Project Title:

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

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One of the hottest topics in the Neurosciences is to understand how experience infleunces the development, refinement and maintenance of neuronal circuits via cellular and molecular processes, in an activity-dependent manner. To minimize computational expense, 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. Such models are called **point neurons**, which assume that the known morphology of brain cells is not important and is thus adequately described mathematically by a system of Ordinary Differential Equations (ODEs). In order to fully describe the spatial nature and dynamical properties of brain cells, however, mathematical descriptions based upon ODEs are **not sufficient** to describe the complex dynamics introduced by a brain cells' spatial extent and can only fully captured using a system of Partial Differential Equation (PDE). As observed in many experiments, real neurons are objects not devoid of spatial structure, being comprised of a soma, a large branching axonal tree and dendrite, where both the axon and soma possess complex spatial geometry. Spatial extent has been largely ignored in the vast majority of theoretical studies for reasons of computational tractability. 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. Specifically, these circuits are composed of cells, whose axon typically makes 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. The underlying rules implemented by such processes which are responsible for the induction of changes in brain circuitry, known as *synaptic plasticity*, are poorly understood. Elucidating the "rules" of synaptic plasticity, which drive changes to brain circuitry, through alterations in both strength and location of an axon forming a synapse (synaptic connection) **is a challenge**; however both current and past experiments have shown that spike timing and calcium have important roles to play.

Previous experiments investigating the phenomenon of spike timing-dependent plasticity (STDP) have shown a plasticity rule characterized by a temporally asymmetric learning window, where the temporal order of pre- and postsynaptic firing is an important factor dictating whether a synapse is potentiated or depressed. Specifically, when pre-synaptic spike input to the synapse precedes post-synaptic firing, then the efficacy of the synapse is strengthened but for the opposite temporal relationship (post-synaptic firing before pre-synaptic input) then the synapse's strength is reduced. The majority of theoretical studies have used integrate-and-fire neuron model (the simplest type of point model) 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 purpose of this research is to understand 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 several processors. The current (version 7.1) and previous versions of the NEURON simulator are freely available and can be downloaded from http://www.neuron.yale.edu.

During the past fiscal year, I have conducted many simulations which I will summarize in the following section. The impressive aspect of the new system with regards to my own simulations is the increase in speed. Originally, using RSCC, heavy simulations took three days to finish, now with the new system the same computations take nine hours to complete; an 800% increase in speed. So during the last year, I have used about 42% of cpu time on RICC.

Results

A small scale network was constructed, consisting of several equally sized groups of correlated afferent fibers, with no correlation between the groups. These groups form synaptic connections over the dendrite of a reconstructed layer 2/3 pyramidal cell. This model was be used to study the evolution and final spatial arrangements of synaptic strength over the dendrite, especially the role of STDP in a well investigated phenomena called ocular dominance formation. In the cortex, Ocular dominance formation is an activity-dependent process where pyramidal cells in the visual cortex learn to respond vigorously to stimulation from a single eye, but weakly to the other.

A new biophysical neuron model was previously developed which quantitatively reproduces several important experimental observations seen in layer 2/3 pyramidal cells.

This model was used to investigate how activity and the degree of competition between synapses, leads to spatially segregated efficacy clusters, when stimulated by four or more equally sized groups. I 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).

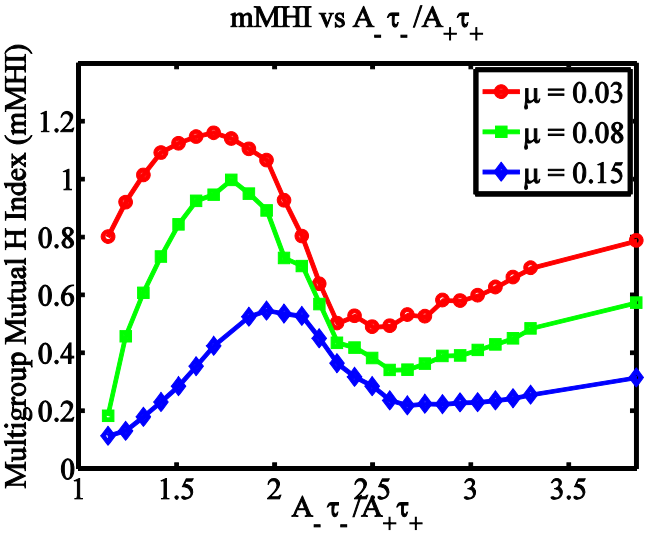

Figure 1: Systematically altering the degree of balance in the STDP initially favors the emergence of the dendritic mosaic but beyond a critical point the M-index collapses indicating that the quality of the mosaic is drastically reduced. This is illustrated for three different values mu=0.03, 0.08, and 0.15.

Furthermore, we have identified that in the case where four or more groups of afferents provide the stimulation to the cell that a **dendritic mosaic** emerges but depends on the degree of competition introduced by the nonlinear STDP rule and the frequency of inputs to the biophysical model neuron (see publication for further details).

Finally, we have investigated how modulating 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 $A_-\tau_-/A_+\tau_+$ and it needs to be greater than 1 for stable learning to take place. As an example, Figure 1 shows how changing the degree of balance in the learning rule leads to quantitative changes in the degree of spatial segregation and the quality of the dendritic mosaic as illustrated through the multigroup mutual information index given by

$$M = \sum_j \frac{W_{\bullet j}}{W_{tot}} \sum_m \pi_{jm} \ln\left(\frac{\pi_{jm}}{\pi_m}\right)$$

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, as seen in Figure 2.

