

Project Title:

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

Name: Dr. Nicolangelo Iannella, Dr. Thomas Launey

Laboratory at RIKEN: Launey Research Unit for Molecular Neurocybernetics

Project Background and Purpose

Neuroscientists are trying to understand how visual experience and neuronal activity are influenced by developmental processes, refinement and maintenance of neuronal circuits via cellular and molecular processes. Theoretical studies have typically investigated questions concerning single cell responses and cellular network dynamics using simplified descriptions of neurons which ignore the spatial morphology of the neuron and to minimize computational expense. Such descriptions are called **point neurons or single compartment models** and 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). In order to fully describe the spatial nature and dynamical properties of brain cells, however, mathematical descriptions that ignore spatial extent are **not sufficient** to describe their complex dynamics, which can only be fully captured using a system of Partial Differential Equations (PDEs). As observed in many experiments, real neurons are objects not shaped like balls, but have an intricate spatial morphology. Neuron, as observed under the microscope, are comprised of a soma, a large branching axonal and dendritic trees. Both the axon and dendrite possess complex spatial geometry. Admittedly, the spatial complexity of the neuron's morphology and the spatial pattern of synaptic connectivity converging onto both the soma and dendrite introduce a new intricacy in understanding how brain circuits are formed, refined and maintained. Understanding how and where

axons from one cell make synaptic connections onto the dendrites of other neurons where the strength and spatial location are altered over time by specific activity-dependent cellular and molecular processes is still not known. The underlying rules implemented by such processes that are responsible for changes in brain circuitry, known as *synaptic plasticity*, are poorly understood. Elucidating these rules governing the changes in both strength and location of an axon forming a synapse (synaptic connection) **is a major challenge**. Notably both current and past experiments have shown that spike timing, membrane depolarization and calcium influx into the cytoplasm have important roles to play.

Previous experiments investigating the phenomenon of spike timing-dependent plasticity (STDP) typically present a plasticity rule characterized by a temporally asymmetric 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). The majority of 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 whether or not there is some structural correlate or specific spatial organization, such as clustering, underlying functional properties of neurons which emerged during STDP learning, thus providing testable predictions for future experimental studies.

Usage status 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 Crank-Nicholson 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. The NEURON simulation environment can simulate both networks and single neurons on either a single processor/core or in parallel (using MPI) over multiple processors. The current (version 7.3) and previous versions of the NEURON simulator are freely available and can be downloaded from

<http://www.neuron.yale.edu>.

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 phenomena 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 been 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.

We have been investigating 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 should be near zero. For a pair based STDP rule, this ratio is A_{τ_-}/A_{τ_+} and it needs to be greater than 1 for stable learning to take place. We have also found that the mean input frequencies of synaptic inputs and the degree of STDP balance jointly influences the emergence of the dendritic mosaic. We are currently collecting spike train data to illustrate how changing the degree of balance in the rule impacts the average firing rate of the cell. Once this data is collected and processed, these results will be included into our manuscript and promptly submitted.

. Conclusion

To date, the results achieved so far have indicated that STDP learning in spatially extended dendrites supports the emergence of clustered spatial organization of functional inputs. The emergence of spatially segregated clusters and the overall patterning of the dendritic mosaic jointly depends on the degree of competition, the mean input frequency and the degree of intrinsic balance introduced by the STDP rule. The latest results indicates that there is a complex multi-dimensional parameter space where a small distinct region of this space supports the formation of spatially segregated clusters across dendrites.

Future Prospects & Schedule

Our paper discussing the issue of STDP balance in spatially extended dendrites is almost published as we in the process of finishing the review process, we

expect this to be published soon. We are also rewriting our symmetry breaking paper and will submit this in the next few months as well. To date all simulations for the symmetry breaking paper have been completed.

In future, I will plan to further develop parallel network simulations and eventually apply the model to three different cortical areas (Cerebellum, Rat barrel cortex and the Early visual cortex of the cat) using NEURON. This stage initially involves refining our current parallel network model, based upon embedding a single biophysically detailed cell into a large scale network of single compartment spiking neurons. The network model will, at first, represent a generic yet nonspecific region of the brain. It is envisaged that it will be extended by replacing the single compartment neurons of the network with multi-compartmental based neurons and later 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 this proceeds smoothly, then we plan to make specialized models of the cat. primary visual cortex. Such models are expected to provide insights 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.
- **Completed.**
- Build a simple parallel network and test NEURON's check-pointing capabilities for parallel network simulations. **Almost finished**
- Investigate ways to carry out better load balance by adopting strategies which utilize splitting the more complex cell over different cpus. **On going still struggling with this**
- Build a prototype network consisting of a reconstructed neuron embedded into a large scale network of single compartment models of spiking neurons and fine tune so that it

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reproduces important network dynamics such as orientation and direction selectivity, ocular dominance and oscillations. **In progress.**

- Based upon this prototype network, refine and extend this network to specialized models that represent some specific cortical area such as the early visual system of the cat. **Not yet started.**
- Use the networks to find whether there is some emergent structural correlate (a specific spatial pattern of organization) of synaptic efficacies underlying the development of functional properties, such as orientation and direction selectivity. **Not yet started.**
- For the model of the early visual system of the cat try to find the dendritic origin/causes 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. **On going – Now developing an innovative synapse model to do this based upon cable theory. Draft paper written.**

I have a GENERAL USER account and I wish to continue using the system for the fiscal year 2015, so that I plan to complete the papers. However I plan downgrade to Quick User status for the purposes of testing and debugging code. For this phase, I will not be able to use the minimum 1% of computing resources (800,000 cpu hours - even if I tried). over the fiscal year regardless of being a General or Quick user. If I can keep my status as a General user, then I would be grateful if not then Quick User is fine with me.

Unfortunately I was not able to use the allocated time for several reasons beyond my control. Firstly, I have finished all necessary simulations and have been busy writing and revising papers directly related to the use of RICC (this is still ongoing – one

paper has almost passed the review. Secondly, demand for cpu time was difficult especially in the lead up in the final 6 months of using the RICC system.