Modelling STDP: sequence learning and recall

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Long term synaptic plasticity underlies many important learning processes in the brain. Recent physiological data have shown that the precise relative timings of pre- and post-synaptic neuron firings at a synapse determine both the direction of modification (potentiation or depression), and magnitude of this modification. We model this form of plasticity using a model based on calcium dynamics and show that, in addition to reproducing experimental data for both paired and triplet spike paradigms, the model allows a reciprocally connected network of hippocampal pyramidal neurons to store and recall short temporal sequences.

Introduction

Long term synaptic modification has been repeatedly shown to be a major basis of memory storage in the brain. The exact details of how this modification depends on the firing patterns of neurons are critical to our understanding of memory processes.

Hebb's postulate is that when one neuron(A) contributes to the firing of another neuron(B), the synaptic strength between A and B should be increased. This form of plasticity allows networks to act as autoassociators, storing patterns and recalling those patterns from fragments of the original - a form of data based memory. Previous physiological studies have shown that so called "Hebbian learning" occurs in some biological neural networks, providing a possible candidate mechanism for episodic (memory of specific events in time and space) memory function. However, most existing studies focus on a time-symmetrical Hebbian modification (so that synaptic strength from A to B increases whenever A and B fire in close temporal proximity, but without dependence on the order of firing).

Spike time dependent plasticity

Data from hippocampal neurons examining the effect of spike timing on changes in synaptic efficacy have shown

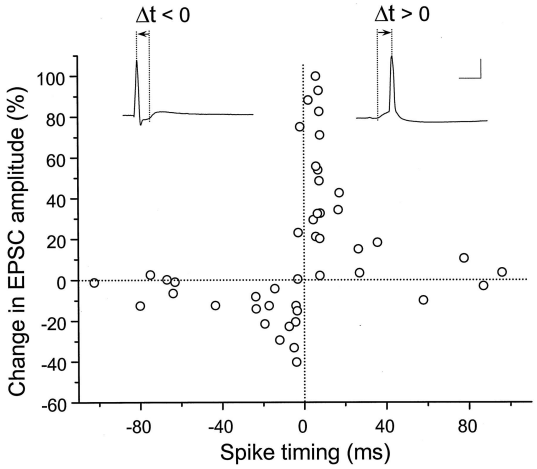

Figure 1: Change in synaptic strength relative to inter-spike interval (taken from [2])

that the precise timing of pre- and post-synaptic spikes is critical to the direction and magnitude of the change in synaptic strength produced by spike association[2].

This spike-time dependent plasticity (STDP) leads to an increase in synaptic strength if the pre-synaptic spike at a synapse preceeds the post-synaptic neuron's firing, and a decrease in synaptic strength if the reverse is true. The time window over which the change from negative to positive strength change occurs is very small (approx 5ms - see figure 1).

This "causal Hebbian" modification adds an important temporal aspect to synaptic plasticity. Not only does it balance LTP (Long Term Potentiation) and LTD (Long Term Depression), to prevent overall network activity from becoming too high or low, but a reciprocally connected network of neurons with this form of plasticity should be capable of storing temporal information about a series of inputs provided to it.

Considerable research has been performed investigating the exact mechanisms of LTP and LTD and while these mechanisms involve complex protein signalling chains, it should be possible to produce a model based

loosely on these physiological mechanics, which accuratley reproduces the STDP effect, allowing in depth examination of the overall effects on biological networks of this form of plasticity.

The hippocampus and temporal sequences

The hippocampus is a widely studied brain region, thought to be responsible for storage of new episodic memories[3], without which humans cannot function in society. For many memories, temporal information is important and so we might expect the hippocampus to posess a mechanism of storing and recalling this temporal information.

Recent research based on rats' running experiments[15] has shown that when rats explore a maze for food reward, during the periods of slow wave and REM sleep following this exploration, segments of place cell activity are replayed temporally. These place cells form while the rats explore as representations of certain locations in space. That the sequence of neuron firings is preserved, at least in part, in memory, shows that the hippocampus is capable of storage and recall of temporal sequences, confirming other existing data[5].

