Project Title:

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

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Neuroscientists are racing to understand how experience influences 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** and assume that a brain cells' spatial morphology is does not affect electrical conduction and thus it is not important. Point models are those in which the membrane potential for the cell can be 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 which 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 devoid of spatial structure, being comprised of a soma, a large branching axonal tree and dendrite, where both the axon and dendrite 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. Understanding the origins of the **connectome**, and specifically, how axons from one cell 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 is still not known. 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 these rules underlying alterations in both strength and location of an axon forming a synapse (synaptic connection) **is the grand challenge**. Notably both current and past experiments have shown that spike timing and calcium influx into the cytoplasm 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 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. 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 7.1) and previous versions of the NEURON simulator are freely available and can be downloaded from http://www.neuron.yale.edu.

Results

A small scale 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 introduced by the nonlinear STDP rule and the frequency of inputs to the biophysical model neuron.

Finally, we have show that 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. 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 1

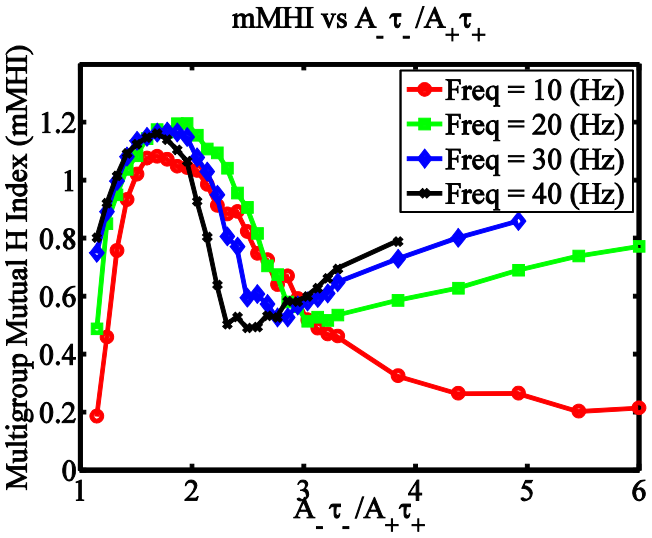

Figure 1: Both mean input frequency and the degree of STDP balance are important parameters dictating the quality of the dendritic mosaic. Note that the maximal mMHI value occurs at nearly the same value of balance for the mean input frequencies of 10, 20, 30, and 40 Hz, respectively.

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During the last financial year we have been making some headway in developing parallel NEURON simulation whereby a morphologically detailed cell is embedded into a network of simpler neurons. Here we have identified some issues which can cause the simulation to crash completely, especially the case of load balancing, which can have a profound effect on simulations. We are currently trying to develop sensible loading strategies by equally dividing neurons and communications loads between available computational nodes.

. 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 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 in spatially extended dendrites and 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 importantly, 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 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. 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**
- 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.**
- 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**
- 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 looking at a new innovative method to do this based upon cable theory.**
- 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. **Not yet started**

I have a GENERAL USER account and I wish to continue using the system in fiscal year 2012, 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 time** that I have if not then 1% minimum for general users will be more than substantial. Last year (2011) I have tried to finish all program development, however this was not possible. Unfortunately the M9 earthquake and the following Fukushima nuclear meltdown has delayed a lot of previous projected work. After these natural disasters the entire RICC system unstable due to the lack of supply as reflected in the number of emails which stated that the entire system had crashed. It wasn't until later July early September that I felt confident that the system was stable, but at this I had to start lecturing which severely limited my time. To date, I have used little cpu resources as I am still in the program development stage.

Fiscal Year 2011 List of Publications Resulting from the Use of RICC

[Publication]

None due to earthquake & Fukushima

[Proceedings, etc.]

[Oral presentation at an international symposium]

[Others]