Project Title:

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

Name:
Dr. Nicolangelo Iannella
Dr. Thomas Launey

Affiliation:
Launey Research Unit, Neural Circuit Function Research Core,
Brain Science Institute, Wako Institute

Background and Purpose of the Project

A current hot topic in the Neurosciences is to understand how experience regulates the development, refinement and maintenance of neuronal circuits, through activity-dependent cellular and molecular processes. To minimize computational expense, theoretical studies have typically investigated questions concerning single cell responses and cellular network dynamics using simplified descriptions of neurons. The most extensively used description used by computational neuroscientists is the **point neuron model** paradigm. These are models which assume that the known spatial extent or 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 the latter two possess complex spatial geometry. Spatial extent has been largely ignored in the vast majority of theoretical studies. 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 has an important role 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.

Since the official start of operation of the new RICC system (from October 1), 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 200,000 cpu hours from the old system but only 43367.2 cpu hours on RICC.

Results

A small scale network was constructed, consisting of several (two or more) equally sized groups of correlated afferent fibers, with no inter-group correlation forming 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 known phenomena, such as 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.

In order to improve upon our previous reported model, a new neuron model was developed which quantitatively reproduces several important experimental observations seen in layer 2/3 pyramidal cells.

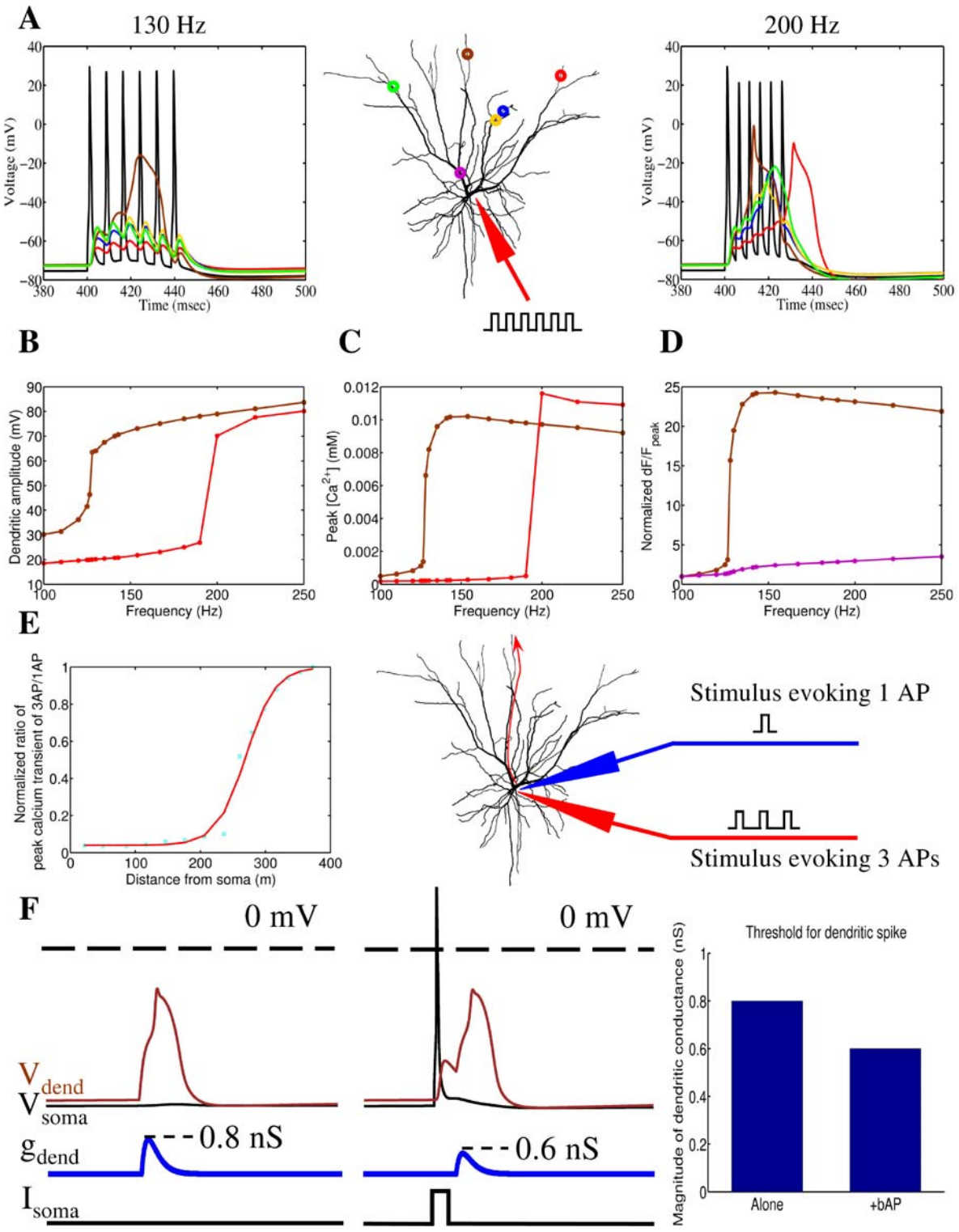

Figure 1: The new model reproduces several experimental observations including frequency-dependent generation of dendritic spikes, a nonlinear distance-dependent increase of peak calcium transients, and a 25% reduction in the threshold for dendritic spike generation when dendritic input is paired with a somatic spike.

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).

Recently, we found a very interesting phenomenon when the neuron model is stimulated with four or more groups; after STDP learning a unique spatial organization emerges via STDP. The resulting imprint, shown in Figure 2, effectively forms a tessellated pattern of synaptic strength across the dendrite, which we call a **dendritic mosaic**.

