulation (DBS) used to treat symptoms of Parkinson’s Disease (PD). An electrophysiological hallmark of PD is oscillatory neural activity in the Basal Ganglia, which produces the characteristic tremor [2, 3, 5]. DBS suppresses the Parkinsonian tremor by disrupting the oscillatory activity in the BG using high frequency stimulation (HFS) [3]. This suppresses the oscillatory activity and the Parkinsonian tremor while it is turned on but when the stimulation is off, the oscillations and tremors reemerge [4, 6]. To improve upon this stimulation protocol, new neural stimulation strategies have been developed to more effectively and efficiently desynchronize pathologically synchronous neuronal networks.

Recently, control-theoretic approaches have been used to design more effective and energy efficient desynchronization strategies [1]. These optimal stimulation protocols include phase reset [6]-[11] and closed-loop delayed feedback [12]-[16] approaches. The phase reset approach designs a control input to push the phase of the neurons to a phaseless set-point. The network’s inherent noise then randomly resets the phase of each neuron. The net effect of this random reset is an asynchronous population activity. The closed-loop delayed feedback control approach feeds delayed and processed average network dynamics into the system to desynchronize the network. This produces a desynchronization input only when the network is synchronous. While these approaches provide an optimal desynchronization strategy, they assume that the network connections are static and ignore the inherent plastic nature of neuronal synapses [17].

Hebbian plasticity is a well-known form of activity-dependent synaptic plasticity [17]. This form of plasticity enforces productive connections between neurons and depresses unproductive connections. A typical way to model activity-dependent synaptic plasticity is in the form of spike-time dependent plasticity (STDP) [18]. This rule increases the weight of a synaptic connection when the pre-synaptic neuron fires before the post-synaptic neuron within a given time window and decreases the weight when the order is reversed [18]. An increase or decrease in the synaptic weight is coined long-term-potentiation (LTP) or long-term-depression (LTD), respectively. The introduction of plasticity into a neuronal network creates multiple stability points with different levels of synchronous activity [1, 19, 20]. Since the connections are plastic, an external stimulus can move the network from one stability point to another in order to drive the network from a synchronous to an asynchronous state.

To incorporate the synaptic plasticity within the desynchronization stimulation protocol, Coordinate Reset (CR) based stimulation strategies have been developed [19] - [25] which temporarily makes the pathologically synchronous stability point unstable to move the network into the asynchronous state by harnessing synaptic plasticity [19] -
In this approach, the network is driven to the asynchronous regime in the presence of external stimulation because of the inherent tendency of LTD in asynchronous networks. Once the CR stimulation moves the network from the synchronous to the asynchronous stability point, the stimulation input is no longer required [19, 20]. This results in a network that remains desynchronized long after the stimulation protocol is turned off [23]. While this protocol is effective in decreasing synaptic weights of the network by harnessing synaptic plasticity, it has its own limitations. For example, the CR based stimulation strategy could fail to desynchronize neural activity of networks where LTP dominates LTD. Moreover, this strategy only provides a way to desynchronize neural activity and not to control the synchronization level of the network.

In this work, we have developed a novel stimulation strategy “Forced Temporal Spike-Time Stimulation (FTSTS)” which addresses above shortcomings of the CR-based stimulation approach. While all other stimulation strategies focus on desynchronizing neural activity within a network, our strategy focuses on harnessing the underlying synaptic plasticity of the network to control the average network synaptic strength by forcing the spiking neurons to fire in specific temporal patterns. Thus, our strategy provides a complete control over the synchrony level of networks for a long period of time, not just desynchronization. We demonstrate the efficacy of FTSTS strategy in controlling a desired synchrony level in large excitatory-inhibitory (E-I) networks. We show in simulation that the FTSTS strategy can effectively desynchronize the neural activity in networks where LTP dominates LTD on average. Further, we combine the FTSTS strategy with the CR stimulation strategy to demonstrate how this can enhance the overall performance of the CR stimulation strategy in desynchronizing large networks.

