

Precise Synchronization of Active and Silent States in EI-units using an Excitatory-Inhibitory Model (Final Project 11.6.5)

Martijn Brouwer (6859488)

Mathematical Neuroscience (WISL413)

Master, Mathematical Sciences. Utrecht University

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Abstract

This report focuses on the reproduction and confirmation of the results of the paper by Volgushev et al. [1] by performing numerical simulations. They showed that during non-REM sleep, slow-wave oscillations in the membrane potential involves all neocortical neurons. Besides this, they showed that the synchronization of the onsets of silent states was more precise than the onsets of activity which would imply the existence of a yet undiscovered network mechanism. We showed that indeed the onset of activity in a specific neuron laterally propagates to its neighboring neurons using an excitatory-inhibitory model. Moreover, we showed that the standard deviation of the onset delays were generally smaller for silent states relative to active states suggesting a higher degree of synchronization in silent state transitions. Finally, it turned out that increasing the noise and coupling increases respectively the amount of spontaneous switching and elongated the duration of laterally propagating states. All code is available on this GitHub-page.

I. ARTICLE ANALYSIS

Volgushev et al. researched in article [1] the underlying mechanisms of the alternation between periods of activity and silence in neocortical networks during slow-wave sleep (non-REM sleep). The study aims to understand state synchronization across distant neocortical regions. Understanding this large-scale network mechanism is crucial for comprehending brain rhythms in both normal function and pathology.

By recording local field potentials and intracellular activity of multiple neurons simultaneously in the neocortex of cats, they studied the alternating periods between active (up-states) and silent states (down-states). Active states are characterized by the depolarization of the neuron, firing and high activity levels; whereas the silent states are represented by hyperpolarization and inactive levels. It is hypothesized that these state transitions originate from the initiation of activity which subsequently iteratively spreads to its neighboring neurons. They researched the synchronization of this state spread, *i.e.* the temporal relationship between when a neuron transitions from an active to a silent state (or vice versa) and the same state transition in its neighboring neurons. This lateral propagation of states forms a systematic pattern with consistent onset delays across the neural network.

The article describes two methods used for state detection.

1. The first method sets two thresholds based on the bimodal distribution of the membrane potential to determine its state. The period that the membrane potential stays above the upper threshold is defined as an active state and the period below the lower threshold as a silent state. Threshold crossings for only a small period were not labeled as a state transition and when there was a separation present of a small period between two equal states, they were merged.

2. The second method calculates the mean and standard deviation (SD) of the membrane potentials in a small time frame. Then, peaks in a 3D-(mean,SD,counts)-plot identifies the active and silent states.

Since both methods yield similar results, we will focus on the first method. Next, the article proposes two strategies employed to examine the temporal patterns of neuronal states across various locations.

1. The first strategy involved searching for clusters consisting of groups of active or silent states that occurred simultaneously in all recorded neurons in the anteroposterior direction. To qualify as a cluster, the states had to fulfill two criteria: (1) they occurred in all recorded neurons, and (2) their onsets were separated by less than a small specified time. Note that with 'onset' we mean the moment in time at which the state transition occurs. Subsequently, the delays of the state onset in the neurons relative to the cluster mean were calculated. The results confirmed the spread of the states supporting the previously stated hypothesis of lateral propagation (with some exceptions in a reverse order).
2. The second strategy involved analyzing pairwise comparisons of state onsets in a range of pairs of simultaneously recorded neurons. This strategy confirmed the findings of the first strategy and complemented it by showing a synchronous involvement of neurons across a spatial extent of up to 12 mm, more precisely for silent states relative to active states. This last argument was concluded since the standard deviation of onset delays of silent states was smaller than for active states.

Volgushev et al. showed that slow-wave oscillations in the membrane potential involves all neocortical neurons and that the spread of states originates from a local focus. Most intriguingly, they showed that the onsets of silent states were synchronized more precise than the onsets of activity over a 12-mm spatial area. This would imply the existence of a yet undiscovered network mechanism since synchronous onset of states in distant neurons cannot rely solely on the properties of the individual neuron.