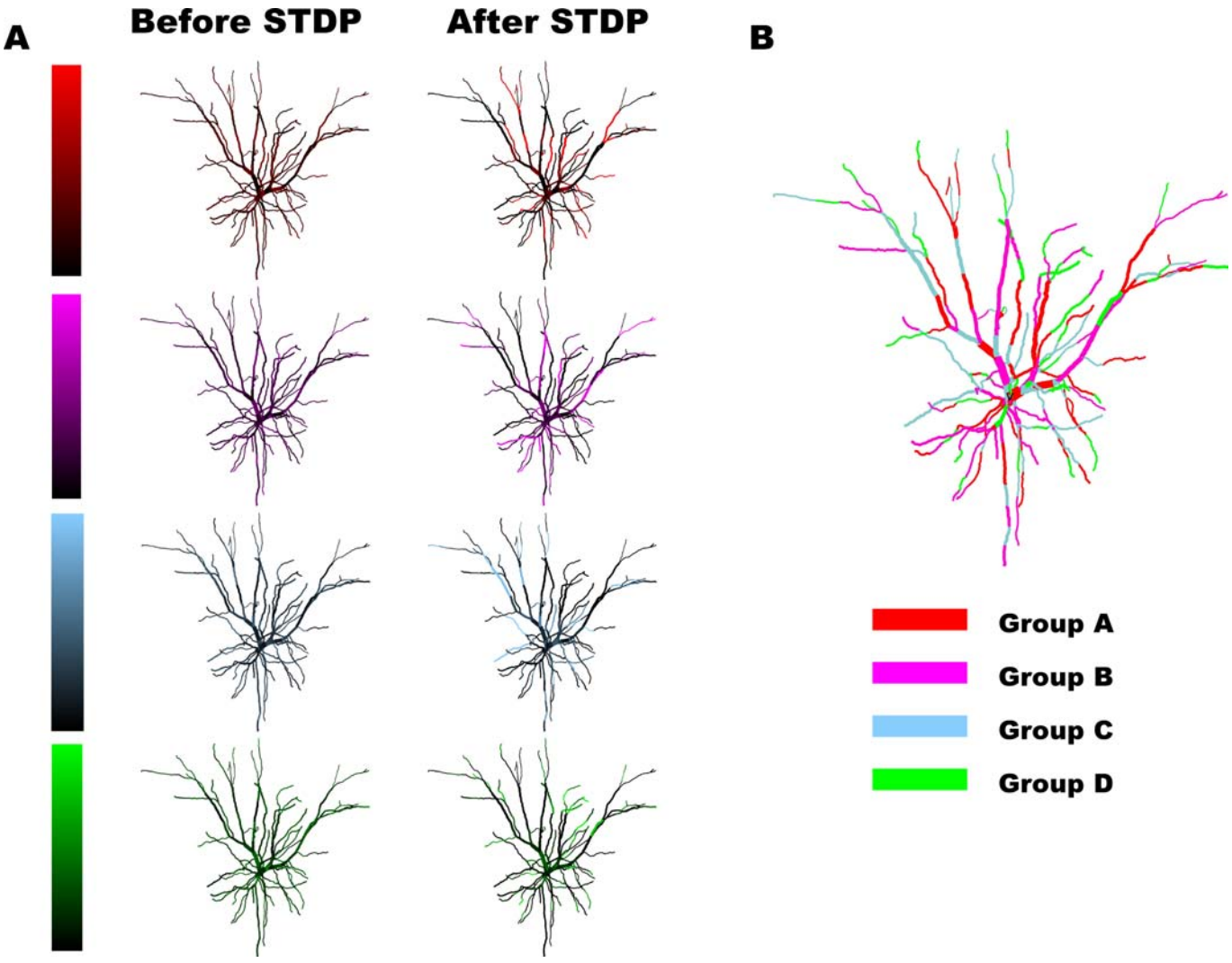

Figure 2: The organization of synaptic weights before and after STDP using four competing groups of afferents. Note that a dendritic mosaic emerges, where the winning group is color coded at each dendritic position

Furthermore, we have found that the emergence of such a dendritic mosaic depends on the degree of competition introduced by the nonlinear STDP rule, as shown