The paper begins with a description of models used to describe the spiking E-I networks dynamics, STDP rules, and a measure of synchrony as well as the stability analysis of E-I networks in Section 2. In Section 3, we first provide a mechanistic understanding of the FTSTS strategy by considering control of synchrony in a two neurons E-I network. We then demonstrate the efficacy of the FTSTS strategy in desynchronizing large E-I networks subject to uncertainties in the network parameters and the designed stimulation parameters. Finally, we show how the FTSTS strategy can be incorporated within the CR stimulation strategy to improve the overall performance of the CR stimulation strategy. The paper ends with a detailed discussion on the comparison of our approach with the existing stimulation strategies for desynchronization of spiking neural networks as well as the limitations of our strategy in Section 4.
2. System Model

2.1. Excitatory-Inhibitory (EI) Network Model

We consider networks of 2,000 and 10,000 spiking neurons consisting of 80% excitatory (E) and 20% inhibitory (I) neurons [12, 26]. The following Leaky-Integrate-and-Fire (LIF) model describes a single excitatory or inhibitory neuron’s dynamics in the E-I network.

\[
\tau_m \frac{dv_E(t)}{dt} = v_{\text{rest}} - v_E(t) + Z_E(t) + \mu_E + \sigma_E \sqrt{\tau_m} \chi(t) + V_{\text{stim}}^E(t), \quad (2.1a)
\]

\[
\tau_m \frac{dv_I(t)}{dt} = v_{\text{rest}} - v_I(t) + Z_I(t) + \mu_I + \sigma_I \sqrt{\tau_m} \chi(t) + V_{\text{stim}}^I(t). \quad (2.1b)
\]

Here, \(v_E(t)\) and \(v_I(t)\), in millivolts (mV), represent the membrane potential of the excitatory and inhibitory neurons respectively. \(\tau_m\) (in ms) is the membrane time constant and \(v_{\text{rest}}\) (in mV) is the membrane resting potential. \(Z_i(t)\) denotes the synaptic input to the \(i^{th}\) population of neurons where \(i \in \{E, I\}\). The synaptic input function \(Z_i(t) = \frac{J_{ij} C_{ij}}{N_i} S_{ij}(t)\) (2.1c) defines the input to the \(i^{th}\) neuron population. In this function, \(J_{ij}\) represents the synaptic strength between a presynaptic neuron in population \(j\) and postsynaptic neuron in population \(i\), in mV, where \(i \in \{E, I\}\) and \(j \in \{E, I\}\). The synaptic strength of a I-to-E synapse is \(J_{EI}\). \(C_{ij} = \epsilon N_i\) denotes a scaling factor where \(\epsilon\) is the connectivity probability and \(N_i\) is the number of neurons in population \(i\). \(S_{ij}(t)\) is the synaptic function. The Gaussian distributed baseline current to the \(i^{th}\) type neuron is denoted as

\[
\mu_i + \sigma_i \sqrt{\tau_m} \chi(t) \quad (2.1d)
\]

with a mean baseline current of \(\mu_i\) and variance of \(\sigma_i^2 \tau_m\). Finally, \(V_{\text{stim}}^i(t)\) denotes the external stimulative input to the \(i^{th}\) neuron population.

The synaptic function \(S_{ij}(t)\) is modeled as [26]:

\[
\tau_d \frac{dS_{ij}(t)}{dt} = -S_{ij}(t) + X_{ij}(t), \quad (2.2a)
\]

\[
\tau_r \frac{dX_{ij}(t)}{dt} = -X_{ij}(t) + W_{ij}(t) \delta(t - t_{\text{pre}} + t_{\text{delay}}). \quad (2.2b)
\]

Here, \(X_{ij}\) describes the input to the \(i^{th}\) population of neurons from the \(j^{th}\) population of neurons. The time constants governing the decay and rise time are \(\tau_d\) (in ms) and \(\tau_r\) (in ms) respectively. Synaptic connections between the \(i^{th}\) and \(j^{th}\) neuron populations are randomly connected with a probability of \(\epsilon\). The weight of each synaptic connection is defined as \(W_{ij}\). Throughout the work, we assume that E-to-I connections (\(W_{IE}(t)\)) are plastic and the I-to-E connections (\(W_{EI}\)) are static. Unless otherwise specified, we further assume no synaptic connectivity among neurons in excitatory or inhibitory
populations. The Dirac-Delta function \( \delta(t - t_{\text{pre}} + t_{\text{delay}}) \) models the synaptic input to a postsynaptic neuron from a presynaptic neuron when the presynaptic neuron fires at time \( t_{\text{pre}} \) (in ms) with a synaptic delay of \( t_{\text{delay}} \) (in ms).