II. THE MODEL

Generally, two population models describing activities u_e, u_i of an EI-unit (*i.e.* an excitatory-inhibitory neuron) in which one population is excitatory (e) and the other is inhibitory (i) are given by [2]:

$$\begin{cases} \tau_e \dot{u}_e = -u_e + F(w_{ee}u_e - w_{ei}u_i + I_e) \\ \tau_i \dot{u}_i = -u_i + F(w_{ie}u_i - w_{ii}u_e + I_i) \end{cases} \quad (1)$$

in which the dots denote time derivatives and F an activation function. We will only consider the sigmoidal activation function defined by, $F(x) = \frac{1}{1+e^{-x}}$. Excitatory neurons increase activity of neighboring neurons by depolarizing them, whereas inhibitory neurons decrease activity by hyperpolarizing them. Furthermore, we will make use of the parameter values as defined in [2] (page 353): $\tau_e = 5$, $\tau_i = 3$, $w_{ee} = 16$, $w_{ie} = 24$, $w_{ei} = 10$, $w_{ii} = 6$, $I_e = -3.7$ and $I_i = -6.7$.

However, in order to connect neighboring EI-units using the dynamics of system 1, we will only adapt the activities present in the activation function by taking the average over its neighbours. Now, for the j th neuron ($j = 1, \dots, N$) we will redefine $(u_e)_j =: u_j$ and $(u_i)_j =: v_j$ such that for the excitatory activity,

$$\begin{aligned} \dot{u}_j &= \frac{-u_j + F(w_{ee}\bar{u}_j - w_{ie}\bar{v}_j + I_e) + \eta_j}{\tau_e}, \\ \bar{u}_j &= (1 - c_e)u_j + \frac{c_e}{2}(u_{j+1} + u_{j-1}) \end{aligned} \quad (2)$$

and for the inhibitory activity,

$$\begin{aligned} \dot{v}_j &= \frac{-v_j + F(w_{ei}\bar{u}_j - w_{ii}\bar{v}_j + I_i) + \zeta_j}{\tau_i}, \\ \bar{v}_j &= (1 - c_i)v_j + \frac{c_i}{2}(v_{j+1} + v_{j-1}). \end{aligned} \quad (3)$$

In these equations, c_e, c_i are respectively the excitatory and inhibitory coupling constants between the neurons while η_j, ζ_j are independent random noise terms distributed standard normal. Larger independent noise for the excitatory and inhibitory neurons may induce more spontaneous switching, whereas stronger coupling may enhance the spread of state changes across the network.

III. METHODS AND IMPLEMENTATION

We will create two matrices u and v containing respectively the excitatory and inhibitory activity values of 100 neurons over 1000 time steps with $dt = 0.1$. It makes use of a random initialization for the neurons for both u, v at $t = 0$. We will apply the Euler forward method looping over all time steps and all neurons filling in the matrix according to,

$$\begin{aligned} u_{j+1} &= u_j + dt \cdot \dot{u}_j \\ v_{j+1} &= v_j + dt \cdot \dot{v}_j. \end{aligned} \quad (4)$$

Now that we have obtained both activity levels of all neurons over time, we want to detect the active and silent states following the first method of the article. We will set two thresholds based on the bimodal distribution of the activity levels. Note that from now on we will only consider activity levels instead of membrane potential since these variables are directly related to each other. When the membrane potential exceeds a certain threshold, activity increases and when it decreases below some lower threshold, activity decreases. First, we will simulate an example distribution for the some activity levels in Fig. 1 in order to determine the threshold levels. We used the parameter values $c_i = 5$, $c_e = 5$ and $\eta_j, \zeta_j = \text{noise} \cdot Z_j$ with $\text{noise} = 0.4$ and Z a standard normally distributed random variable.

