Metaplasticity and the Unified Calcium Model lead to input selectivity in spiking neurons

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Abstract: Intracellular calcium concentration has been proposed as the key associative signal for the Hebbian synaptic plasticity. The Unified Calcium Model has been able to account for various plasticity-induction protocols, such as rate-based and spike time-dependent plasticity. Here, we investigate the properties of this model in a multi-synapse neuron receiving inputs with different spatiotemporal spike-train statistics. In addition, we present a physiological form of metaplasticity, an activity-driven robustness-inducing regulation mechanism. A neuron thus implemented is stable and spontaneously develop selectivity to a subset of the stimulating inputs.

Keywords: synaptic plasticity, Hebbian learning, STDP, calcium, NMDA.

1. Introduction

A considerable body of experimental evidence suggests that the intracellular ionic calcium concentration $[Ca]$ plays an important role in activity-driven synaptic changes. For example, different magnitudes and patterns of postsynaptic $[Ca]$ can selectively induce long-term potentiation (LTP) or long-term depression (LTD) (Lisman, 1989; Abraham and Bear, 1996; Cummings et al., 1996; Yang et al., 1999). The functional dependence of plasticity on $[Ca]$ has been described as U-shaped (Cho et al., 2001; Cormier et al., 2001): low levels of $[Ca]$ induce no synaptic changes, while modest levels lead to LTD and higher ones, to LTP. The rise of $[Ca]$ concentration depends in part on back-propagating action potentials (BPAPs) (Markram et al., 1995; Isomura and Kato, 1999) in the postsynaptic cell; most interestingly, when these action potentials are paired with sub-threshold excitatory postsynaptic potentials (EPSPs), the dendritic $[Ca]$ transient is substantially higher than the one produced by EPSPs or APs alone (Magee and Johnston, 1997).

Based on these observations, the *Unified Calcium Model* (UCM) has been proposed by Shouval et al. as the common mechanism shared by the diverse forms of bi-directional synaptic plasticity (Shouval et al., 2002a). In this model, the neuronal activity is translated locally into the dendritic calcium concentration $[Ca]_i$ through the voltage and time-dependence of the NMDA channels. In addition, there is a global contribution of $[Ca]$ due to BPAPs with a slow after-depolarizing tail. The total $[Ca]_i$ determines the sign and magnitude of the synaptic plasticity through a U-shaped function $\Omega[Ca_i]$. This more biophysical approach rids the model of ambiguities as to which of the cellular activity measures (rate, depolarization or spike-timing) one should be consider in a learning rule. It has been argued that each of these depends on different aspects of the model; therefore they can coexist (Yeung et al., 2002b).

With the aid of simulations, we investigate the collective behavior of the UCM such as cooperativity and competition, and examine how they give rise to input selectivity. Input selectivity is a general feature of many cortical neurons, and underlies the formation of receptive

fields and topographic mappings. A simulated neuron is called *selective* to a specific input if it has a potentiated pathway for it. Previous work had shown that, in this model, selectivity arises only within a narrow range of parameters (Yeung et al., 2002a). Metaplasticity, the activity-dependent modulation of synaptic plasticity, is essential for the robustness in other systems such as the BCM neuron (Bienenstock et al., 1982). Furthermore, it has significant experimental support (Kirkwood et al., 1996). Originally, metaplasticity was formulated for systems in which cellular activities were regarded as continuous-valued variables. We find that, with a proper biophysical formulation compatible with the UCM, the stabilizing properties of metaplasticity can be extended for spiking neurons, widening its applicability to more realistic scenarios.

2. Metaplasticity and selectivity to spike-train correlations

The development of neuronal selectivity depends on the statistical structures of the inputs. For spiking neurons, these structures involve a combination of spatiotemporal statistics of higher orders. We first address exclusively the special domain using a simple scenario adapted from Rudolph and Destexhe, 2001. In this environment, half of the synapses (group *B*) receive noisy Poisson spike trains with a mean rate $<r_{in}>$; the other half (group *A*), receives correlated spikes with the same rate $<r_{in}>$, but with an enhanced probability of arriving together. We expect that, by firing together, group *A* will gain control of the post-synaptic firing times and thus be potentiated, while group *B* will be depressed, in a manner similar to the STDP described by Song et al., 2000.

It has previously been shown that this approach gives rise to segregation of the final weights, the uncorrelated half of which is depressed while the correlated half is potentiated (Yeung et al. 2002a). This happens because the cooperativity among the synapses of group *A* enhances its probability of generating a post-spike, which, in turn, generates a BPAP. Such a strong depolarization, combined with the NMDA channels, which are still open due to a recent pre-spike, potentiate these synapses in a Hebbian-associative fashion. Group *B* will fire with equal probability before and after a post-spike, and the low value of the NMDA conductance g_m ensures that, on average, depression takes place. However, these results only hold for a narrow range of input parameters: consistent with the rate-based and the rate-dependent STDP protocols (Sjoström et al., 2001), for low and high enough $<r_{in}>$, all the synapses are depressed and potentiated, respectively.

