Modulators of Spike Timing-Dependent Plasticity

Francisco Madamba
Department of Biology
University of California, San Diego
La Jolla, California
fmadamba@ucsd.edu

Abstract

Spike Timing-Dependent Plasticity (STDP) is a Hebbian form of learning that captures the temporal relationship between pre- and postsynaptic spikes. Recent studies have uncovered that the relative concentration of neuromodulators, in addition to the timing of pre- and postsynaptic spikes, can affect the polarity of STDP. In this paper we sought to modify existing STDP rule implementing neural networks to account for experimental findings and observe the corresponding changes in the synaptic weights. Initial conclusions support the notion that minimal changes in A_P or A_D have little effect on rate of synaptic changes however further work must be done to verify or refute these findings.

1 Introduction

Long-term potentiation (LTP) and long-term depression (LTD) are well known mechanisms for cortical synaptic plasticity. Traditionally, the given outcome, LTP or LTD, was determined by varying the presynaptic firing rate or the postsynaptic membrane potential during conditioning. With the discovery that when a presynaptic spike precedes a post synaptic spike by several seconds LTP results and when a postsyanptic spike precedes a postsynaptic spike by several seconds LTD results, the temporal relationship between the presynaptic and postsynaptic spike became an important factor in the study of synaptic plasticity.

The discovery of spike timing-dependent plasticity [1] [2] has led to many developments in the study of neural networks. It was found that oscillations greatly facilitate STDP's ability to detect repeating patterns. Specifically, Masquelier et al.[3] were able to demonstrate, in simulations, how a single neuron equipped with STDP robustly detects a pattern of input currents automatically encoded in the phases of a subset of its afferents, and repeating at random intervals. In addition it was demonstrated that a model network of cortical spiking neurons modulated with the neuromodulator dopamine (DA) could solve the distal reward problem [4].

Surprisingly, much of the recent progress of STDP involves implementing the STDP rule into neural networks, and not on the STDP rule. Only recently has significant progress been made to control the rules of STDP, specifically the given outcome and the time window for coincidence detection. A recent study found that the relative activation of neuromodulator receptors coupled to adenylyl cyclase (AC) and phospholipase C (PLC) signaling cascades can override the order of the timing of the pre- and postsynaptic spikes [5]. In addition, they found that these modulators could also increase the window of coincidence detection and effectively "prime" neuron synapses into plastic states.

The aim of this project was to attempt to modify existing STDP rule implementing neural networks to account for experimental findings on neuromodulators. Since the experimental findings were found in an in vitro system, and hence their release and uptake were tightly controlled, biologically relevant concentration and kinetics could not be obtained. As a result, the focus of this project was to model the possible changes that addition of particular neuromodulators can have on the system.

2 Methods

2.2 Leaky Integrate and Fire Neurons

In single neuron or simple neuronal networks, conductance-based models, such as the Hodgkin-Huxley (1952) and Morris-Lecar (1981) models, can be useful because such models contains variables and parameters that have well-defined biophysical meanings that can be measured experimentally [6]. However when neuronal network contain many constituents, the number of connections and the vast amount of differential equations that must be solved can become computationally taxing. Furthermore, such models, which contain detailed accounts of axon potential generation and conductance, often obtain parameters from many neurons which are averaged to produce a value.

For our present purposes, it is thus convenient to use a simple model which faithfully reproduces the most important neurcomputational features of the neuron (voltage threshold, reset, membrane potential) and omit some of the more taxing features (detailed action potential generation and propagation).

Leaky Integrate-and-fire neurons (LIF neuron) are the simplest possible neural model. In this model, complicated conductances responsible for action potential generation have been omitted and instead the spiking mechanism is replaced by a potential threshold, v_{thres} [7]. When $v(t_1) = v_{thres}$ has been reached, a spike it emitted at t_1 and the potential is reset to zero. In this model, the membrane potential follows the differential equation:

$$C\frac{dv}{dt} = -\frac{v}{R} + I, t > 0$$

where $I = I(t)$ is a stimulation current and $v(0) = 0$ is an initial condition. Without input current and at steady state, the membrane potential is equal to the resting membrane potential value of the model, which in this case is zero. If an input current is present, the synaptic inputs to a LIF neuron can be simulated as a conductance change:

$$I_{syn}(t) = \sum_{n=1}^{n_{ex}} g_{ex}(t, t_{ex,n})(v - v_{ex}) + \sum_{n=1}^{n_{in}} g_{in}(t - t_{in,n})(v - v_{in})$$

Due to their relative simplicity, LIF neurons can be easily expanded to LIF networks. LIF neurons in networks operate according to a specific order: (1) check for an input spike at the current time, *t*, and for networks spikes from previous time, *t-dt*; (2) update conductances based on the input spikes and network spikes recorded in (1); (3) update potentials, recorded spikes, and return to (1).