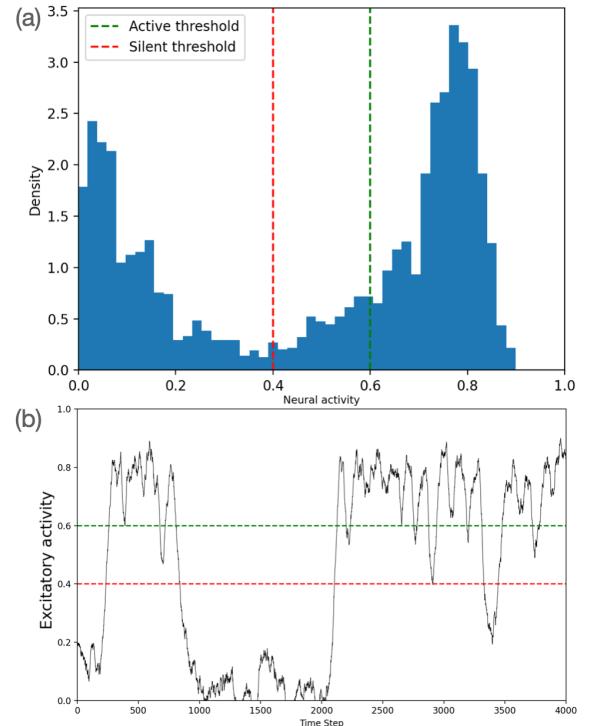


Figure 1. In figure (a), we plotted the binomial density distribution of the excitatory activity levels from figure (b) up to 4.000 time steps. We set the level of the active threshold at 0.6 and for the silent threshold at 0.4.

In Fig. 1(b), we can clearly see the switching of active and silent states. We set the two thresholds fixed at 0.6 and 0.4 for respectively active and silent states. However, now we want to detect over which region the activity is in which state. We will follow again the first method I of the article such that threshold crossings for smaller than 100 time steps are not labeled as a state transition and that gaps between equal states are merged for periods smaller than 100 time steps (see Fig. 2).

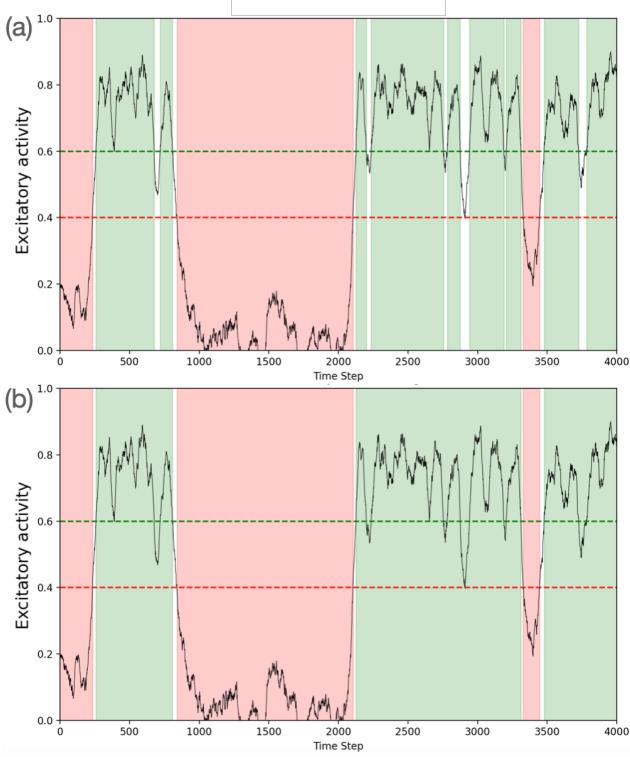


Figure 2. In figure (a), we plotted the excitatory activity with green and red regions representing respectively active and silent states based on the previously set thresholds. In figure (b), these gaps are extended for crossings of at most 100 time steps.

To investigate the temporal patterns, we will create a contour plot of the activities of all neurons over the considered time and we will quantify the standard deviations (SDs) of the onset delays. These onset delays thus refer to the time difference between the start of a state in a particular neuron and the start of the same state in its neighboring neurons. The standard deviation quantifies the dispersion (*i.e.* spread) of these onset delays.

We will make use of the second strategy of the article. By iterating over the amount of neurons minus one, we ensure considering pairs of neighboring neurons. We will calculate the onset delays by subtracting the start time of the state transitions of a considered neuron from the start times of its neighboring neurons. We check if the neighboring neuron has any state transitions and if not, skip the current iteration. This will be done for the delays of both the active and silent states. Finally, we calculate the SD of both lists of delays.