in Figure 3A. The frequency of input spikes is another important parameter which influences the emergence of the dendritic mosaic is depicted in Figure 3B.

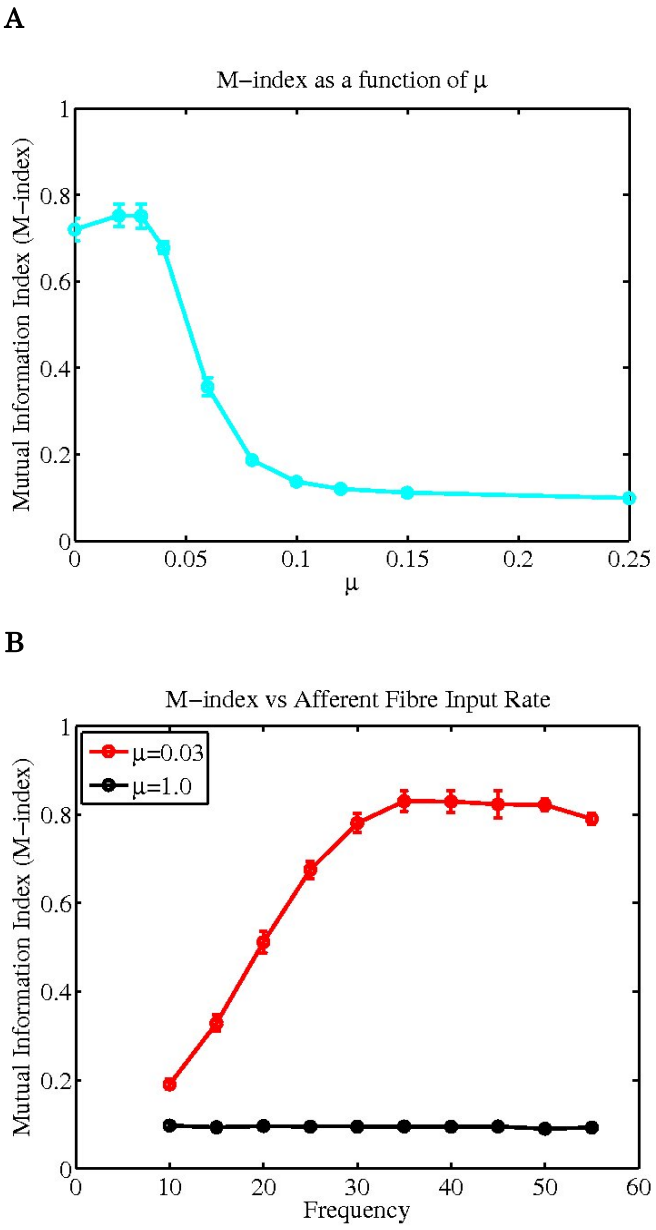

Figure 3 A), Plot of the M-index versus μ a parameter which controls the degree of competition introduced by the nonlinear STDP. B) The corresponding changes to the M-index as a function of changing input frequency.