Finally, LIF networks can be modeled with the STDP rule resulting in plastic network. The network equations for the weight increases and decreases are presented below which occur when the LIF network order (see above) reports that cell *k* fires in the interval [*j*dt, (*j*+1)dt). In order to limit the maximum weight gain, the potentiation of the presynaptic weight is hard bounded by $(W_{max} - W_{k,k_{pre}}^{j})$ and the depression of the postsynaptic weights

is hard bounded by $W^{j}_{k_{post},k}$.

$$W^{j+1}_{k,k_{pre}} = W^{j}_{k,k_{pre}} + A_P exp\left(\frac{T_{k_{pre}} - (j+1)dt}{\tau_P}\right)(W_{max} - W^{j}_{k,k_{pre}})$$

$$W^{j+1}_{k_{post},k} = W^{j}_{k_{post},k} + A_D exp\left(\frac{T_{k_{post}} - (j+1)dt}{\tau_D}\right)W^{j}_{k_{post},k}$$

2.2 Neuromodulator sources and kinetics

In their paper, Seol [5] identified isoproterenol (Iso) and 4-[N-(3-Chlorophenyl) carbamoyloxy]-2-butynyltrimethylammonium chloride (McN) as the neuromodulators that (McN) and that induced associative LTP or LTD respectively. Iso is an agonist of β-adrenergic receptors coupled to the AC cascade and Mcn is a muscarinic cholinergic receptor M1 agonist coupled to the PLC cascade.

In order to model their effects, the equations used by Izhikevich (2007) [4] to model the effects of dopamine were adapted to account for Iso:

$$\dot{P_{AC}} = -\frac{P_{AC}}{\tau_{P_{AC}}} + STDP(t_{post} - t_{pre})\delta(t - t_{\frac{pre}{post}})$$

$$\dot{S_P} = P_{AC}A_{Iso}$$

$$\dot{A_{Iso}} = \frac{B_{Iso}}{\tau_{Iso}} + ISO(t)$$

Where P_{AC} refers to the activation of an enzyme important for plasticity; A_{ISO} describes the extracellular concentration of Iso; $\delta(t - t_{\frac{pre}{post}})$ is the Dirac delta function that step-increases the variable P_{AC}; S_P is the potentiating contribution to the synaptic weight; τ_{ISO} refers to the time constant of Iso uptake or its diffusion away from the receptors; and ISO(t) models the source of Iso. Likewise, the equations for the effects of McN are below with parameters exactly as for Iso but adapted for McN.

$$\dot{D_{PLC}} = -\frac{D_{PLC}}{\tau_{D_{PLC}}} + STDP(t_{post} - t_{pre})\delta(t - t_{\frac{pre}{post}})$$

$$\dot{S_D} = D_{PLC}B_{McN}$$

$$\dot{B_{McN}} = \frac{B_{McN}}{\tau_{McN}} + McN(t)$$

2.2 Weight increase and decreases

The experiments described by Seol [5]were conducted in an in vitro system consisting of layer IV to layer II/III inputs in the rat visual cortex. Although they modulated STDP, Iso and McN represent foreign neuromodulators and hence the values for their concentration at the synapse, their uptake rates, and production rates have not yet been (or simply cannot be) obtained. The values for dopamine found in Izhikevich's paper could not be used due to fundamentally different situations.

In Izhikevich's paper [4], dopamine served as an extracellular reward used to identify the correct source of STDP and reinforce the correct pre- post synaptic connection.

In our present paper, neuromodulators directly increase or decrease the weights at the synapse and do not serve to pick out a particular synaptic connection. As a result, until biological relevant neuromodulators are identified in vivo, as well as their kinetics measured, we will proceed in our experiment to absorb the values of $\dot{S_P}$ into A_P and the values of $\dot{s_D}$ into A_D.

$$W_{k,k_{pre}}^{j+1} = W_{k,k_{pre}}^{j} + A_P exp\left(\frac{T_{k_{pre}} - (j+1)dt}{\tau_P}\right)(W_{max} - W_{k,k_{pre}}^{j})$$

$$W_{k_{post},k}^{j+1} = W_{k_{post},k}^{j} + A_D exp\left(\frac{T_{k_{post}} - (j+1)dt}{\tau_D}\right)W_{k_{post},k}^{j}$$