IV. RESULTS

A. State alternation and lateral propagation

We will consider 100 neurons over 2.000 time steps coupled according to equations 2 and 3. In this subsection, we consider the parameter setting: $c_e = 3$, $c_i = 3.5$ with noise = 0.4.

First, we will execute the described methods of section III and we obtain Fig. 3. Notable is that the alternation between the active and silent states are clearly visible in Fig. 3(a) and that the neurons undergo similar state transitions. Also temporal patterns are visible as branching lateral propagation of states in Fig. 3(b). Next, we calculate the standard deviation of the onset delays of this specific case which gives,

$$\begin{aligned} \text{active state SD: } & 331.36 \text{ time steps} \\ \text{silent state SD: } & 294.79 \text{ time steps.} \end{aligned}$$

Moreover, taking the average over 100 different seeds and calculating the mean of the SDs yield,

$$\begin{aligned} \text{average active state SD: } & 315.36 \text{ time steps} \\ \text{average silent state SD: } & 292.93 \text{ time steps.} \end{aligned}$$

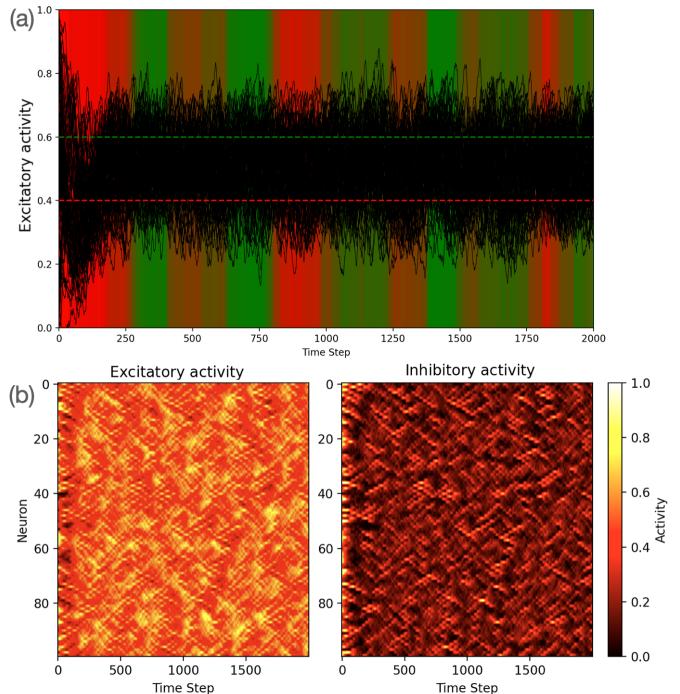


Figure 3. 100 neurons over 2.000 time steps with $c_e = 3$, $c_i = 3.5$, noise = 0.4. The alternation between the active and silent states are clearly visible in figure (a).

B. Influence of noise and coupling constants

In this section, we will perform some simulations researching the effect of the noise and coupling constant value c . In Fig. 4, we plotted contour plots for varying noise levels and fixed $c_i = 5 = c_e$. As the noise increases, the amount of neurons of which its activity laterally propagates to neighboring neurons increases as well.