2.2. Spike-timing dependent plasticity (STDP) model

The coupling value of the plastic E-to-I synapse \( (W_{IE}(t)) \) is governed by STDP [18], which is defined as follows:

\[
W_{IE}(t) = W_{IE}(t) + \Delta W_{IE}(t),
\]  

(2.3a)

where \( \Delta W_{IE}(t) \) is given as

\[
\Delta W_{IE}(t) = \eta_e a_{\text{LTP}} A_{\text{post}}(t) \quad \text{if} \quad t_{\text{pre}} - t_{\text{post}} < 0,
\]

(2.3b)

\[
\Delta W_{IE}(t) = \eta_e a_{\text{LTD}} A_{\text{pre}}(t) \quad \text{if} \quad t_{\text{pre}} - t_{\text{post}} > 0.
\]

(2.3c)

Here, \( \Delta W_{IE}(t) \) defines the change in the synaptic weight determined by the spike-time of a presynaptic \( (t_{\text{pre}}) \) and postsynaptic \( (t_{\text{post}}) \) neuron. The rate at which the E-to-I synaptic coupling changes is governed by the learning rate \( \eta_e \). Additionally, the relative contribution of LTD and LTP to \( \Delta W_{IE}(t) \) is denoted by \( a_{\text{LTP}} \) and \( a_{\text{LTD}} \) [18]. \( A_{\text{post}}(t) \) and \( A_{\text{pre}}(t) \) are described by the following two exponential functions:

\[
\tau_{\text{LTP}} \frac{dA_{\text{post}}}{dt} = -A_{\text{post}} + A_0 \delta(t - t_{\text{post}}),
\]

(2.3d)

\[
\tau_{\text{LTD}} \frac{dA_{\text{pre}}}{dt} = -A_{\text{pre}} + A_0 \delta(t - t_{\text{pre}}).
\]

(2.3e)

Here, the size of the LTP and LTD time window is defined by the STDP time constants \( \tau_{\text{LTP}} \) and \( \tau_{\text{LTD}} \), respectively [18]. Upon the firing of a presynaptic or postsynaptic neuron, a small value \( A_0 \) is added to the appropriate exponential STDP decay function. The E-to-I synaptic weight is defined as the coupling value multiplied by the synaptic strength \( (J_{IE}W_{IE}(t)) \).

2.3. Synchrony Measurement

The average synchrony \( (\chi_{\text{syn}}(T_k)) \) of the excitatory neuron population over a discrete time interval \( (T_k) \) is determined by the ratio of the average membrane potential variance \( (\sigma_{\bar{v}}^2) \) divided by the average variance for each individual neuron’s membrane potential in the population \( (\sigma_{v_i}^2) \) [27].

\[
\bar{v}(t) = \frac{1}{N_E} \sum_{i=1}^{N_E} v_i(t),
\]

(2.4a)

\[
\sigma_{\bar{v}}^2 = \langle [\bar{v}(t)]^2 \rangle_{T_k} - \langle [\bar{v}(t)]_{T_k} \rangle^2,
\]

(2.4b)

\[
\sigma_{v_i}^2 = \langle [v_i(t)]^2 \rangle_{T_k} - \langle [v_i(t)]_{T_k} \rangle^2,
\]

(2.4c)
Figure 1. The synchrony level and stability points of a plastic 2000 spike neuron E-I network. (A) The average synaptic weight either converges to the maximum or minimum value. The stability threshold is depicted as a blue dashed line. (B) The synchrony level of the network increases with increasing average synaptic weight ($J_{IE} W_{IE}(t)$).

$$\chi_{syn}(T_k) = \frac{\sigma_v^2}{N_E \sum_{i=1}^{N_E} \sigma_{v_i}^2}.$$ (2.4d)

Here, $N_E$ represents the number of excitatory neurons. The membrane potential of the $i^{th}$ neuron is defined as $v_i(t)$ and the average membrane potential for the population is $\bar{v}(t)$.

2.4. Determination of Synchronous and Asynchronous Regimes

It is well-known that plastic neural networks exhibit multiple stability points [1, 18, 19, 20]. Similar to other networks, our E-I network exhibits two stability points at a high and low average E-to-I synaptic weight value. Figure 1A shows the average E-to-I synaptic weight converging to either $J_{IE} W_{IE} = 10$ mV or $J_{IE} W_{IE} = 290$ mV. The average synaptic weight converges to $J_{IE} W_{IE} = 290$ mV if the initial average synaptic weight is greater than 150 mV and converges to $J_{IE} W_{IE} = 10$ mV when it less than 150 mV. Additionally, we find that the network becomes more synchronous as the average E-to-I synaptic weight increases, which is shown in Figure 1B. Therefore, the network exhibits a high level of synchrony at high synaptic weights and a low level of synchrony at low synaptic weights.