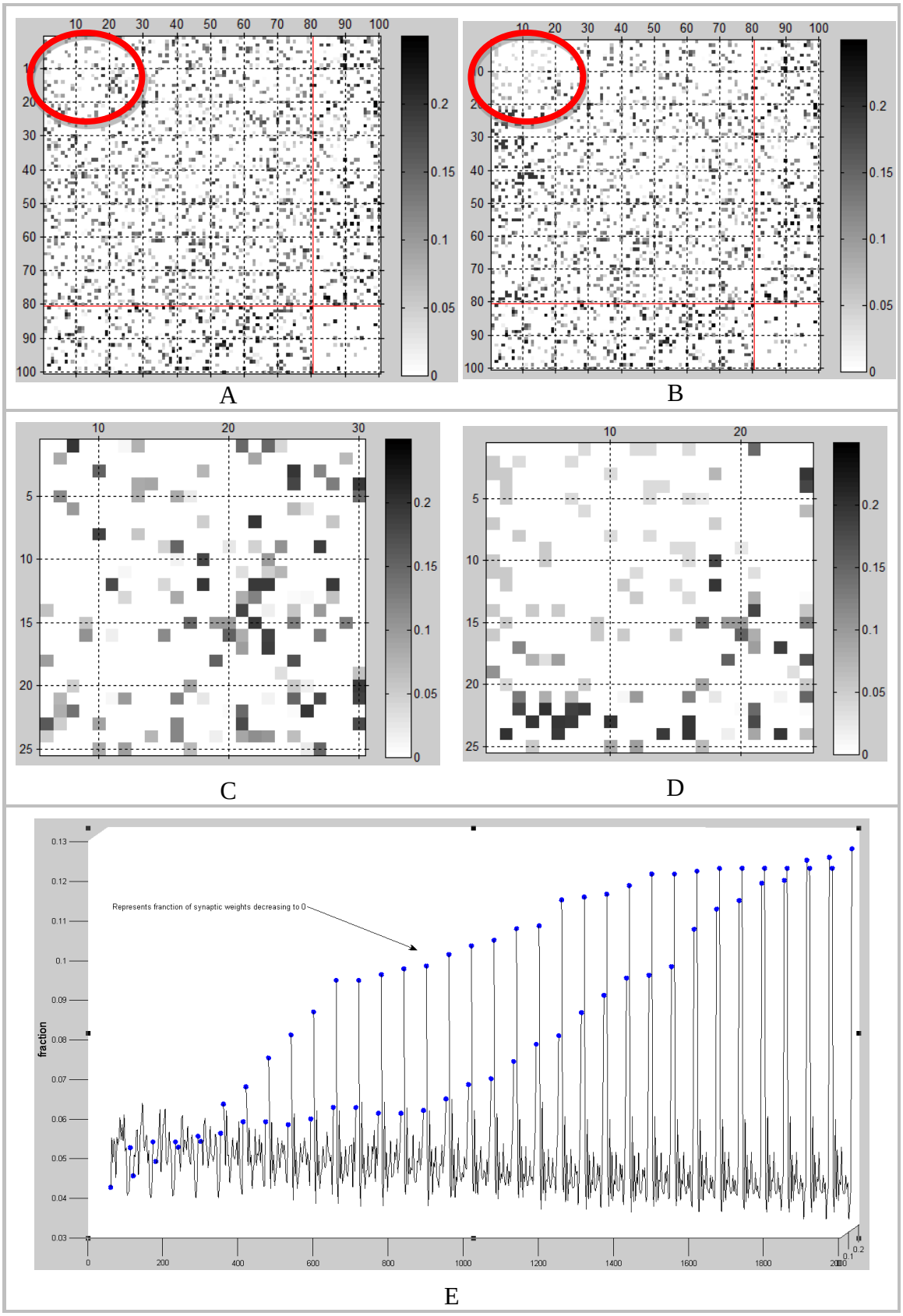
3 Results

3.1 Establishment of controls

A neural network (with the STDP rule) [8] of 100 neurons, 80 excitatory cells and 20 inhibitory cells, was used to establish a baseline value (the code is found in [8]). The matrix of weights between excitatory-excitatory, excitatory-inhibitory, and inhibitory-excitatory cells was set at 25% connectivity whereas the matrix of weights of inhibitory-inhibitory cells was set at 5%. A simultaneous input was delivered to the excitatory conductance's of the first 16 excitatory cells causing them to fire synchronously just before the simulation.

A simulation with $A_P = 0.1$, $A_D = 0.3$, with a time course of two seconds was run (Fig 1). A plot of synaptic weights at the beginning of the simulation (Fig 1A, 1C) and after (Fig 1B, 1D) clearly show that following the simulation, the synaptic weights of the first 16 excitatory neurons show decreased strength, evident in the brighter plots found in Fig 1B, 1D compared to Fig 1A, 1C. As the first 16 neurons were simultaneously driven by an input stimulus, the synaptic connections between neighboring neurons were expected to degrade over time as the external input would override the minimal contribution of the synaptic weights.