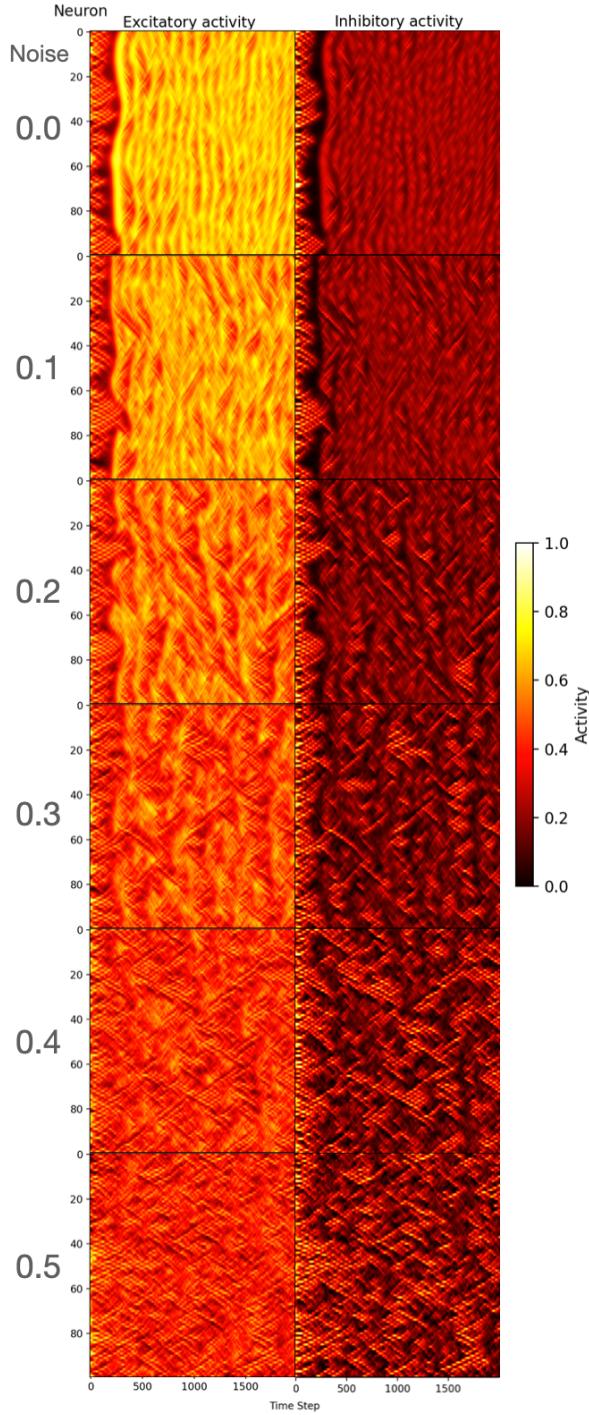


Figure 4. Plots with varying noise levels for fixed coupling constant $c_e = 5 = c_i$.

Next, we will perform some simulations researching the effect of the coupling constant $c = c_i = c_e$ for fixed noise level 0.4. We find that as the coupling constant increases, the duration of the laterally propagating states enlongates.