Modelling STDP

We wish to determine:

- If it is possible to develop a simple model of synaptic plasticity, based on neurophysiological calcium dynamics, that resulted in STDP of the form shown in [2] (figure 1, and also reproduced other experimental data for which timing is critical[6]).
- Whether use of this model would allow a simple reciprocally connected network to store and recall temporal information about a sequence of inputs.

Neuron model

The neuron model used is a leaky integrate-and-fire spiking neuron based loosely on that used in [14]. The neuron incorporates glutamate activated excitatory NMDA and AMPA mediated currents, GABA activated inhibitory $GABA_A$ and $GABA_B$ currents and an inactivating after-hyperpolarisation (AHP) current. We separate excitatory currents into those that are NMDA and AMPA mediated because this distinction seems to be important - NMDA mediated calcium influx is essential for both LTP and LTD to occur, but the mechanism by which the potentiation becomes permanent involves AMPA receptor trafficking[9]. Also the different dynamics of NMDA and AMPA (AMPA response is fast, occurring over approximately 2-5ms, NMDA response is much slower, occurring over approximately 120ms) are important for the temporal response of the network.

The neuron equation used was:

$$C\frac{dV}{dT} = I_{LEAK} + I_{AHP} + I_{NMDA} + I_{AMPA} + I_{GABA_A} + I_{GABA_B} \quad (1)$$

where I_{LEAK} is a leak current, negative above the neuron's resting potential, I_{AHP} is an inactivating after-hyperpolarisation current, and the synaptic currents (NMDA, AMPA and GABA A and B) are modelled with two channel kinetic variables representing fractions of open channels, which give rise to positive (NMDA, AMPA) or negative ($GABA_A$, $GABA_B$) currents.

We posit that STDP arises as the interaction between two processes with similar mechanisms, one responsible for potentiation and one for depression. Both of these processes depend on calcium chains in the postsynaptic density. When calcium levels are very low, neither process produces significant effects. When calcium levels increase, the depotentiation process dominates and net LTD is seen. When calcium levels are higher still, the potentiation process dominates and overall LTP occurs. The time courses of the reactions involved give rise to the time-dependent form shown in[2].

We therefore model two separate components, each of which depends on pre- and post-synaptic firing and results in the movement of AMPA receptors[9].

Hence the learning equation developed incorporates a postive component:

$$\Delta W_{LTP} = k_{LTP} Ca_{NMDA} Ca_{LTP} Ca_{MKII} \quad (2)$$

and a negative component:

$$\Delta W_{LTD} = k_{LTD} Ca_{NMDA} Ca_{LTD} \quad (3)$$

such that the resultant learning is given by:

$$\Delta W = \Delta W_{LTP} + \Delta W_{LTD} \quad (4)$$

(with k_{LTD} negative). We explain these equations more fully below.

NMDA dependence

It has been shown that NMDA activity is necessary for both LTP and LTD, even if the LTP/LTD is achieved by the movement of AMPA receptors[16, 12]. Therefore, we incorporate a dependence, Ca_{NMDA}, on NMDA mediated calcium inflow in our model, as included in equations (2) and (3).

This variable models a calcium concentration arising from the opening of magnesium gated NMDA channels. We simulate the fraction of open channels using a two kinetic variable system:

$$\frac{dx}{dt} = \phi(\alpha_x \sum_j \delta(t - t_j) - x/\tau_x) \quad (5)$$

$$\frac{ds}{dt} = \phi(\alpha_s x(1 - s) - s/\tau_s) \quad (6)$$

Where the sum is over pre-synaptic spike times. The varible s then represents the fraction of open channels, and we have $\frac{dCa_{NMDA}}{dt} = k_{Ca_{NMDA}} s - Ca_{NMDA}/\tau Ca_{NMDA}$ where $k_{Ca_{NMDA}}$ is a constant.