2.5. Model Parameters

We use the model parameters defined in Table 1 unless stated otherwise. All the simulation are run in Matlab R2016b. The differential equations are solved using Euler’s method with a step size of 0.1 ms. We will make all our codes and simulation parameters available on our research webpage after the publication (https://webpages.uidaho.edu/gkumar).
### Table 1. The model parameters of our E-I network.

<table>
<thead>
<tr>
<th>Neuron Parameters [12, 26]</th>
<th>Value</th>
<th>Plasticity Parameters [18]</th>
<th>Value</th>
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<tr>
<td>$v_{\text{rest}}$</td>
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<td>$W_{E}I$</td>
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<td>16.5 mV</td>
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</tr>
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<tr>
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<td></td>
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<tr>
<td>$J_{EI}$</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$J_{IE}W_{IE}(t)$</td>
<td>$\in [10, 290]$ mV</td>
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3. Results

We begin by providing an insight into the underlying mechanism of our stimulation strategy “Forced Temporal Spike-Time Stimulation” (FTSTS) using an illustrative example of two neurons E-I network in Section 3.1. Next, we demonstrate the efficacy of the FTSTS strategy in controlling synchronized activity of 2000 and 10000 neurons E-I networks (see Sections 3.2, 3.3). We then show the robustness of the FTSTS strategy in the presence of uncertainties in the designed stimulation pulses, model parameters and network connectivity (see Sections 3.4, 3.5, 3.6). Finally, in Section 3.7, we combine the FTSTS strategy with the existing coordinate reset (CR) stimulation strategy to show the efficacy of the FTSTS-CR strategy over the CR stimulation strategy.

3.1. Control of E-to-I synaptic weight in two neurons network

We considered an excitatory-inhibitory (E-I) network of two neurons to develop our “Forced Temporal Spike-Time Stimulation” (FTSTS) strategy. We set a scaling factor of $C_{ij} = 10N_i$ and probability of connectivity of $\epsilon = 1$ (see Section 2.1 for the meaning of these variables). Based on the STDP rule of activity-dependent plasticity, we designed stimulation inputs for both the inhibitory ($V_{I}^{\text{stim}}(t)$) and excitatory ($V_{E}^{\text{stim}}(t)$) neuron that forced the postsynaptic inhibitory neuron to spike before the presynaptic excitatory neuron, as shown in Figures 2B and 2C respectively. The protocol stimulated the postsynaptic inhibitory neuron and the presynaptic excitatory neuron using charge-balanced rectangular pulses with an equal and opposite amplitude ($U_{\text{stim}}$). Figure 2E shows the induced firing patterns in neurons, which decreased the average E-to-I synaptic weight of the network as shown in Figure 2D. On the other hand, the average E-to-I synaptic weight increased when $V_{E}^{\text{stim}}(t)$ and $V_{I}^{\text{stim}}(t)$ were switched such that the presynaptic excitatory neuron fired before the postsynaptic inhibitory neuron. The increased synaptic weight observed from the induced spiking pattern in Figure 2G is
Figure 2. The FTSTS protocol for a two neuron E-I network. (A) shows an excitatory-inhibitory network. (B) and (C) show the FTSTS input pattern for the inhibitory and excitatory neuron, respectively. The FTSTS pulse parameters are $U_{stim} = 300$ mV, $T_{stim} = 1$ ms, and $T_{neutral} = 10$ ms. This FTSTS protocol depresses the E-to-I synaptic weight as shown in (D). The drop in synaptic weight is due to FTSTS inducing a post-before-pre spiking pattern in the E-I network, which is shown in (E). On the other hand, (F) shows how swapping the FTSTS inputs to the excitatory and inhibitory neuron increases the E-to-I synaptic weight. This induces the pre-before-post spiking pattern shown in (G).