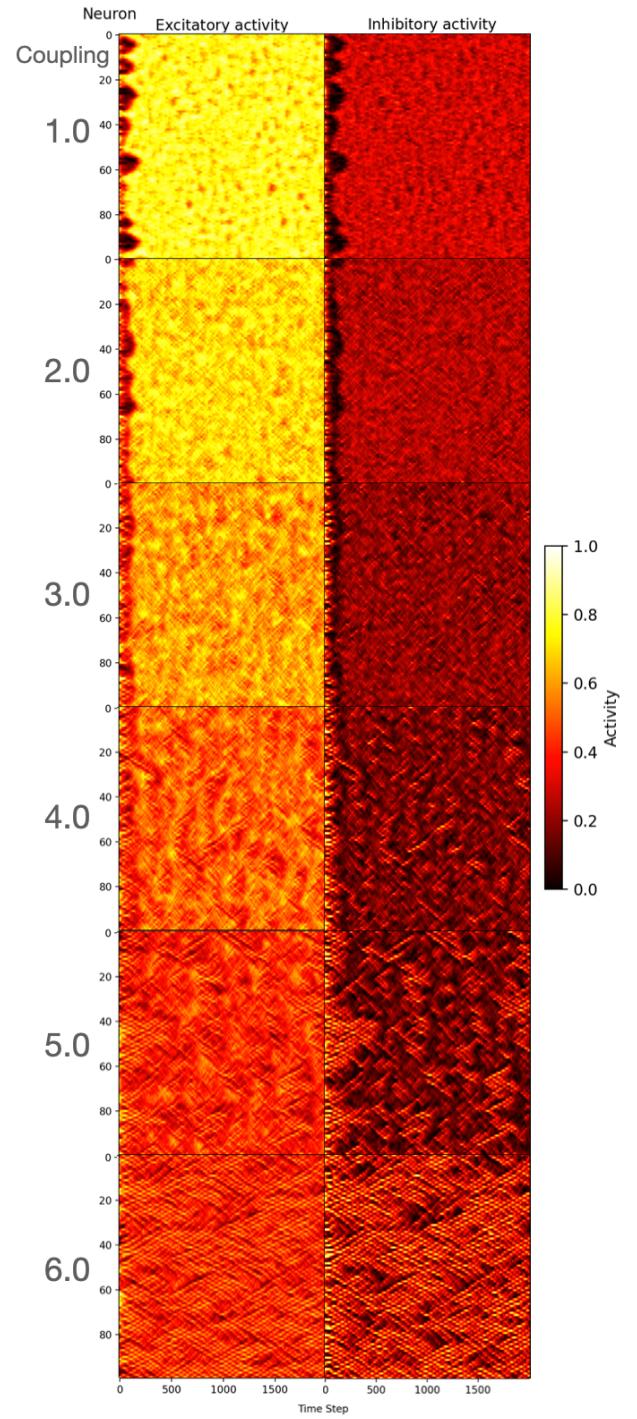


Figure 5. Plots with varying coupling constant $c = c_e = c_i$ for fixed noise level 0.4.

V. DISCUSSION

In section IV, we first showed plots of a parameter setting which confirmed the ability of the model to simulate lateral propagating states and state alternations. In Fig. 3(a), we have seen that the coupling of neurons causes the alternation of the active and silent state in (almost) all involved neurons just as the article showed. Furthermore, in Fig. 3(b) we have seen the clear lateral propagation of activity in a branching manner. These temporal patterns which formed a cascade of activity levels to neighboring neurons was one of our goals to show.

After finding the parameter setting for which the state alternation occurred, we averaged over 100 seeds calculating the standard deviation of the onset delays. We have shown that this standard deviation was generally smaller for the silent states relative to the active states. A smaller standard deviation indicates that the onset delays between neighboring neurons are grouped closer together, suggesting a higher degree of synchronization in the silent state transition just as the article showed.

And last, we researched the influence of the independent noise and coupling constant(s) on the appearance of the temporal patterns. We found that as the noise level increases, the amount of neurons that spread their activity to neighboring neurons increases as well. Besides this, a larger independent noise for the neurons induced more spontaneous switching. Similarly, a stronger coupling constant enhanced the spread of state across the network by elongating the temporal trajectory of the onsets over the neurons. This is expected, since neighboring neurons are more connected.

VI. CONCLUSION

In this report, we focused on the reproduction and confirmation of the results of the paper by Volgushev et al. [1] by performing numerical simulations.

They showed that during non-REM sleep, the slow-wave oscillations in the membrane potential involves all neocortical neurons and that this spread originates from a local focus. It also turned out that the synchronization of the onsets of silent states was more precise than the onsets of activity (over a 12-mm spatial area). This would imply the existence of a yet undiscovered network mechanism.

We have shown using an excitatory-inhibitory population model that the onset of activity in a specific neuron laterally propagates to its neighboring neurons (iteratively). Besides this, we showed that the standard deviation of the onset delays were generally smaller for the silent states relative to the active states suggesting a higher degree of synchronization in the silent state transition. Finally, we researched the effect of noise and coupling between neighboring neurons. It turned out that increasing the noise, induced more spontaneous state switching; whereas stronger coupling elongated the duration of the laterally propagating states to neighboring neurons.

These results are indeed in agreement with the results of Volgushev et al.

[1] *Precise Long-Range Synchronization of Activity and Silence in Neocortical Neurons during Slow-Wave Sleep*, by Volgushev, Chauvette, Mukovski and Timofeev, *Journal of Neuroscience* 24 May 2006, 26 (21) 5665-5672; DOI: <https://doi.org/10.1523/JNEUROSCI.0279-06.2006>

[2] *Mathematical foundations of neuroscience*, by B. Ermentrout and D. Terman, pp. 350-367, volume 35, *Springer, Interdisciplinary Applied Mathematics*, 2010.