Project Title:

Self-organization of synaptic efficacy clusters and symmetry breaking effects across the dendrite via STDP

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1. Background and purpose of the project, relationship of the project with other projects

The goal of Neuroscience is to understand how neuronal activity and experience influence brain development and refine neuronal circuits via cellular and molecular processes. Numerious theoretical studies have typically addressed questions concerning single cell responses and cellular network dynamics using simplified descriptions of neurons which ignore the spatial morphology of the neuron, to minimize computational expense. Such descriptions are called **single compartment or point neuron models.** They assume that a brain cells' spatial morphology plays no useful role in information processing.

Point models are those in which the membrane potential for the cell can be described mathematically by a system of linear or nonlinear Ordinary Differential Equations (ODEs). To fully describe the spatial nature and dynamical properties of brain cells, mathematical descriptions that ignore spatial extent are not enough. Describing the complex dynamics of neurons can only be fully achieved using a system of Partial Differential Equations (PDEs). Neuron, as observed under the microscope, consists of a soma, a dendrite and an axon. Both the axon and dendrite have processes that branch out (like the branches of a tree) and possess complex spatial geometry. The spatial complexity of the neuron's morphology and the spatial pattern of synaptic connectivity converging onto the soma and dendrite introduce a new intricacy.

Understanding how and where axons from one cell make synaptic connections onto the dendrites of other neurons and how it might be altered over time by specific activity-dependent cellular and molecular processes (known as *synaptic plasticity)* is a major challenge. Fully understanding how underlying biological processes leads to activity-dependent changes in neural circuits has important and immediate implications in computer science and engineering, especially for architectures reliant on deep learning paradigms.

Previous experiments investigating a specific type of learning phenomenon called spike timing-dependent plasticity (STDP) typically present a plasticity rule characterized by a temporally learning window, where the temporal order of pre- and postsynaptic firing dictates whether synaptic strength is increased (pre-before-post) or decreased (post-before-pre). Previous theoretical studies have used the point model paradigm to study how STDP influences the evolution and final distribution of synaptic weights. Instead, few STDP studies have used spatial or compartmental models to investigate changes in synaptic strength across spatially extended dendrites.

The ultimate purpose of this research is to understand the origin of the microscopic architecture

of the cortical connectome (neuron to dendrite connection patterning). Specifically, how STDP impacts neuronal circuit formation through shaping the spatial arrangements and strengths of synapses across the dendrite, the branched projections originating from the cell body (soma), for both a single neuron and network of cells.

This project has several goals. The first goal is to study the emergence of functional clusters, its robustness and the fine scale spatial structure of such clusters in the dendrites of single neurons, while being stimulated by two or more groups of afferents. The second goal is to elucidate how the effects symmetry breaking emergences from STDP, and their functional impact. The third goal is to investigate the role of spike timing and the impact of STDP in developing cellular functional properties using network simulations. The final goal is to find if there is some structural correlate or specific spatial organization, such as spatial clustering, underlying functional properties of neurons which emerged during the learning process, thus providing testable predictions for future experimental studies.

2. Specific usage status of the system and calculation method

Simulations were conducted using the NEURON simulation environment, a popular and convenient environment for building and simulating either networks of neurons or single cells of any desired spatial and biophysical complexity. A variety of numerical schemes can be used by NEURON such as the Crank-Nicholson method and CVODES (developed by A. Hindmarsh et al.). The simulators' strength lies in its efficiency in building and simulating morphologically and biophysically detailed model neurons and network of such cells. Recent additions to NEURON include improved parallelization performance and Python-to-Neuron interoperability and the ability to carry out **multiscale simulations** that consider both cellular electrical activity and sub-cellular molecular reaction-diffusion based processes. The NEURON simulation environment can simulate intracellular biochemical signaling cascades, networks and single neurons on either a single processor/core or in parallel (using MPI) over multiple processors. The current and previous versions of the NEURON simulator are freely available and can be downloaded from https://neuron.yale.edu/neuron/

3. Results

A small-scale feed forward network has been constructed, consisting of several equally sized groups of correlated afferent fibers, with no correlation between the groups. These groups form synaptic connections at random positions over the dendrite of a reconstructed layer 2/3 pyramidal cell. This model has been used to study the evolution and final spatial arrangements of synaptic strength over the dendrite, especially the role of nonlinear STDP in a well investigated phenomenon called ocular dominance formation, being an activity-dependent process where the cell learns to respond vigorously to stimulation from one eye, but weakly from the other. An accurate biophysical model was previously developed which quantitatively reproduces several important experimental observations seen in layer 2/3 pyramidal cells.

This model was used to show how the degree of competition between synapses and the pattern of incoming inputs, leads to spatially segregated efficacy clusters, when stimulated by several equally sized groups. We have previously shown how different variations to the input leads to symmetry breaking in the mean weight, in a model stimulated by two afferent groups and the correspondence in the final spatial organization of synaptic strength. I found that there exists a range of parameter values where synaptic weight distributions segregated according to the nature of their input correlations and mean input frequencies, by using a nonlinear

STDP rule (Gutig et al 2003).