3.2. FTSTS effectively controls the neuronal synchronization in 2000 neurons network

We applied the FTSTS strategy to a E-I network of 1600 excitatory and 400 inhibitory neurons to demonstrate how our strategy can be used to control the synchrony of neuronal activity in large networks. In a larger network of neurons, our strategy forces the postsynaptic inhibitory population of neurons to spike before the presynaptic excitatory neuron population. We assumed that all the neurons in each specific population receives the same input. The applied FTSTS inputs to each neuron population are shown in Figures 3A and 3B. These inputs induced a specific spiking pattern, as shown in Figure 3F, which depressed the average E-to-I synaptic weight.
(shown in Figure 3C). The period of stimulation is highlighted with a solid black line in Figure 3C. Since the network has an asynchronous regime that converges to a low average E-to-I synaptic weight, we only required enough input to drive the network into the asynchronous regime. Therefore we provided enough input to depress the synaptic weight to 125 mV which is slightly over the synchronous-asynchronous regime boundary (see Figure 1). As a result, the system naturally converged to the low synaptic weight stability point when the FTSTS protocol was turned off. The synchronous and asynchronous firing patterns before and after the stimulation protocol are displayed in Figures 3E and 3G respectively. The synchrony level of the network as it transitioned from the synchronous to asynchronous regime is shown in Figure 3D. The activity of the E-I network in prior to the applied stimulation (the first 2 seconds) was measured around 0.4. When the stimulation protocol was turned on, the measured synchrony level became very high (see Figure 3D). This is due to the large induced bands of spiking and silent activity of relatively equal proportion in the excitatory neuron population from the stimulation protocol. When the FTSTS protocol was turned off, the network stayed in the asynchronous regime for a long period of time at the measured network synchrony level of 0.1 (see Figure 3D).

Next, we demonstrate how our FTSTS strategy can also be used to synchronize the asynchronous network activity. To do so, we swapped the inputs to the inhibitory and excitatory neurons used in the desynchronization case, which are shown in Figures 4A and 4B. This stimulation protocol forced the presynaptic excitatory neuron population to fire prior to the postsynaptic inhibitory neuron populations, which is shown in Figure 4F. Similar to the two neuron case, swapping the inputs to the excitatory and inhibitory neurons induced LTP in the network and increased the average E-to-I synaptic weight of the network, as shown in Figure 4C. Again we are only required to drive the network into the synchronous regime (i.e., the average E-I synaptic weight above 150 mV) to synchronize the network. Therefore, the stimulation protocol was turned off when the average E-to-I synaptic weight reached 175 mV, which was slightly over the threshold. The network stayed in the synchronous regime and the average E-to-I synaptic weight converged to the high synaptic weight stability point. The spiking patterns of the E-I network before, during and after the FTSTS protocol are shown in Figures 4E, 4F and 4G respectively. Figure 4D shows the changes in the network synchrony level before, during and after the FTSTS protocol. As shown in Figure 4D, the network synchrony level slightly increased during the stimulation and finally converged to approximately 0.3 after the removal of the stimulation. It should be noted that the synchrony level didn’t increased significantly during the stimulation in this case compared to the case of desynchronization (see Figure 3D for comparison). This may be due to a larger induced spiking neuronal activity band compared to the silent neuron activity band where no neurons fired, as shown in Figure 4F. The larger spiking neuron activity band increased the variance of the spike-times and lowered the measured synchrony level.
Figure 3. Desynchronization of neural activity in 2000 neurons E-I network. (A) shows the FTSTS waveform for inhibitory neurons. (B) shows the FTSTS waveform for excitatory neurons. (C) shows the time evolution of the average E-to-I synaptic weight. As shown here, the average E-to-I synaptic weight of network is decreased to 125 mV (blue-line), where the stimulation is turned off. (D) shows the synchrony level of the network as a function of time. (E), (F), and (G) show the spiking patterns before, during, and after the FTSTS protocol respectively.
Figure 4. Resynchronization of neural activity in 2000 neurons E-I network. (A) shows the FTSTS waveform for inhibitory neurons. (B) shows the FTSTS waveform for excitatory neurons. Note that the FTSTS waveforms for inhibitory and excitatory populations are swapped from the desynchronization case (see Figures 3A and 3B). (C) shows the time evolution of the average E-to-I synaptic weight. As shown here, the average E-to-I synaptic weight of network is decreased to 175 mV (blue-line), where the stimulation is turned off. (D) shows the synchrony level of the network as a function of time. (E), (F), and (G) show the spiking patterns before, during, and after the FTSTS protocol respectively.
3.3. Desynchronization of neural activity in large E-I networks

We applied our FTSTS protocol to demonstrate its applicability in larger networks. For demonstration purpose, we considered a E-I network with 8,000 excitatory and 2,000 inhibitory neurons. We set the probability of connectivity of the E-to-I and I-to-E synapses $\epsilon$ to 0.01 and I-to-E synaptic strength $J_{EI}$ to 225 mV. The FTSTS protocol induced the same post-before-pre firing patterns in the larger network which decreased the average E-to-I synaptic weight, as shown in Figure 5A. The stimulation protocol desynchronized the network in approximately 10 seconds, which is comparable to the desynchronization time of the 2,000 neuron network. The changes in the network synchrony level before, during and after the FTSTS protocol are shown in Figure 5B. As noted in Figure 5B, the initial synchrony level of 0.5 reduced to approximately 0.05 after the FTSTS protocol. Once the stimulation protocol reduced the average E-to-I synaptic weight below 125 mV (i.e., the asynchronous regime), we no longer required the external inputs to keep the network in the asynchronous regime.