Positive terms

The Ca_{LTP} concentration is dependent on post-synaptic firing (and hence based on a process involving backpropagating spikes from the soma to the dendrites of the post-synaptic cell):

$$\frac{dCa_{LTP}}{dt} = \alpha_{Ca_{LTP}} \sum_i \delta(t - t_i)(0.9 - Ca_{LTP})^2 - \frac{Ca_{LTP}}{\tau_{Ca_{LTP}}}. \quad (7)$$

The Ca_{MKII} term represents a store of Calcium-CaM-dependent protein kinase II (CaMKII) which is essential for NMDAR dependent LTP[8]. It is activated by Ca^{2+}, so we calculate is as:

$$\frac{dCa_{MKII}}{dt} = \frac{-Ca_{MKII}}{\tau_{Ca_{MKII}}} + \alpha_{Ca} Ca_{free} \quad (8)$$

where α_{Ca} and $\tau_{Ca_{MKII}}$ are constants and Ca_{free} is the concentration of freely available post-synaptic calcium. Ca_{MKII} is hypothesised to provide an anchoring site for AMPA receptors, enhancing synaptic efficacy.

We presume that LTP occurs when the backpropagation (post-synaptic) activated calcium, NMDA mediated activity and Ca_{MKII} are co-activated and represent this in the model by multiplying these components.

Negative terms

The negative term Ca_{LTD} also represents post-synaptic calcium available for synaptic strength change (dependent on backpropagating spike activity), again this calcium density increases with post-synaptic firing, however the timescale over which it builds up and decays is longer than for the LTP calcium:

$$Ca_{leak} = \alpha_{Ca_{in}} \sum_i \delta(t - t_i) - \frac{Ca_{leak}}{\tau_{Ca_{in}}} \quad (9)$$

$$Ca_{LTD} = k_{in} \int (Ca_{leak} - Ca_{leak,thresh}) - \frac{Ca_{LTD}}{\tau_{Ca_{LTD}}} \quad (10)$$

As with the LTP, we require this calcium to be present simulataneously with NMDA mediated calcium for synaptic strength change to occur.

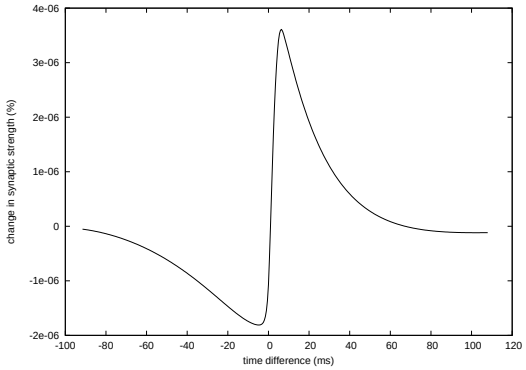

Figure 2: Change in synaptic strength as a function of time interval between pre- and post-synaptic firing (simulated)

Parameter choices

Where possible, parameters have been chosen to match experimental results (for example time constants of AMPA and NMDA mediated post-synaptic potentials). Where no experimental data exist, we have chosen values that produce a learning curve to fit in with that shown by Bi and Poo.

Result

Adding positive and negative terms using constants k_{LTP} and k_{LTD} chosen to balance the positive and negative components gives us the final version of the learning algorithm.

Simulating the change in synaptic strength resulting from varying the time interval between single pre- and post-synaptic spikes produces a result (figure 2) very close to that of [2] (see figure 1).

Storage and recall of temporal sequences

To determine whether this form of plasticity is useful for storing temporal information about sequences, we simulated a network of reciprocally connected pyramidal cells, as might be found in the hippocampal CA3 region.

The test network

The test network consisted of 100 reciprocally connected pyramidal-type cells with a single inhibitory interneuron, reciprocally connected with the pyramidal cells, with connection strengths chosen to limit overall network activity.

The input sequence consisted of five blocks of five neurons each, presented for 50ms with no interval between presentations (see figure 3). After network activity had

died away, we then replayed the first element of the sequence to determine whether the network could "fill in" the remaining elements.

Results

After an initial learning period consisting of three presentations of the input patterns, the network responded to re-presentation of the first pattern by producing the remaining patterns in sequence (figure 4). The recall does not preserve precise temporal information, but the sequence of firings is preserved.