Finally, we have recent preliminary data investigating how robust is the emergence of such a dendritic mosaic when the number of groups is increased from 2 groups to 20 groups. Our preliminary data seems to suggest that functional clustering between neighboring synapses persists despite increasing the number of different groups stimulating the cell.

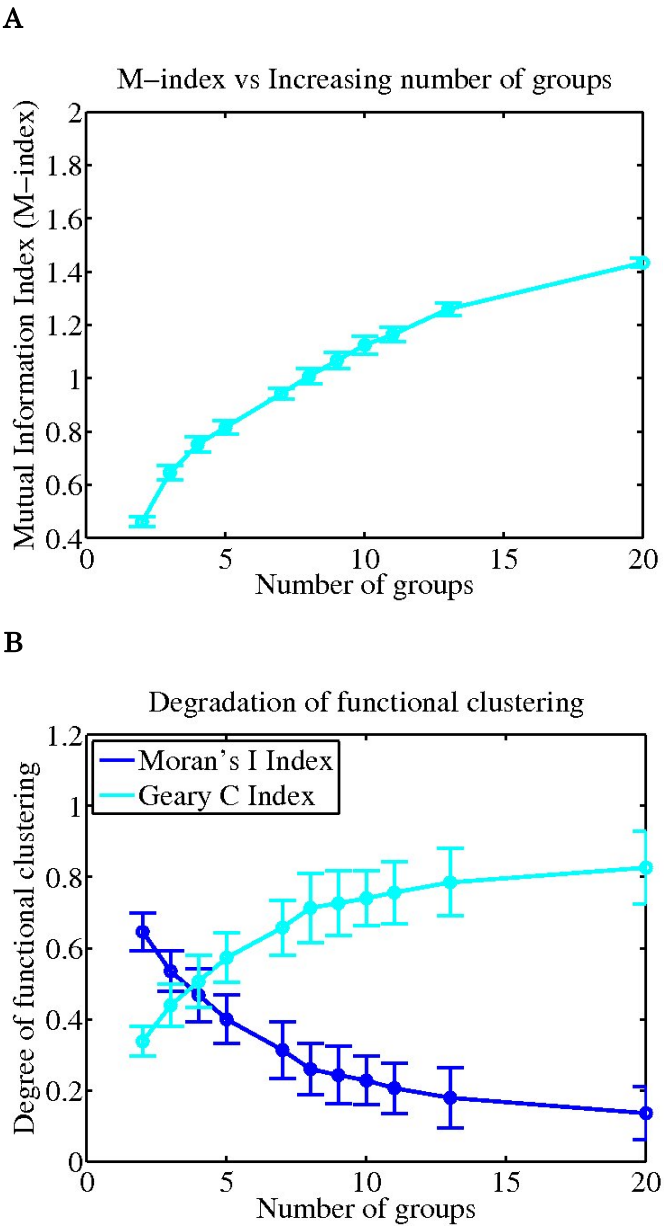

Figure 4: A) The M-index grows as the number of afferent groups providing stimulation increases. B) Depicts both Moran's I index and the Geary C index, where both are respectively global and local statistical measures of functional association between neighboring synapses, and thus indicating the existence of functional clustering.

Conclusion

To date, the data results achieved so far have indicated that STDP learning in spatially extended dendrites supports the emergence of clustered spatial organization of functional inputs and are robust to various perturbations introduced by altering the degree of synaptic competition, the

nature of the input characteristics, and number of groups providing stimulation to the cell. We showed that a mosaic pattern of synaptic strength emerges when stimulation was provided by four groups, and furthermore, show results indicating that the neighboring synapses remain functionally associated even when the number of groups is increased.