3.4. Robustness to uncertainties in the FTSTS pulse parameters

We here demonstrate the robustness of our protocol in desynchronizing 2000 neurons E-I network against uncertainties in the FTSTS pulse parameters. We particularly considered uncertainty in the FTSTS pulse amplitude $U_{stim}$ which we modeled in the form of Gaussian distribution with mean $U_{stim}$ and variance $\frac{U_{stim}}{10}$. Each of the applied pulse amplitude during stimulation was randomly chosen from this distribution. As shown in Figure 6B, the FTSTS strategy efficiently desynchronized the network by driving the network into the asynchronous regime. Figure 6A shows the changes in the average synaptic weight of the network before, during and after the FTSTS protocol.
3.5. Robustness to uncertainties in the network model parameters

In this section, we show the robustness of our FTSTS strategy against uncertainties in the network model parameters. For demonstration, we considered variations in the membrane time constant $\tau_m$ of neurons in the network. We randomly assigned the membrane time constant of individual neurons in the 2000 neurons E-I network from two different Uniform distributions to show the efficacy of our FTSTS strategy in desynchronizing the network activity. In the first case, we chose the membrane time constant $\tau_m$ for individual neurons from a uniform distribution $\mathcal{U}(8, 12)$. In the second case, we chose the membrane time constant $\tau_m$ for individual neurons from a uniform distribution $\mathcal{U}(5, 15)$. Figures 7A and 7C show our simulation results for $\tau_m \in \mathcal{U}(8, 12)$. As shown in Figure 7A, the FTSTS protocol forced the average E-to-I synaptic weight of the network into the asynchronous regime within approximately 13 seconds of stimulation which led to desynchronization of the network activity after the removal of the stimulation, as shown in Figure 7C.

Figures 7B and 7D show our simulation results for $\tau_m \in \mathcal{U}(5, 15)$. As shown in Figure 7B, the stimulation protocol pushed the average E-to-I synaptic weight of the network into the asynchronous regime within approximately 8 seconds of stimulation which led to desynchronization of the network activity after the removal of the stimulation, as shown in Figure 7D. As noticed here, the stimulation protocol desynchronized the network faster in this case compared to the first case where the variations in the membrane time constant was small. This is not surprising as an increase variability in the membrane time constant would induce more noise and desynchronized firings among neurons.
Figure 7. Robustness of the FTSTS strategy against uncertainties in the membrane time constant of neurons in the 2000 neurons E-I network. (A) and (C) show the changes in the average E-to-I synaptic weight of the network and the network synchrony level respectively for the case where the membrane time constant $\tau_m$ of individual neurons in the network is drawn from a uniform distribution $\mathcal{U}(8,12)$. (B) and (D) show the changes in the average E-to-I synaptic weight of the network and the network synchrony level respectively for the case where $\tau_m \in \mathcal{U}(5,15)$. The applied FTSTS pulse parameters are $U_{\text{stim}} = 300$ mV, $T_{\text{stim}} = 1$ ms, and $T_{\text{neutral}} = 10$ ms.

3.6. Addition of E-to-E and I-to-I synaptic connections

In this section, we show the efficacy of the FTSTS strategy in desynchronizing 2000 neurons E-I network in the presence of E-to-E and I-to-I synaptic connectivity. We assumed that the synaptic strength of all synapses within the network is static except E-to-I synapses. We set the synaptic strength of the static I-to-E, E-to-E and I-to-I synapses as $J_{EI} = 90$ mV, $J_{EE} = 50$ mV, and $J_{II} = 50$ mV respectively with scaling factors of $C_{EE} = N_{\text{tot}}$ and $C_{II} = N_{\text{tot}}$, where $N_{\text{tot}} = N_E + N_I$. The addition of E-to-E and I-to-I synapses within the E-I network didn’t change the bifurcation of the regime into synchronous and asynchronous with respect to the network average E-I synaptic weight qualitatively. Our simulation results show that the FTSTS strategy effectively desynchronized the network activity, shown in Figure 8B, in the presence of E-to-E and I-to-I synapses by driving the average E-to-I synaptic weight of the network into the asynchronous stability regime, as shown in Figure 8A.
3.7. Integration of FTSTS with the Coordinate Reset strategy

