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Modeling of topology-dependent neural network plasticity induced by activity-dependent electrical stimulation*

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Abstract

Activity-dependent electrical stimulation can induce cerebrocortical reorganization *in vivo* by activating brain areas using stimulation derived from the statistics of neural or muscular activity. Due to the nature of synaptic plasticity, network topology is likely to influence the effectiveness of this type of neuromodulation, yet its effect under different network topologies is unclear. To address this issue, we simulated small-scale three-neuron networks to explore topology-dependent network plasticity. The induced neuroplastic changes were evaluated by network coherence and unit-pair mutual information measures. We demonstrated that involvement of monosynaptic feedforward and reciprocal connections is more likely to lead to persistent decreased network coherence and increased network mutual information independent of the global network topology. On the contrary, disynaptic feedforward connections exhibit heterogeneous coherence and unit-pair mutual information sensitivity that depends strongly upon the network context.

I. Introduction

The human brain, composed of billions of neurons and connected by trillions of synapses, undergoes modification regarding its internal structure and functional properties by intrinsic and extrinsic activities throughout life. During that process, the ability of the brain to change, referred to as neuroplasticity, plays an important role in coordinating neural interactions on different levels, from cellular changes resulting in improved memory and intelligence to wide-range cortical remapping due to recovery from brain injuries.

The working mechanism of neuroplasticity for single synapses has been revealed in much detail. Based upon this knowledge of monosynaptic plasticity, external electrical stimulation

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has been used to explore cortical plasticity for research and rehabilitative purposes, as it can actively induce plastic changes and lead to systematic reorganization in cortical networks [1, 2]. Such a manipulation, however, is very likely to involve multiple synapses spread throughout the network. To date, however, there is no specific rule to account for or predict polysynaptic plastic changes, and the manifestation of synaptic plasticity across multiple synapses is not well understood. The complexity arising from multiple cell types and large network sizes when networks are scaled up also hinders the exploration of network-level plasticity.

The present work is aimed at analyzing neuroplastic changes induced by activity-dependent electrical stimulation in the context of the simplest model networks containing feedforward, reciprocal, convergent and divergent connections. A number of studies indicate the existence of both local and global structural features of brain networks across different species [3, 4]. The non-random local connection motifs are considered to be the basic building blocks of the network and perform important functional roles [5, 6]. Thus, a reductionist approach examining three-neuron networks allows us to begin examining the influence of local circuit structure on the effectiveness of activity-dependent electrical stimulation. As a result, we may gain insight into the manifestation of neuroplasticity across multiple synapses.

II. Methods

A. Network Model

As a first step toward constructing large-scale models, the computational models of three-neuron networks used a linear Leaky-Integrate-and-Fire (LIF) neuron model [7], as shown in (1), where $C_{memb} = 200$ pF and $\tau_{memb} = 20$ ms denote the membrane capacitance and time constant, and V_{memb} and $E_{rest} = -70$ mV denote the membrane and resting potentials. LIF dynamics mimic neurons' subthreshold responses induced by external current input I_{input} , which was composed of background activities responsible for keeping the neurons' spontaneous firing rates at physiologic values, synaptic inputs from other neurons in the network, and the potential electrical stimulation input. The background activities were modeled as 200 Poisson spike trains at a rate of 0.8 spikes/s. When V_{memb} exceeds a threshold value $V_{thr} = -50$ mV, a neuron fires an action potential and V_{memb} is reset afterwards to E_{rest} . There is 1 ms delay of the action potential propagation along synapses. A 2 ms absolute refractory period is applied after a neuron fires to prevent the generation of a second spike in such a short period.