The STDP rule in the neural network also causes synaptic weights to either increase to a maximal value (in this case, 0.2) or decrease to zero over time (Fig 1E). The value of $A_D = 0.3$ is represented by the top blue dots; the value of $A_P = 0.1$ is represented by the bottom blue dots. The greater value for A_D compared to A_P results in synaptic weights decreasing much quicker to 0 then increasing to 0.2 Fig 1F illustrates the initial random distribution of possible synaptic weights before the simulation has begun (red trace) and after the simulation has completed (green trace); as time passes, the fraction of neurons at synaptic values of 0 or 0.2 increases.


A
B
C
D
E
Represents franction of synaptic weights decreasing to 0
fraction

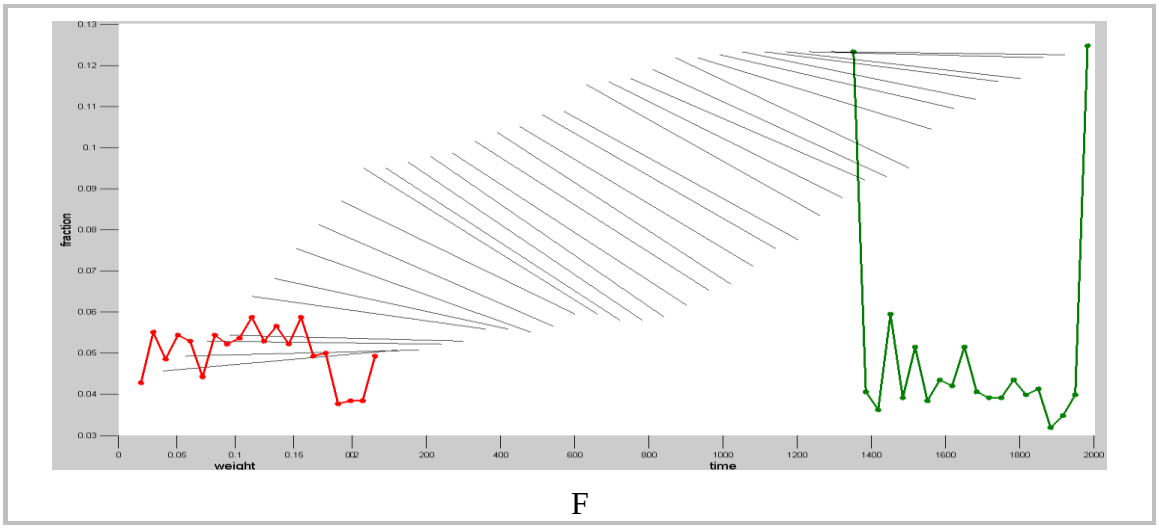
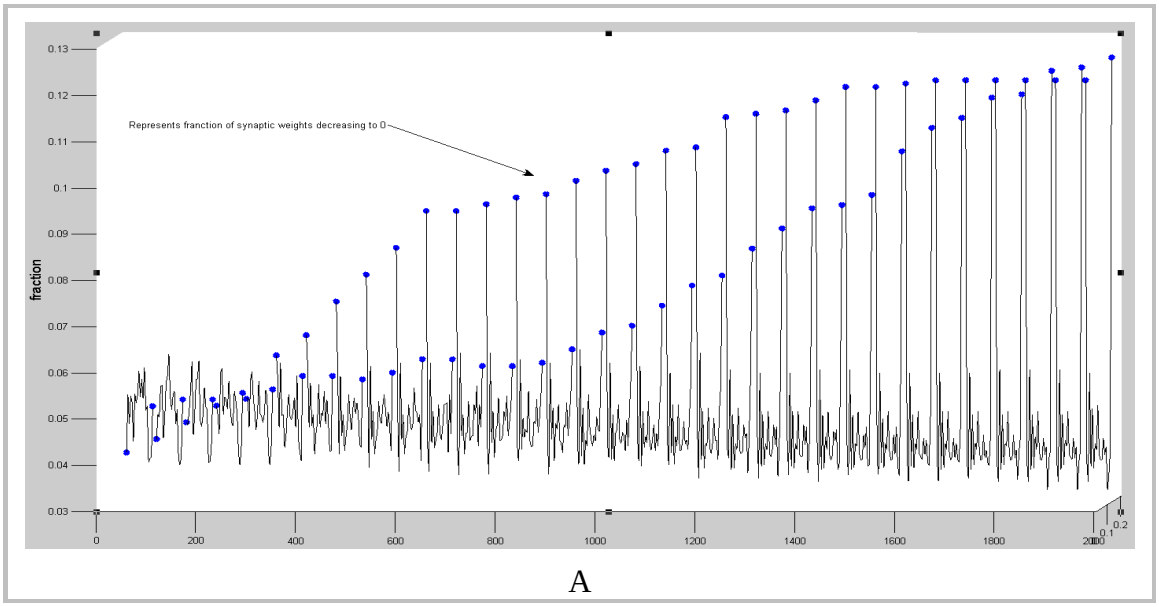
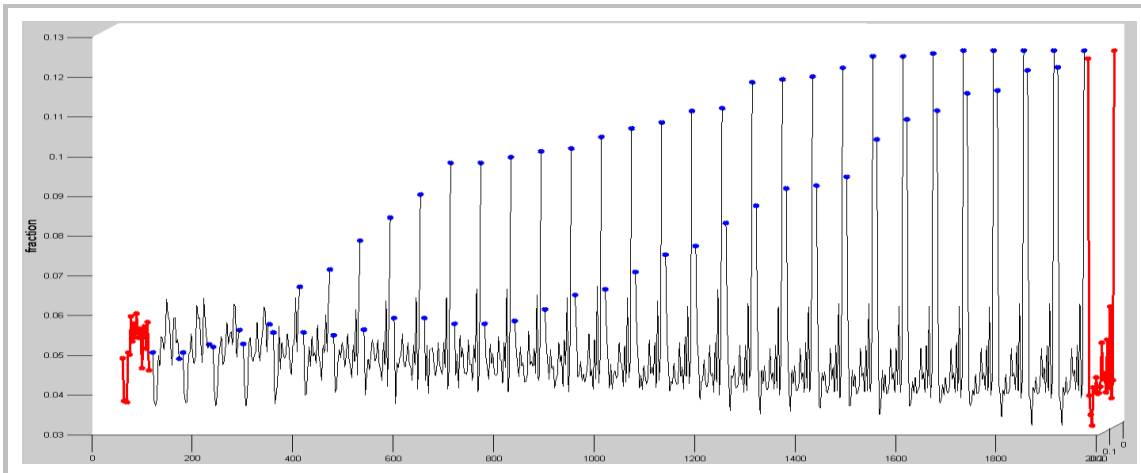