The BCM theory has previously proposed that the threshold between LTD and LTP should move as a function of the history of postsynaptic activity (Bienenstock et al., 1982). This type of activity-dependent regulation in the properties of synaptic plasticity, or *metaplasticity*, was developed to ensure selectivity and stability within the framework of an abstract learning model. Several experimental results, however, have linked metaplasticity to the magnitude of the NMDA conductance, by showing that, as the cellular activity increases, NMDA conductance is down-regulated, and vice-versa (Carmignoto and Vicini, 1992; Quinlan et al., 1999; Watt et al., 2000; Philpot et al., 2001). This is a particularly suitable interpretation under the scope of the UCM, and sets the ground for a more physiological formulation of the metaplasticity (Shouval et al., 2002b). NMDA conductance is understood as the total number g_m of NMDA channels inserted in the membrane of the postsynaptic terminal. Consider a simple kinetic model in which these channels are in equilibrium with g_i intracellular NMDA channels, with voltage-dependent removal rate $k_- V^\alpha$ and a insertion rate k_+:

$$g_m \underset{k_+}{\overset{k_- V^\alpha}{\rightleftarrows}} g_i ,$$

where V is measured with respect to the membrane resting potential. This leads us to a dynamic equation for g_m, $\dot{g}_m = -(k_- V^\alpha + k_+) g_m + k_+ g_t$, where g_t is the normalization factor, $g_t = g_m + g_i$. The fixed point is:

$$g_m^* = \frac{g_t}{\left(k_- / k_+\right) V^\alpha + 1} .$$

If, in this model, cellular activity is translated into $[Ca]$, then g_m can be loosely interpreted as a function of the inverse of the BCM sliding threshold θ_m (Shouval et al., 2002b). Notice that in the original form of BCM, θ_m is the time average of a non-linear function of the postsynaptic the activity level. In order to reinforce competition, g_m should not depend solely on local (synaptic) variables, but should rather detect changes of the global patterns of cellular activity. In what we do here, this activity-signaling global variable is the postsynaptic membrane potential.

Implementation of metaplasticity widens significantly the range of input frequencies in which segregation between the weights of correlated and uncorrelated synapses is observed, as shown in Figure 1a (for detailed methods, see Yeung et al., 2002b). At low spiking activity, the sub-threshold depolarization levels prevent inward Ca currents. g_m grows such that pairing of pre-spikes with small depolarizations allows occasional potentiation. This effect is amplified when the potentiated synapses generate a post-spike, due to the large amplitude of the BPAP. Because the synapses of group A have a higher probability of, jointly, generating post-spikes, it will be selectively potentiated. Persistent post-spike generation will lead g_m and therefore $[Ca]$ to decrease, hence scaling the synaptic weights downwards. Competition arises as the system searches for the balance between the selective positive feedback of a standard Hebbian rule and the overall negative feedback of a sliding threshold mechanism. Increasing the fraction of correlated inputs weakens the final weight of the correlated group (Figure 1b), suggesting that less potentiation is needed for this group to control the timing of the output. On the other hand, strengthening the correlation increases segregation (Figure 1c), evidencing the effects of lateral

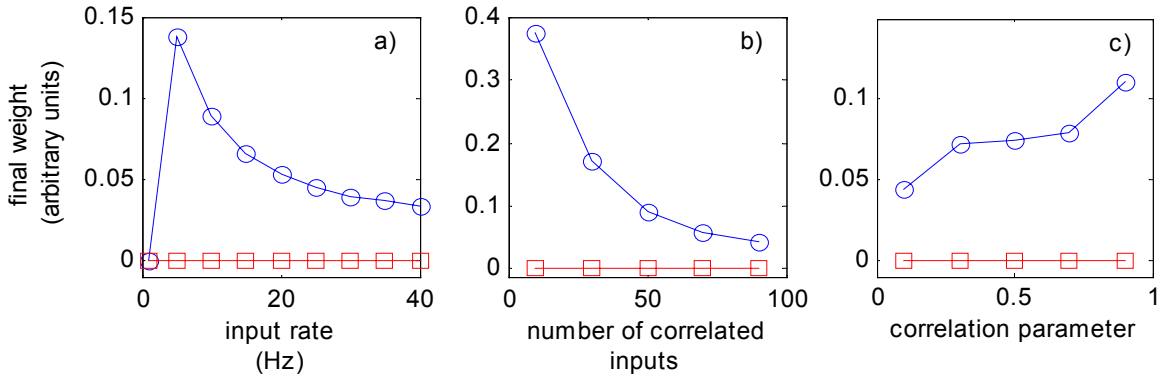

Figure 1: Metaplasticity widens the range of stimulus rate for which segregation between correlated (circle) and uncorrelated (square) inputs. Segregation decreases with the increase of input rate (a), evidencing the regulation of the excitability of the cell through metaplasticity. Segregation also decreases with the number of correlated inputs (b) but increases with the increase of the correlation parameter (c).