In this section, we demonstrate how our FTSTS strategy could be incorporated within the standard coordinate reset (CR) stimulation protocol to effectively stimulate a large population of neurons. In the CR stimulation protocol, the entire population is typically divided into 4 subpopulations of neurons. Each subpopulation is then stimulated in a random sequence, one at a time, using charge-balanced rectangular pulses which disrupt the synchronous firing patterns among neurons in the entire population effectively using only a few number of stimulating electrodes. Figure 9C shows a typical CR stimulation protocol where burst of 4 pulses was randomly cycled through each of the 4 subpopulations in the excitatory and inhibitory neuron populations.

We integrated this strategy with the FTSTS strategy and applied on a E-I network, consisting of 2000 neurons, in the presence of E-to-E and I-to-I synaptic connectivity. We randomly divided each excitatory and inhibitory population into 4 subpopulations. Then we applied the appropriate FTSTS input for each excitatory and inhibitory subpopulation depicted in Figures 3A and 3B to force post-before-pre spiking pairing between the each randomly selected inhibitory and excitatory subpopulation. For a single FTSTS-CR pulse, we set $U_{stim} = 500$ mV, $T_{stim} = 1$ ms and $T_{neutral} = 8$ ms. Figure 9D shows an example of two cycles our FTSTS-CR approach. We repeated this stimulation protocol to stimulate other subpopulations in a random sequence. Our protocol forced the inhibitory neurons of the selected E-I subpopulation to fire prior to excitatory neurons, which depressed the average E-to-I synaptic weight of the entire population as shown in Figure 9A. Once the average E-to-I synaptic weight reached a preset value of 125 mV (asynchronous regime), we turned off the stimulation protocol. Figure 9B shows that the network remained in the desynchronized state for the entire time of simulation after the removal of the FTSTS-CR protocol.
Figure 9. Efficacy of the FTSTS-CR strategy in desynchronizing 2000 neurons E-I network in the presence of E-to-E and I-to-I synaptic connectivity. Each excitatory and inhibitory population of neurons is randomly divided into 4 subpopulations. (A) and (B) show the changes in the average E-to-I synaptic weight of the network and the network synchrony level respectively when the FTSTS-CR strategy is applied. (C) shows the standard coordinate reset (CR) stimulation protocol for each subnetwork. (D) shows the two cycles of the FTSTS-CR stimulation protocol. The designed FTSTS pulse parameters are $U_{\text{stim}} = 500$ mV, $T_{\text{stim}} = 1$ ms, and $T_{\text{neutral}} = 8$ ms.

4. Discussions

In this paper, we developed and presented a novel stimulation strategy “Forced Temporal Spike-Time Stimulation (FTSTS)” for controlling synchronous activity of neurons in large spiking neural networks. Compared to other desynchronization strategies for large-scale spiking neural networks reported in the literature, our strategy focuses on controlling the average network synaptic weight by harnessing synaptic plasticity using a Hebbian-based spike-timing dependent plasticity (STDP) protocol that as result controls the synchronization of neurons within the network. We presented a two
neuron excitatory-inhibitory (E-I) network as an example to provide a mechanistic understanding of our approach. We later demonstrated the efficacy and robustness of the FTSTS strategy on large networks by varying the model parameters, synaptic connectivity and noisy inputs to the networks. One of the prominent features of our FTSTS strategy is that it allows both synchronization and desynchronization of network activity by reversing the stimulation protocol (Figures 3 and 4), thus provides complete control over the synchronization level of neural activity within a given network.

Our FTSTS strategy differs from existing stimulation strategies for desynchronizing spiking neural networks in many ways. Our strategy is based on harnessing the underlying synaptic plasticity compared to most of the desynchronization strategies reported in literature [6]-[16]. Most of these strategies ignore the inherent synaptic plasticity among neurons in the network in designing the stimulation protocol for desynchronizing the network activity (One exception is “Coordinate Reset (CR) [19]-[25]”). As a result, these strategies effectively desynchronize the network activity if the stimulation protocol is active. Once the stimulation protocol is turned off, the network resynchronizes rapidly because of the disappearance of the asynchronous regime in the absence of stimulation. Our strategy alleviates this problem, like CR, by considering and harnessing Hebbian-based STDP, which allows the network to stay in the asynchronous regime for a longer-time period after the stimulation is turned off (Figure 3).