Figure 1: Baseline values. (A) A plot of synaptic weights before the simulation; A_P = 0.1, A_D = 0.3, total time = 2000msec; x and y axis denote neuron number; red lines differentiate the weight matrices; the red circle encloses the first 16 excitatory cells (B) A plot of synaptic weights after the simulation. (C) Blow up the 16 excitatory cells in (A) before the simulation. (D) Blow up of the 16 excitatory cells in (B) following the simulation. (E) Plot of the fraction of synaptic weights over time (in msec); top blue dots represents fraction of synaptic weights at 0; bottom blue dots represents fraction of synaptic weights at 0.2 (F) The red trace is distribution of synaptic weights at the beginning of the simulation. The green trace is the distribution of synaptic weights at the end of the simulation.

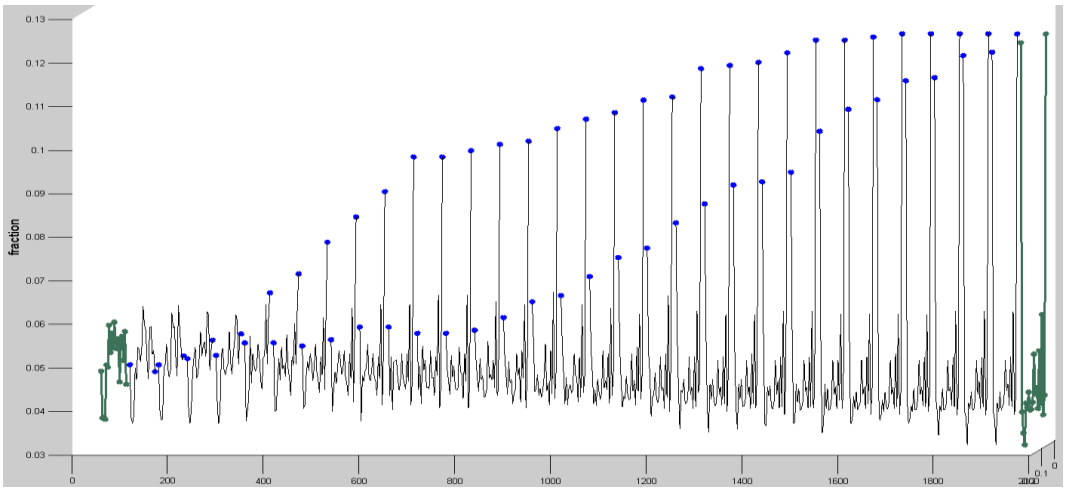
3.2 Neuromodulators and increase in synaptic weights