Current input is modeled with (2) using an alpha-wave characteristic similar to actual synaptic dynamics [8], where w denotes directed synaptic connection strength between a pair of pre- and postsynaptic neurons. $\tau_{rise} = 5$ ms is the neuronal time constant.

$$\frac{dV_{memb}}{dt} = -\frac{(E_{rest} - V_{memb})}{\tau_{memb}} + \frac{I_{input}}{C_{memb}} \quad (1)$$

$$I = wg(t) = w \cdot te^{-\frac{t}{\tau_{rise}}} \quad (2)$$

$$\Delta w = \begin{cases} A_p e^{-\frac{|\Delta t|}{\tau_p}}, & \Delta t > 0 \\ -A_d w \cdot e^{-\frac{|\Delta t|}{\tau_d}}, & \Delta t < 0 \end{cases} \quad (3)$$

The synaptic strengths between pre- and postsynaptic neurons are modulated by an excitatory synaptic plasticity rule based upon their spiking time difference t in (3) to govern the dynamics of the network, where $A_p = 1\text{pS}$ and $A_d = 0.003$ are the learning constants of potentiation and depression, respectively, with their time constants $\tau_p = 20\text{ ms}$ and $\tau_d = 20\text{ ms}$. This form of spike timing-dependent plasticity (STDP) was chosen because it replicates the observations from cortical neurons and was shown to be able to generate stable synaptic weights with different input conditions [9].

The model was implemented in MatLab2011a (The MathWorks Inc, Natick, MA).

B. Experimental Designs

We built 13 three-neuron networks with all the possible combinations of structural motifs, as shown in Fig. 1 [5, 10]. The synaptic weights w of each network were uniformly initialized at 500 pS and achieved steady states within 20000 s before being perturbed by external stimulation.

To implement the activity-dependent stimulation paradigm, we selected two neurons with one reference neuron N_{ref} and one conditioned or stimulated neuron N_{stim} . The third neuron in the network is not directly involved in the protocol and was named a neutral neuron N_{neu} . The reference neuron's spiking activities were detected and triggered the external stimulation with a 20 ms delay on the conditioned neuron, and each spike from N_{ref} induced the firing of N_{stim} (spike-triggered stimulation, STS) with 50% probability. The stimulation process lasted for 20000 s, and the model ran another 20000 s after stimulation. For each motif, we applied STS with at most six unique pairs of N_{ref} and N_{stim} . The last 400 s of each 20000 s interval before and during STS and the first 400 s of 20000 s interval after STS were used for analysis. Each experiment was repeated 3 times.

C. Analysis

To quantify the neuroplasticity changes induced by STS, we chose two metrics assessing the alteration in synaptic weights and spiking activities, respectively. A network coherence value for each motif was calculated to reflect the influence of external perturbation on the stability of each network. The network coherence is defined as the ratio between the geometric mean and arithmetic mean of a network's synaptic strengths, as shown in (4). Network coherence was devised to assess the dynamical evolution of synaptic connections in neural networks [10]:

$$H(w) = \frac{\left(\prod_{(i,j) \in N_s} w_{ij} \right)^{1/N_s}}{\sum_{(i,j) \in N_s} \frac{w_{ij}}{N_s}} \quad (4)$$

where N_s is the number of synapses in a network, and w_{ij} is the strength of a synapse from neuron i to neuron j . Network coherence is used to reflect the similarity of the synaptic strength of all the synapses in a network, ranging from 0 to 1. The higher the value, the more balanced connection strengths are distributed through the network. By contrast, a lower value indicates some synapses are relatively weak.

The relation of spiking activities between each pair of neurons was evaluated by unit-pair mutual information (MI) calculated over their spike trains [11]; a higher MI indicates that two neurons exhibit more similarity in their spike trains. Unit-pair MI is the difference between the sum of individual neuron's entropy and the joint entropy as shown in (5), where $H(N_i)$ and $H(N_j)$ is the entropy of neuron N_i and N_j , and $H(N_i, N_j)$ is the joint entropy of neurons N_i and N_j . To calculate entropy, a neuron's spike train is digitized into 1 s bins. The spikes in each bin are then counted. In (6) and (7), $p(x_i, x_j)$ is the joint probability distribution function of binned spike counts of N_i and N_j , with $p(x_i)$ and $p(x_j)$ being the marginal probability distribution function of binned spike counts of N_i and N_j , respectively.

$$MI(N_i, N_j) = H(N_i) + H(N_j) - H(N_i, N_j) \quad (5)$$

$$H(N_i) = - \sum_{x_i} p(x_i) \log_2(p(x_i)) \quad (6)$$

$$H(N_i, N_j) = - \sum_{x_i} \sum_{x_j} p(x_i, x_j) \log_2(p(x_i, x_j)) \quad (7)$$

III. Results

To better characterize and understand the influence of network topology and the connecting patterns between N_{ref} and N_{stim} on the induced plasticity, we classified all the paired neurons across 13 motifs into seven categories displayed in Fig. 2, which was based upon directed connections. For each pair of neurons, depending upon whether there are multiple pathways between them, their connecting pattern can have one or multiple categories. Some categories are exclusive to each other, such as 'mf', 'mb' and 'rec'. The categories 'dif' and 'dib' are also exclusive to each other because their combination is named as 'con+div' instead.