Almost all the stimulation strategies focus on desynchronizing the network activity by randomizing the firing patterns of neurons through direct stimulation. In comparison, our FTSTS strategy focusses on decreasing the average synaptic weight of the network by taking advantage of the Hebbian-based STDP protocol, which leads to the desynchronization of network activity. For example, the CR-based stimulation strategy desynchronizes the network activity by randomly stimulating a subpopulation of neurons within the network [19]-[25]. This generates an artificial asynchronous firing pattern that increases the basin of attraction of the asynchronous regime (i.e., lower synaptic weight stability point) [1, 19]. The underlying synaptic plasticity within the network then drives the average synaptic weight of the network towards the lower synaptic weight stability point (see Figures 10 and 11 for comparison of our approach to the CR-based stimulation strategy).

Our developed framework can be incorporated into other desynchronization strategies, such as CR, to improve their efficacy. Figure 10 shows a comparison between the FTSTS-CR and CR performances in desynchronizing a E-I network consisting of 2000 neurons with E-I synaptic plasticity (see Section 3.7 for details of model parameters and specifics about the design of FTSTS-CR stimulation strategy). Since the FTSTS-CR stimulation strategy decreased the average synaptic weight of network that as a result desynchronized the neural activity (see Figures 10A and 10C), this strategy outperformed the CR stimulation strategy as shown in Figures 10B and 10D.

One of the limitations of the CR stimulation strategy is that it works on networks where the long-term depression (LTD) dominates the long-term potentiation (LTP) of the synapses on average. It has been found that LTP dominates in specific aberrant
neuronal pathways and brain regions such as the striatum indirect pathway underlying Parkinson’s disease and hippocampus underlying epilepsy [30, 31, 32]. In such brain networks, the CR stimulation strategy could fail to desynchronize the network activity over a long-period of time. To demonstrate this, we applied the CR stimulation strategy to an E-I network consisting of 2000 neurons where LTP dominates by 2% over LTD. As shown in Figure 11D, the network synchrony level stayed around 0.25 during the stimulation period of 150 s and increased to a synchrony level of 0.4 after the removal of the stimulus. Since CR stimulation only induces an asynchronous firing patterns among neurons, the network average synaptic weight stayed in the synchronous regime the whole time (in fact, increased towards the high synaptic weight stability point), as shown in Figure 11B. As a result, the network resynchronized rapidly after the removal of the stimulus. Figures 11A and 11B show the average synaptic weight evolution and the network synchrony level for the FTSTR-CR stimulation strategy. The FTSTR-CR strategy was able to decrease the average synaptic weight below 125 mV over a stimulation period of 60 s, which forced the network into the asynchronous regime. The
synchrony level stayed close to 0.3 during the entire stimulation period and decreased to 0.05 after the removal of the stimulus.

In this work, we have considered excitatory-inhibitory (E-I) networks with plastic E-to-I synapses. In general, our approach is applicable to other types of spiking neural networks such as purely excitatory or inhibitory networks as well as to networks with other plastic synapses such as E-to-E or I-to-I synapses. One of the limitations of our approach is that it assumes the same stimulus waveform to be delivered to individual neurons within a subpopulation. Although we have demonstrated in simulation that our FTSTR stimulation strategy effectively desynchronizes the neuronal firings in a network even when the stimulation waveform parameters for individual neurons are drawn randomly from a given distribution (see Figure 6), it still requires the relationship between pre and post firings to effectively harness the synaptic plasticity. Multi-laser optogenetics and recent development in optogenetics to excite or inhibit the same neuron using two different light wavelengths could potentially alleviate this limitation for experimental implementation of our strategy [33]. Although we have not optimized the

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**Figure 11.** Comparison of the FTSTS-CR stimulation strategy with the coordinate-reset (CR) stimulation strategy on a network where LTP dominates LTD by 2%. (A) and (C) show the changes in the average E-to-I synaptic weight of the network and the network synchrony level respectively for the FTSTS-CR stimulation strategy. (B) and (D) show the changes in the average E-to-I synaptic weight of the network and the network synchrony level respectively for the CR stimulation strategy.
FTSTR pulses to achieve a better performance or to make it more energy efficient, it is not difficult to formulate optimization problems which minimizes the average synaptic weight, network synchrony level and applied stimulation energy simultaneously to achieve a better overall performance.

5. Acknowledgment

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6. References