In order to replicate the effects of Iso neuromodulator addition, the values for A_P were increased in steps of 0.1 while the value of A_D remained constant at 0.3 (Fig 2A-D). Surprisingly all changes in A_P resulted in identical plots which would either suggest that small variations in A_P would have no effect on the rate of synaptic weight changes or the code is unresponsive to the changes.

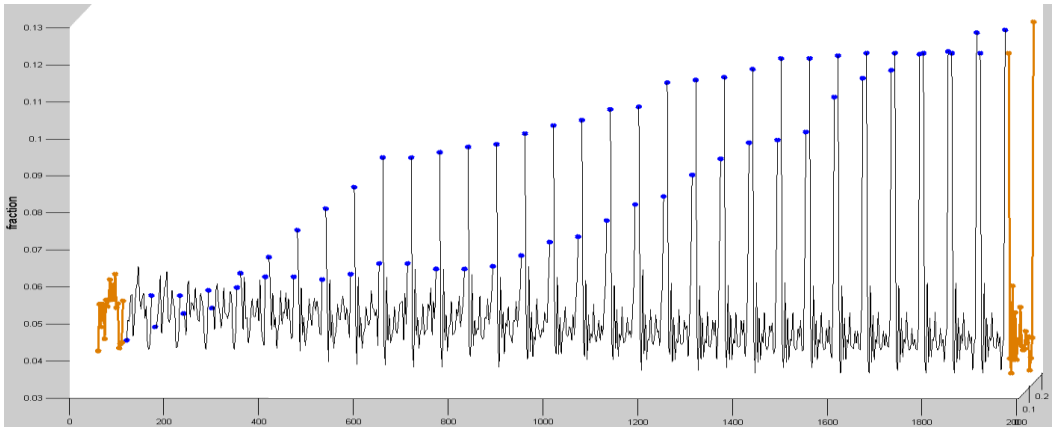




B



C



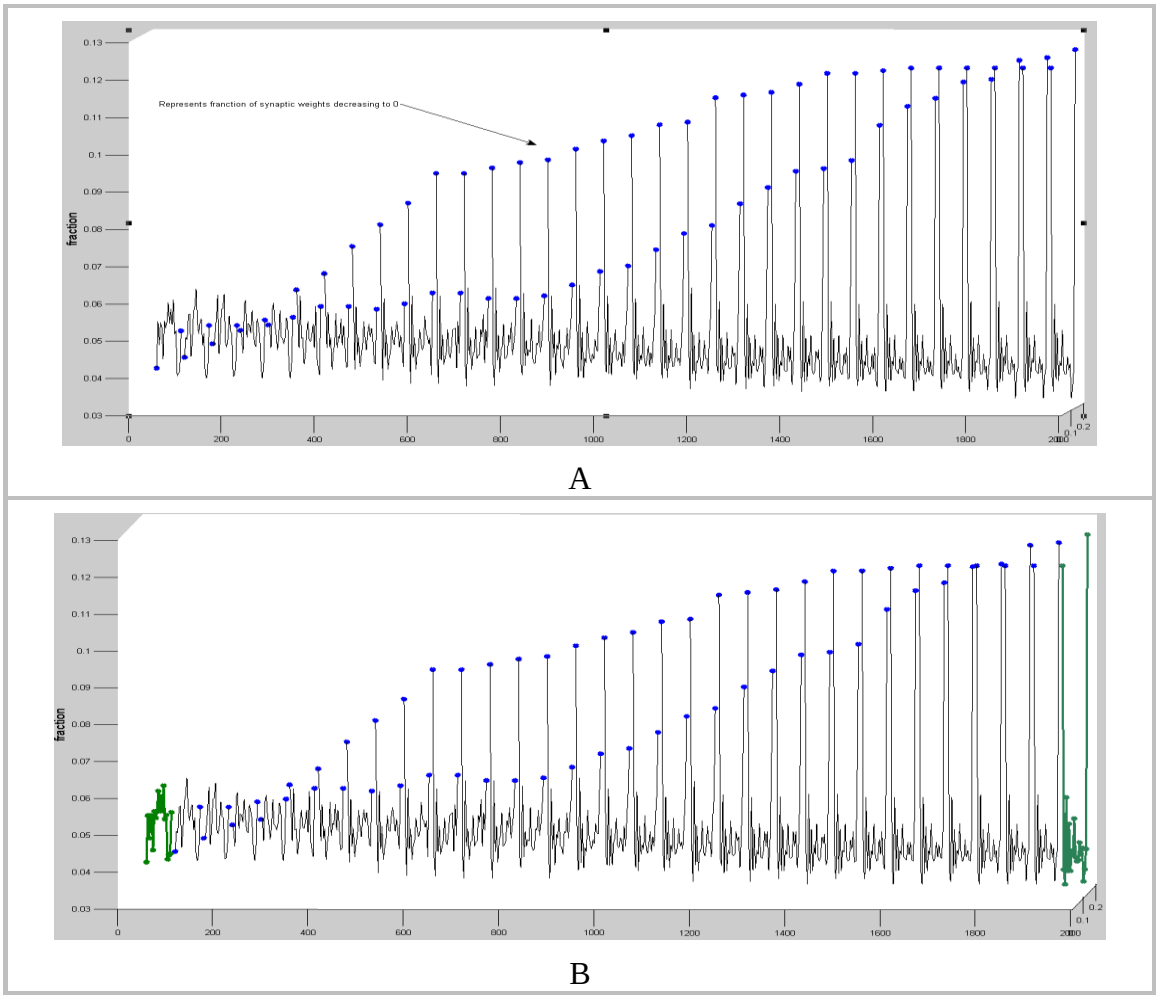
D

191 Figure 2: Variations in A_P; unless noted, top blue dots represent fraction of synaptic weights

at 0 (A) A_P = 0.1, A_D = 0.3, total time = 2000msec (B) A_P = 0.2, A_D = 0.3, total time = 2000msec (C) A_P = 0.3, A_D = 0.3, total time = 2000msec (D) A_P = 0.4, A_D = 0.3, total time = 2000msec

3.3Neuromodulators that decrease in synaptic weights

In order to replicate the effects of Iso neuromodulator addition, the values for A_D were increased in steps of 0.1 while the value of A_P remained constant at 0.1 (Fig 3A-D). Interestingly the results found in changing A_P while holding A_D fixed appeared identical to the ones obtained by changing A_D while holding A_P fixed.