A. Neuroplastic changes in the form of coherence

Fig. 3 (Top) illustrates the uniform coherence achieved for all network motifs with random background input before the onset of STS at time 0. It indicates that without external perturbation, small-scale network topologies lead to a balanced distribution of synaptic

weights. After STS, however, coherence values diverged into different clusters depending upon the connection pattern between N_{ref} and N_{stim} . Fig. 3 (Bottom) shows large variability within each motif, resulting from the different pairs of neurons that were manipulated, and reveals to influence of connecting pattern between paired neurons. For each motif, identical pair configurations were evaluated and displayed only once. Most of 13 network motifs exhibited generally reduced coherence, and motif No. 13 exhibits a uniform change because all 6 pairs are equivalent in terms of their relative positions in the motif.

To clarify the origin of this variability, we sorted the coherence after STS of all paired neurons in Fig. 3 (Bottom) based upon their connecting categories, as shown in Fig. 4 (Top). Manipulations on paired neurons with either an 'mf' or 'rec' connection displayed consistent after-STS effects, eliciting a substantial decrease in coherence, while 'mb' led to significantly smaller coherence values ($p < 0.01$, bootstrap test) but still consistent influence on coherence. It indicates an unbalanced network synaptic weight distribution brought about because one or a few synapses were strongly altered. In addition, the effects of paired neurons with either 'dif', 'div', 'con' or 'dib' were more complex, with a wider range of, yet still decreased, coherence values following STS.

We selected two representative examples from Fig. 4 (Top), 'mf' and 'dif', and further analyzed the influence on coherence of these two and other connecting categories. Network coherence values for 'mf' all decreased following STS (Fig. 4, Middle) and the networks achieved new steady-state configurations. In addition, interaction of 'mf' with 'dif', 'con' and 'dib' brought about more variability to the network synaptic weights compared with 'div'. In the case of 'dif', manipulation on paired neurons connected disynaptically alone induced little discernible change in network coherence. The combination of 'dif' with either 'mf' or 'rec' revealed more influence by those configurations than 'div' or 'con', which implies that the effects of 'mf' and 'rec' dominate the observed trends (Fig. 4, Bottom).

B. Neuroplastic changes in the form of mutual information

Since neurons communicate with each other through all the synapses that link them together, changes in synaptic weights should induce alteration of information flow through the network. Thus, we expected to see changes of unit-pair MI caused by plasticity-inducing external electrical inputs.

Before STS, the unit-pair MI of all pairs of neurons N_{ref}/N_{stim} , N_{stim}/N_{neu} , and N_{ref}/N_{neu} across 13 networks were all around 1 bit/s (data not shown). Similar to the results of network coherence, we also evaluated the changes of MI induced by STS by sorting based upon different connections between N_{ref} and N_{stim} . All 54 pairs of N_{ref} and N_{stim} can be classified into three groups as shown in Fig. 5. When N_{ref} and N_{stim} are connected by 'mf' or 'rec' and an additional parallel pathway 'con', the unit-pair MI of N_{ref}/N_{stim} , N_{stim}/N_{neu} , and N_{ref}/N_{neu} pairs all increased with a similar magnitude (Fig. 5, Top). In Fig. 5 (Middle), the absence of 'con' between N_{ref} and N_{stim} led to the increase of MI only for N_{ref} and N_{stim} following STS, and there was no change for the other two pairs. The influence of absence of 'mf' and 'rec' between N_{ref} and N_{stim} was clearly shown in Fig. 5 (Bottom) that the MI of all three pairs uniformly did not change.