Multiple spike paradigms

An important extension of the paired pre- and post-synaptic spike paradigm is to multiple spikes. It is not clear from [2] what change in synaptic efficacy will occur if, for example, a pre-synaptic spike is followed by a post-synaptic spike which is then followed by a post-synaptic spike. Either net potentiation or net depression could occur here, depending on how the spike pairings interact. An experimental study of this[6] showed that in the triplet case (single pre-synaptic and dual post-synaptic spikes comprising the 1/2 case and dual pre-synaptic and single post-synaptic comprising the 2/1 case), the first interaction dominates, unless the time interval between spikes in the first interaction is large (>70-100ms).

Comparing our simulations with the experimental data shown in[6] and reproduced in figure 5, where the relative timings between the single and double spikes (t1 being the time interval between the first of two spikes and the single spike, t2 being that between the second of two and the single spike) are varied and the net change in synaptic strength plotted, shows that our model can reproduce the experimental data in this case (see figures 6 and 7) as well as the model given in[6], but with a more biologically realistic model.

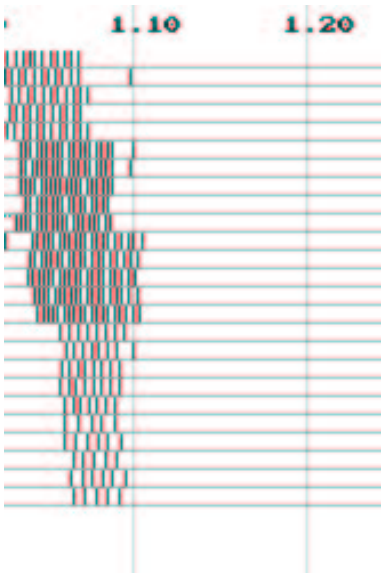

Figure 4: Replay of learnt patterns

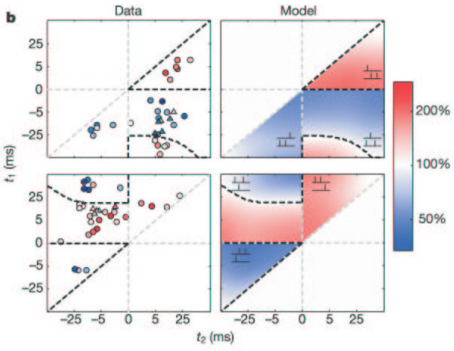

Figure 5: Experimental data and model predictions for the 1/2 and 2/1 triplet spike paradigms, from [6]

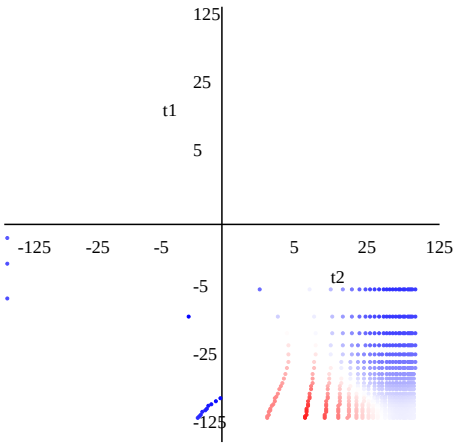

Figure 6: 1/2 triplet spike paradigm changes in synaptic strength (red positive, blue negative)

Discussion and further work

Relation to previous work

A similar model of STDP is given in [13]. The resultant learning form is somewhat different from that of [2], however, having a significant late LTD phase when post-synaptic firing occurs more that 25ms after a pre-synaptic spike. Also, the LTP peak is wider than the LTD trough, whereas in [2], the LTP peak is high and short, and the LTD trough long and shallow. These distinctions may be important, since a network with spontaneous uncoordinated firing will develop a net increase in synaptic strengths if the area under the LTP peak is larger than that of the LTD troughs (assuming that each pair of pre- and post-synaptic spikes produces an independent strength change). Another model is given in [11], however this model concentrates on modification