A

B

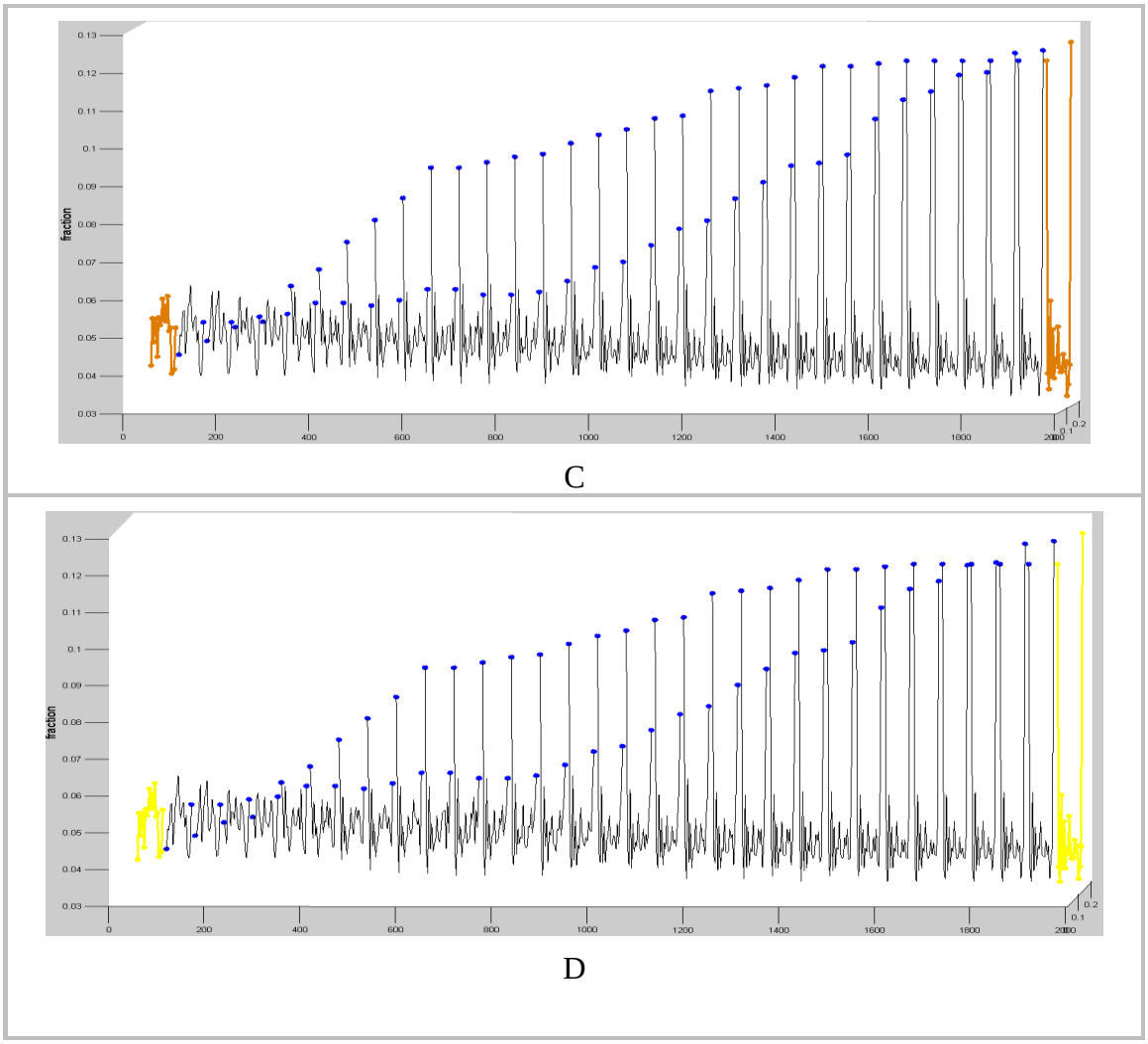


Figure 3: Variations in A_D (A) A_P = 0.1, A_D = 0.3, total time = 2000msec (B) A_P = 0.1, A_D = 0.4, total time = 2000msec (C) A_P = 0.1, A_D = 0.1, total time = 2000msec (D) A_P = 0.1, A_D = 0.5, total time = 2000msec

4 Conclusion

The similarity in the results found in modifying A_P while holding A_D fixed and reverse situation would lead to two different conclusions: either the network it insensitive to minimal changes of A_P or A_D or simply the code was hardcoded to account for only a particular value of A_P or A_D. Although the results would agree with the latter, extensive review of the code would lead to no indication that the values of A_P or A_D are hard coded in the system.

Recent studies also support the conclusion that neural networks supporting the STDP rule are incredibly efficient at learning. Masquelier et al.[3] have found that in the context of learning with phase-of-firing coding (PoFC); learning was possibly even when only ~10% of afferents exhibited PoFC. Further testing on the code by the owners[8] have shown that the STDP rule applied to the random networks provides it the ability of pattern completion.

Ultimately, additional testing in other models [9] is needed to determine whether STDP neural networks are insensitive to small changes in A_P or A_D. Also, consultation of the

literature for larger values of A_P or A_D would be informative though on a first past, no such values were discovered.

5 Acknowledgements

