Usage Report for Fiscal Year 2020

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

How the brain works is what neuroscience strives to understand, whether it be human or mouse. One important focus is how external experience influences brain development and the refinement neuronal circuits through cellular and molecular processes. 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. 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 neuron models are those where the neuron is essentially represented as a "ball" (typically called a single compartment), in which the dynamics of the membrane potential 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 can only be accurately achieved using a system of Partial Differential Equations (PDEs). 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 a specific type of learning phenomenon called 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 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 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

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. Initially, these groups form synaptic connections at random positions over the dendrite of a reconstructed pyramidal cell. This model was used to study the evolution and final spatial arrangements of synaptic strength over the dendrite, especially how nonlinear STDP leads to a neuron to respond more vigorously to one set of inputs, akin to what is seen in ocular dominance formation.

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.

We have also shown that changing the neuron’s shape or morphology affects the emergence of the dendritic mosaic. We found that changing the neuron’s morphology directly impacts the patterning and spatial organization of the mosaic. This has initiated a new question of why and what role morphology plays during the development, learning and memory of neuronal functional properties that is independent to the neuron’s intrinsic electrical response properties.

To investigate this further, controlled simulations were conducted using a predefined idealized branching morphology where the starting dendritic tree was systematically collapsed down to an unbranching cable. An idealized geometry was used possessing three orders of branch points with the branches from the parent dendrite were all the same length and diameter. Using this morphology, the emergence of the dendritic mosaic was simulated. Then, a published reduction scheme, which conserves neuronal electronic properties, was systematically applied, producing a morphologically altered yet electrically equivalent morphology. The emergence of the mosaic was investigated using this altered morphology. This process was conducted in a step by step fashion, starting from the outmost tips, merging these outmost branches first (using the Destexhe scheme), developing and calculating the quality of the emergent mosaic and then continuing this process by applying the Destexhe reduction scheme to merge the resulting branches together until one is left with an unbranched structure. During this process, both the spatial patterning and the quality of the mosaic was drastically altered, highlighting a counter intuitive relationship with morphology and the learning process that requires further investigation.

４． Conclusion

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 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 that aspects of morphology or some underlying structural parameter may play a hidden role that underlies the final pattern of the mosaic. The most recent 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 am still 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. In parallel to this I am also developing a mathematical framework of how learning leads to the emergence of orientation and direction selective cells. This theoretical work is still ongoing.

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), 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. **In progress.**
- 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 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.**

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

There have been many controlled simulations performed investigating how the dendritic mosaic changes, while performing systematic step-by-step changes to an initial idealized morphology, based upon a published method of reducing the complexity of neuronal morphology (Destexhe's method) without altering the electrical properties of the neuron. I have also been building and debugging new simulations. For this reason, fewer CPU hours were used.