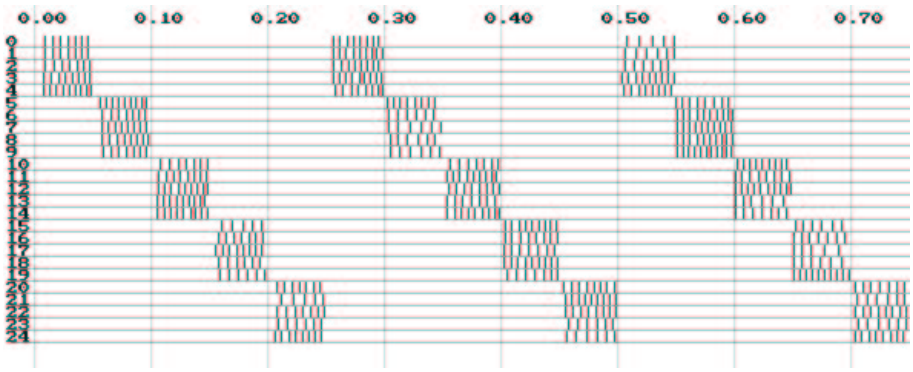

Figure 3: Presentation of patterns to be learned

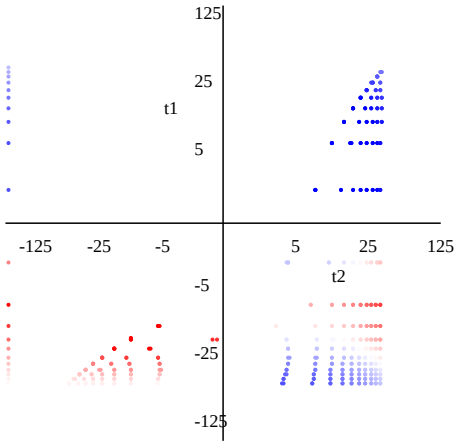

Figure 7: 2/1 triplet spike paradigm changes in synaptic strength (red positive, blue negative)

of presynaptic vesicle release probablity whereas recent research seems to suggest that postsynaptic AMPA trafficking is a more likely candidate mechanism for STDP.

There is also the recent work of[10] who use solely a unified AMPA/NMDA activation analysis (without separation between LTP/LTD components as would seem to be countered by the experimental data of [8] and others), and is different from out approach where the more fundamental Ca dependent components are emphasised. The results of[10], like those of [13] do not entirely replicate the relative sizes of the LTP and LTD peaks shown in [2], which we believe to be important for overall activity balance.

The review article of Abbott and Nelson[1] suggests other useful properties (besides temporal information storage) of networks utilising STDP such as increasing input selectivity and stabilisation of overall network activity, and it would be interesting to investigate whether our model can demonstrate these effects. The review also highlights other forms of STDP (which occur at different types of synapses), including symmetrical and anti-causal learning, which might prove enlightening to model.

More complex multiple-spike paradigms

The paper of Froemke and Dan[6] exaimines the 2/2 (dual pre- and post-synaptic spikes) paradigm but does not give explicit data. If such data were available, we could investigate whether our model can reproduce the correct results.

Use of temporal memory

The temporal aspect of the learning rule clearly allows a reciprocally connected network to store temporal information without assistance. This could be an imporant neural mechanism for sequence learning, both in the hippocampus and other brain areas, such as neocortex (to which it is possible that memories are transferred, and might therefore require storage of temporal information).

Possible addition of theta

Our simple network does not include a simulated theta rhythm. This 5-10Hz oscillation is present in both rat and human brains (in different forms[4]) during exploration and has been proposed as a method of alternating between encoding and retrieval in the hippocampus[7]. A simulated theta rhythm could increase the effectiveness of the learning and allow for more complicated sequences.

Speed of replay

The replay of patterns is much faster than the original rate of presentation, due to the fast dynamics of AMPA activated synapses. It is possible that a controlling theta rhythm could slow this recall down, which could be important for accurate recall.

Conclusion

We have demonstrated that a model of low level calcium dynamics can reproduce important experimental results showing STDP in real neurons, both with paired and triplet spikes. Use of the model in a simple network shows that it provides the capacity for temporal sequence storage and recall, which is important for episodic memory.

The model also allows further exploration of the protein dependent mechanisms underlying the phenomenon of STDP and should allow simulation of the effects on these mechanisms of neuromodulation and neuronal damage, both important to our better understanding of the function of the brain.

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