Thanks to Jeff Bush for his computational input and feedback as well as support and also to Professor Cauwenberghs for providing ideas on how to approach the topic. In addition, thanks to Fabrizio Gabbiani and Steven J. Cox for writing a terrific text on neuroscience and providing an accompanying Matlab code.

References

[1] Bi, G.Q., Poo, M.M (1998) Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type *Journal of Neuroscience* **18**(24):10464-72

[2] Bi, G. & Poo, M. (2001) Synaptic modification of correlated activity: Hebb's postulate revisited. *Ann. Rev. Neurosci.* **24**:139-166

[3] Masquelier, T., Hugues, E., Deco, G. & Thorpe, S.J. (2009) Oscillations, phase-of-firing coding, and spike timing-dependent plasticity: an efficient learning scheme. *Journal of Neuroscience* **29**(43):13484-93.

[4] Izhikevich, E.M. (2007) Solving the Distal Reward Problem through Linkage of STDP and Dopamine Signaling. *Cerebral Cortex* **17**(10):2443-2452.

[5] Seol, G.H., & Ziburkus, J. (2007) Neuromodulators Control the Polarity of Spike-Timing-Dependent Synaptic Plasticity *Neuron* **55**(6):919-929

[6] Izhikevich, E.M. (2007) *Dynamical Systems In Neuroscience*. Massachusetts: MIT Press books.

[7] Gerstner, W., Kistler, W. (2002) *Spiking Neuron Models*. Cambridge: Cambridge University Press

[8] Gabbiani, F. & Cox, S.J. (2010) *Mathematics for Neuroscientists*. London: Academic Pess/Elsevier

[9] Legenstein, R., Pecevski, D., Maass, W. (2008) A learning theory for reward-modulated spike-timing-dependent plasticity with application to biofeedback. *PLoS Comput Biol* **4**(10):e1000180