We have also identified that a unique spatial organization emerges when multiple yet equally sized groups provide the stimulation; a **dendritic mosaic** emerges but depends on the degree of competition and amount of balance introduced by the nonlinear STDP rule and the frequency of inputs to the biophysical model neuron. Furthermore, we have investigated how altering the intrinsic balance within the STDP rule affects the dendritic mosaic. By "balance" we mean the ratio of the area admitting potentiation and depression in the temporal learning window should be near zero; put simply a near equal amount of strengthening and weakening. For a pair based STDP rule, this ratio is $A_{-}\tau_{-}/A_{+}\tau_{+}$ and it needs to be greater than 1 for stable learning to take place. Moreover, we showed that the mean input frequencies of synaptic inputs and the degree of STDP balance jointly influences the emergence of the dendritic mosaic.

Recently, we are investigating how changing the morphology or shape of the dendrite can jointly influence whether the dendritic mosaic emerges alongside to balance. We conducted a quick proof-of-concept investigation on what effects changing neural morphology impacts the emergence of the dendritic mosaic by comparing the dendritic mosaic formation using a reconstructed dendritic morphology and to a simplified cable-like morphology that was obtained by collapsing the original tree into a single cable while preserving the electrical properties of the original neuron. Here, we found that the morphology of the dendrite can directly impact the emergence of the dendritic mosaic. This preliminary result was presented at the international joint conference on neural networks in 2017.

This has initiated a new question of why and what role morphology plays during the development and whether there is some morphological principle underlying learning and memory of neuronal functional properties that is independent to the neuron's intrinsic electrical response properties.

4. Conclusion

To date, the results achieved so far have indicated that timing-based learning, such as STDP and its variants in spatially extended dendrites supports the emergence of clustered spatial organization of functional inputs under the condition that competition between synapses is strong and that the degree of synaptic potentiation and depression are balanced. Specifically, the formation of spatially segregated clusters and the overall patterning of the dendritic mosaic jointly depends on several different intrinsic and extrinsic properties including the degree of competition and the degree of balance introduced by the STDP rule. Moreover, the shape or morphology of the dendrite has been found to have a strong impact on the mosaic patterning, while maintaining the intrinsic electrical properties relatively unchanged. These initial results are indicating that aspects of morphology or some underlying structural parameter may play a hidden role that underlies the final pattern of the mosaic. The latest results indicate that there is some unforeseen morphological principle that underlies the formation of neural circuits that operates in concert with biological processes mitigating brain plasticity.

5. Schedule and prospect for the future

For the next step, I have started developing theoretical techniques to investigate how and why changes in neuronal morphology, while keeping the intrinsic electrical properties relatively unaltered, changes the qualitative patterning of the dendritic mosaic. In the past, I have collected data illustrating that changing the electrical properties (by changing the density of ion channels) of the neuron, without changing the morphology, leads to small changes in

the patterning of synaptic clusters. This is contrary to what was observed when electrical properties were kept constant and the morphology changed. Developing a method that can quantitatively help explain these phenomena is quite challenging and difficult.

Furthermore, I am developing parallel network simulations and another theoretical framework aimed at explaining how STDP can lead to the emergence of orientation and direction selective cells, by focusing on the learning rule. Developing this framework is on-going. Eventually, parallel network simulations and theoretical framework will be applied to model the early visual cortex of the cat using NEURON. This involves conducting a multiscale simulation where a single biophysically and morphologically detailed model is inserted into a large-scale network composed of single compartment cells representing a section of the visual cortex. It is envisaged that the multiscale model will be extended by replacing the single compartment neurons of the network with multi-compartmental based neurons and potentially even include several morphologically complex cells. The network will be used to investigate the role of spike-timing based plasticity in developing known properties of cortical networks. If all these proceeds smoothly, then we plan to make specialized models of the cat. primary visual cortex. Such models are expected to provide insights in how functional properties emerge and more importantly, whether there is an underlying structural correlate. The development stages are as follows

- Compile and test a parallel version of NEURON on new system Bigwave. **To be redone**
- Continue development of theoretical frameworks capable analyzing the outcome of STDP learning in networks (base on single compartment cells), mosaic formation and the impact of changing morphology during STDP learning. **In-progress.**
- Investigate ways to carry out better load balance by adopting strategies which utilize splitting the more complex cell over different cpus. **To be redone.**
- Build a prototype network consisting of a single layer of spiking neurons (including both excitatory and inhibitory cells) to investigate input selectivity where different output neurons learn unique inputs. **In progress.**
- Develop the corresponding theoretical framework that can explain the basis of different output neurons learning unique inputs. **In progress.**
- Once the previous step is complete, a reconstructed neuron is embedded into a 2D largescale network of single compartment models of spiking neurons and fine tune so that it reproduces important network dynamics such as orientation selectivity. **In progress.**
- Based upon this prototype network, a model of the early visual system of the cat will be constructed to investigate how the dendrite contributes to the formation of cellular functional properties. **Not yet started.**
- In parallel, develop a good simplified approximation scheme for any morphologically complex model neuron. This will be useful as it will allow larger networks to be simulated using fewer computational resources. **In progress**

6. If no job was executed, specify the reason.

Some test simulations have been performed, but during the last year I have mainly focused on developing theoretical frameworks that can both help explain how STDP impacts the firing properties of neurons and help explain the emergence of synaptic clusters that contribute to dendritic mosaic. These theoretical frameworks are quite challenging to develop since consideration of spatial morphology (along with excitability and learning) requires the use of advanced mathematics. We hope to succeed in these as they will become valuable additions to future articles. We are planning to restart simulations in 2019.