IV. Discussion

In order to assess the susceptibility of simple neural network motifs, we simulated 13 excitatory three-neuron networks, and applied spike-triggered stimulation (STS) on all the possible pairs of neurons in each network. The results imply that activity-dependent electrical stimulation can modulate network dynamics measured by network coherence and unit-pair mutual information as a function of different features of network topology. They also indicate that in such small-scale local circuits, monosynaptic feedforward and reciprocal connections are likely to result in significant neuroplasticity under any circumstances. The effects of those two connection types upon network coherence and unit-pair mutual information of neurons directly involved in the stimulation process are context-independent and consistent across different motifs. This finding implies that traditional electrophysiology studies of single-synapse excitatory plasticity are likely to be relatively independent of the other neural circuitry in the biological tissue under study.

Under the conditions tested, however, disynaptic connections were highly dependent upon local circuit context for stimulation-induced synaptic changes. Without the contribution of other connection patterns or some other neuromodulatory property, our model indicates that disynaptic feedforward connections represent an ineffective substrate for externally induced plastic changes. This finding also implies that intrinsic neural network plasticity may also be topology-dependent and that observed biological neural network wiring patterns may reflect how information processing becomes altered as well as how it is processed.

Given that disynaptic-only STS was not observed, we were somewhat surprised to find that convergent network configurations (which include a disynaptic feedforward subcomponent) revealed network reconfigurations as strong as any we measured. The forced synchronization of two neurons appears to be sufficient to drive substantial alteration in the synapses of one of these neurons to a common target. Convergence has been reported to be an overrepresented motif in cortical circuits [3], and our findings imply that it may have a disproportionate influence upon both network reorganization and information flow. The ability to modify the connection strength between a neural element being recorded and one not accessible to manipulation could provide a useful option for inducing therapeutic neural plasticity in a variety of brain circuits.

For future directions, we will take inhibitory neurons into consideration, which would enhance the richness and plausibility of the network dynamics. And in light of the small neural circuits, similar methods will be applied for larger networks. Whether the same local neural circuits preserve their plasticity effects once embedded within larger networks will also be investigated.

The ultimate goal of our work is to generate potential rules to characterize the plasticity induced in large networks given the connection patterns among the neurons. With these rules, we could then use activity-dependent electrical stimulation to manipulate the neural network and yield predictable changes, which may be useful in helping design customized stimulation protocols for both polysynaptic plasticity research and rehabilitative purposes.

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Figure 1.

Three-neuron networks with all 13 possible connectivities.

Figure 2.
Connecting category of paired neurons. DC: 'don't care'.

Figure 3.

(Top) Coherence over simulation time of all 13 network motifs with up to six unique paired neuron configurations. Magenta, red and blue denote all the pairs with 'rec', 'mf' and 'mb' connections respectively. Green denotes all the pairs without 'rec', 'mf' or 'mb' connections. (Bottom) Average coherence of all 13 network motifs between 20000 s and 20400 s. Each motif has at most six unique paired neurons for STS; no plots are shown for identical pairs.

Figure 4.

(Top) Coherence following STS across 13 network motifs segregated by the connecting patterns between N_{ref} and N_{stim} . Each box shows the distribution of coherence values of paired neurons whose connection pattern at least includes the category displayed on the horizontal axis under that box. (Middle) Coherence following STS across 13 network motifs of paired N_{ref} and N_{stim} with at least an 'mf' connection, with both 'mf' and at least one of 'dif', 'div', 'con' and 'dib' connections, and with 'mf' only. (Bottom) Coherence following STS across 13 network motifs of paired N_{ref} and N_{stim} with 'dif' connection, with both 'dif' and at least one of 'mf', 'rec', 'div', 'con', 'mb' and 'dib' connections, and with 'dif' only.

Figure 5.

MI difference of paired neurons N_{ref} with N_{stim} (black), N_{stim} with N_{neu} (gray), and N_{ref} with N_{neu} (white) between, following, and before STS. (Top) N_{ref} and N_{stim} with either 'mf' or 'rec' and 'con' connections. (Middle) N_{ref} and N_{stim} with either 'mf' or 'rec' but without 'con' connection. (Bottom) N_{ref} and N_{stim} with neither 'mf' nor 'rec' connection.