Usage Report for Fiscal Year 2021

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

One important focus for both experimental and computational neuroscientist is how external experience influences brain development and the refinement of neuronal networks through cellular and molecular processes that underlie synaptic plasticity. Numerous theoretical studies have addressed questions such as neural coding, responses, and computation, using single neuron and cellular network dynamics using simplified descriptions of neurons that ignore the spatial morphology of the neuron and assume that spatial morphology plays no useful role in information processing.

Such models are classified as single compartment or point models, in which their dynamics is described 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 requires using Partial Differential Equations (PDEs) to better capture their dynamical properties. All the different types of neurons, 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.

Understanding how and where axons from one cell make synaptic connections onto the dendrites of other neurons and how these connections are 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 the fields of Artificial Intelligence, Computer Science and Engineering, especially for architectures reliant on learning paradigms.

Previous experiments investigating spike timing-dependent plasticity (STDP) typically present a plasticity rule where synaptic weights are increased (potentiated) or decreased (depressed) according to the timing difference and temporal order of pre- and postsynaptic firing, where synaptic strength is increased when pre- occurs before post-synaptic spike or decreased (post-before-pre) otherwise. 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 biophysically inspired spatial models to investigate changes in synaptic strength across dendrites.

The ultimate purpose of this research is to

understand the origin of the microscopic architecture of the cortical connectome (neuron to dendrite connection patterns). Specifically, how the learning process may impact 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, their robustness and the fine scale spatial structure of such clusters in the dendrites of single neurons, while being stimulated by two or more streams of activity. 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, intracellular diffusion in 1D in single neurons and networks 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. Result

Using a small-scale feed forward network, we have already shown how randomly organized synaptic inputs from several equally sized yet independent input streams lead to patterns of spatially segregated clusters of synaptic efficacies, where each independent input group dominated some spatial section of the dendrite resulting from an underlying winner-take-all in the spatial domain.

A biophysical detailed 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. Furthermore, we have also shown that changes in the neuron's morphology impacts the patterning and spatial organization of the mosaic. We have shown that systematically reducing the morphology of an idealized dendrite so that its electrical properties remain largely unchanged leads to drastically altered spatial patterning and the quality of the mosaic. This highlighting a counter intuitive relationship with morphology and learning. Details of this have been provided in previous reports.

4. Conclusion

The results achieved so far have indicated that 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 balance and competition introduced by the STDP rule. Moreover, the 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 results indicate further studies are required to better understand how the formation of neural circuits operates in concert with biological processes mitigating brain plasticity.

5. Schedule and prospect for the future

For the next step, I have beeno developing a mathematical framework of how learning leads to the emergence of orientation and direction selective cells in the hope that it will allow me to predict the outcome of STDP learning in networks spiking neurons. Developing such a tool has proven mathematically challenging and is still ongoing research.

Eventually, this 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. **A** multiscale model of the early visual cortex incorporating both single compartment and morphologically detailed models will be built. The network will represent a multiscale model of the cat visual cortex and used to study how plasticity leads to functional properties like orientation and direction selectivity and more importantly, whether there is an underlying structural correlate.

The development stages are as follows

- Continue development of theoretical frameworks capable analyzing the outcome of STDP learning in networks (base on single compartment cells). **In-progress.**
- Investigate ways to carry out better load balance by adopting strategies which utilize splitting the more complex cell over different cpus. **Completed for now but may need re-addressing.**
- 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. **Completed.**

- 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 large-scale network of single compartment models of spiking neurons and fine tune so that it reproduces important network dynamics such as orientation selectivity. **In progress.**
- Develop new stimulation modules for NEURON that represent stochastic activity originating from simple 1D input features that obeys periodic boundary conditions, and other modules that represent the activity from 2D orientated moving bar and moving grating stimuli. **Completed.**
- 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. **In progress.**

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

Apart from being busy with writing grant applications, I have very recently built new NEURON simulation modules for visual stimuli that will be used in future simulations. These modules produce random activity over a 1D feature space that randomly changes the input feature (described by Gaussian functions equally distributed over a 1D feature space) and correspondingly, random inputs representing oriented moving bar and grating pattern over a 2D input space. These have been developed and tested on my laptop and will be used on the cluster for future simulations as described in the previous section.

I have also started constructing new simulations that will use these new inputs in new models of the visual system, where we will also examine the impacts of several recently published learning rules on their ability to reproduce known firing properties, their corresponding input patterns and underlying dendritic computations.

For these reasons, few cpu hours have been used. I am hoping to greatly increase cpu usage in the coming year.