Future Prospects & Schedule

A preprint about these current results has already been prepared and will be submitted shortly. Three more papers are being prepared for submission (hopefully this year). The first one is about the balance of STDP learning, the second is the study on symmetry breaking and the final one is about the fine scale spatial structure of efficacy clusters. Most of the simulations for the symmetry breaking paper and the paper about balance have been completed. More data for the last paper will have to be collected.

Furthermore, I plan to set up parallel network simulations using NEURON. This stage involves building a network model, initially 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 on the RSCC and compare to a set of known simulations. **To be attempted in the coming months.**
- Build a simple parallel network and test NEURON's check pointing capabilities for parallel network simulations.
- 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.
- Based upon the prototype network, build specialized networks that represent some specific cortical area. One instance is a prefrontal cortex and the other is the early information processing pathway of the primary visual system.
- 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.
- 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 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 2010, so that I can attempt to complete the above mentioned parallel network computations. I also wish to simply carry over the remaining that I have. 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. Ever since RICC started full operation, I have just been able to use 5.4% of my allocated cpu hours. There are several reasons for the low usage. Firstly, the was a good 6-8 week period just after operations started where it was almost impossible to use the cluster since it was crashing almost three time a week. Secondly, I have been writing/editing the above mentioned paper for several months, and additionally, I have been analyzing other data for subsequent articles. By the end of September 2010, I expect to have used most of my allocated cpu hours. The next set of simulations focusing on the fine spatial scale structure of efficacy clusters will be intensive since we are required to simulate the model neuron with nearly 5 times the spatial resolution of the current model and use check pointing simply to complete single trial runs. I expect that approximately 25% of my currently allocated cpu hours will be used. I plan to have the bulk of these simulations done by the end of April if not sooner. The remaining ~70% will be used for parallel network simulations where I suspect these simulations will use at least 50 or more cores concurrently.

Fiscal Year 2009 List of Publications Resulting from the Use of RICC

[Publication]

Spike timing-dependent plasticity as the origin of the formation of clustered synaptic efficacy engrams (submitted, under review)

[Oral presentation at an international symposium]

Invited talk at the Okinawa Institute for Science and Technology (OIST)
Title: **Spike timing-dependent plasticity in spatial model neurons.**

Abstract

Cortical circuits and their constituent neurons are able to simultaneously adapt and refine their input/output characteristics and information processing capabilities. One specific issue is how synaptic plasticity affects the strength and functional organization of such inputs within the dendrite is not known. This ultimately relies on understanding how the interplay between synaptic plasticity, synapse location, and the non-linear properties of the dendrite shapes both the strengths and spatial arrangements of convergent afferent inputs to neuronal dendrites. Recent experimental and theoretical studies support a clustered plasticity model, a view that synaptic plasticity promotes the formation of clusters or hotspots of functional synapses.

Here, we propose that Spike timing-dependent plasticity (STDP) may have an important role to play, where changes to synaptic efficacy are driven by timing differences between pre-synaptic inputs and the generation of local dendritic spikes. To this end, a network was constructed, where a compartmental model of a reconstructed Layer 2/3 pyramidal cell received correlated synaptic inputs from two independent yet equally sized groups of afferent fibers, mimicking the spike activity originating from two different neuronal populations. Through computer simulations, we show that STDP induces symmetry breaking, resulting in a clustered yet spatially segregated organization in the strength of synaptic inputs across the dendrite, reflecting the nature of such correlated activity. Significantly, this resulting organization resembles an interdigitated series of clusters, a spatial arrangement observed ensuing ocular dominance formation, consistent with our previous study. We found that synaptic competition, within-group correlation strength and the rate of pre-synaptic input are important parameters which influence symmetry breaking. Furthermore, we illustrate that a homogeneous synaptic state is restored simply by increasing the within-group correlation strength, leading to drastic degradation of both clustering and spatial complementarity. Our model indicates that STDP may be an important mechanism shaping the spatial organization of synapses across the dendrite and additionally suggests that the outcome of synaptic plasticity may favor the formation of clustered synaptic efficacy engrams.