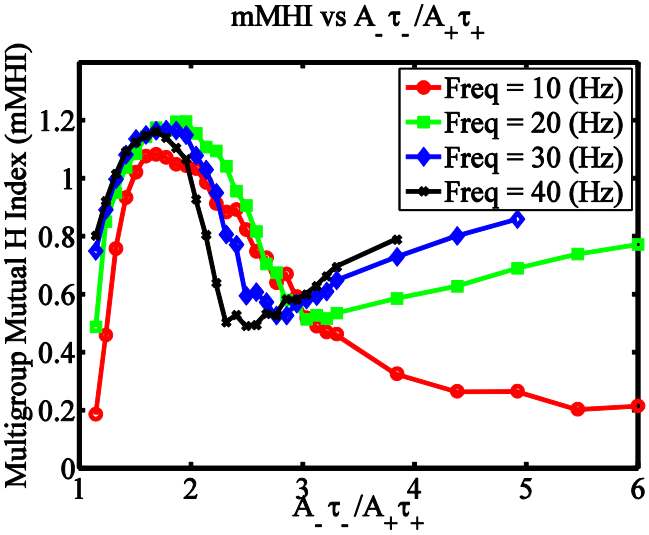

Figure 2: Both mean input frequency and the degree of STDP balance are important parameters dictating the quality of the mosaic. Note that the maximal M-index occurs at nearly the same value of balance for the mean input frequencies of 10, 20, 30, and 40 Hz, respectively.

Conclusion

To date, the new 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 instrinic 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

We are currently preparing a paper discussing the issue of STDP balance which includes the results presented in this report. Another paper about symmetry breaking is simultaneously being prepared for submission in the next few months as well. Most of the simulations for the symmetry breaking paper and the paper about balance have been completed. More data for another article investigating the fine scale structure will be collected during this year.

More importantly, I plan to set up 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 building a 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 in developing known properties of cortical networks. If all this proceeds smoothly, then we plan to make specialized models of different cortical regions e.g. frontal and visual cortex. Such models are expected to provide insights how functional properties emerge and more importantly, whether there is an underlying structural correlate. This stage of the project will depend on whether a parallel version of NEURON can be compiled and successfully run on the cluster. I expect with the current version of NEURON (version 7.1), which has improved parallel computation capabilities over previous versions; few problems are expected to be encountered. 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**
- 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 reproduces important network dynamics such as oscillations. **Almost completed.**
- Based upon this prototype network, refine and extend this network to specialized models that represent some specific cortical area such as the Cerebellum, Barrel cortex of the rat, and the early visual system of the cat.
- 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.
- For the model of the early visual system of the cat try to find the dendritic origin/causes of cellular functional properties.
- 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. **A theoretical model, based upon the work by Pinsky and Rinzel has been formulated but still needs to be thoroughly tested to see whether this model is a good representation of such morphologically complex cells.**

- Replace the single compartment models of spiking neurons, which make up the bulk of the network, with multi-compartmental based models and assess the impact of these alterations to the network.
- Incorporate several morphologically detailed neurons into the network and assess both the emergence of structural correlates within the network and between these morphologically detailed cells.

I have a GENERAL USER account and I wish to continue using the system in fiscal year 2011, so that I can attempt to complete most of the above mentioned parallel network computations. I also wish (if possible) to simply carry over the remaining that I have if not then 1% minimum for general users will be more than substantial. In the past months, I have run many simulations on the RICC, but also I have been writing a paper with the results presented in this report. To date I have consumed about 42% of my allocated cpu hours. There are several reasons for this. Firstly, I been writing several research lengthy grants and secondly I have been writing/editing and analyzing data for the two papers mentioned in this report. Once these are submitted and I have finished testing the parallel network, parameter searches using this new model should consume more cpu hours. The plan for parameter searches using the parallel network is to run 10 simultaneous trials where each trial uses 50 cpus for a three days (if possible).

I hope by the end of this financial year, I expect to have used most of my allocated cpu hours. The next sets of simulations will mainly focusing on development and parameter searches, using parallel network simulations of Cerebellum and the early visual cortex of the cat. Also during this year we aim to extensively investigate the fine scale structure of spatially segregated clusters. These simulations will also be intense requiring 5 times the spatial resolution of current simulations and the use of check pointing where a single simulation trial will need to be run over several 3 day blocks and for extended simulation times.

Fiscal Year 2010 List of Publications Resulting from the Use of RICC

[Publication]

N. Iannella, T. Launey, S. Tanaka, Spike timing-dependent plasticity as the origin of the formation of clustered synaptic efficacy engrams, Frontiers in Computational Neuroscience, 403:24-29 (2010).

Supplementary information for above paper attached

[Proceedings, etc.]

[Oral presentation at an international symposium]

[Others]

Poster

The 4th Australian workshop on mathematical and computational neuroscience, Brisbane, Australia (NeuroEng2010, Nov 20-22)

N. Iannella, T. Launey, Modulating the balance in STDP learning impacts dendritic mosaic.