3. Selectivity to patterns of rate distribution

An alternative input environment is one in which the rates vary not only spatially, but also over time. This is a plausible representation for sensory neurons that are differentially excited. A straightforward method is to use rate distributions that are piecewise constant. We use a simple example in which the rate distribution are non-overlapping square patterns, as illustrated in Figure 2a (for detailed methods, see Yeung et al., 2002b). The patterns are randomly presented to the neuron, being switched at regular epochs. As the mean switching time is constant and much smaller than the time course of learning, each synapse receives the same average input over time. However, we observe that, after training, the neuron spontaneously breaks the symmetry, as a subset of synapses becomes potentiated, while others are depressed (Figure 2b, notice that all weights have the same initial condition). It should be noticed that, because the choice of the training pattern at each epoch is random, the selected pattern is different at each run.

These results are robust across different pattern amplitudes and pattern dimensions (not shown), and also hold for more complex input rate distributions. An example is shown in Figure 3, where the simplified environment described above is substituted by a set of overlapping Gaussian distributions.

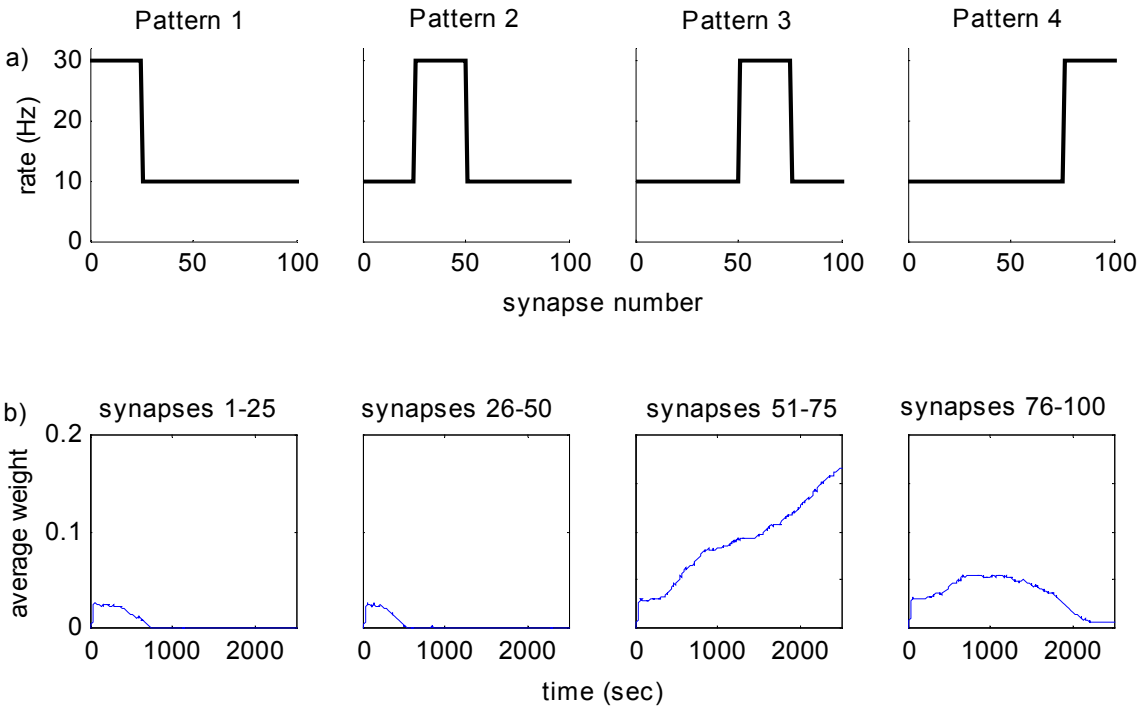

Figure 2: a) Patterns of input rate distribution across 100 excitatory synapses; shown is an example of 4 non-overlapping patterns. b) Typical time-evolution of the average synaptic weight across each subset of 25 synapses. All synapses have the same initial weight. It is clear that, in this case, the neuron develops selectivity to pattern 3.

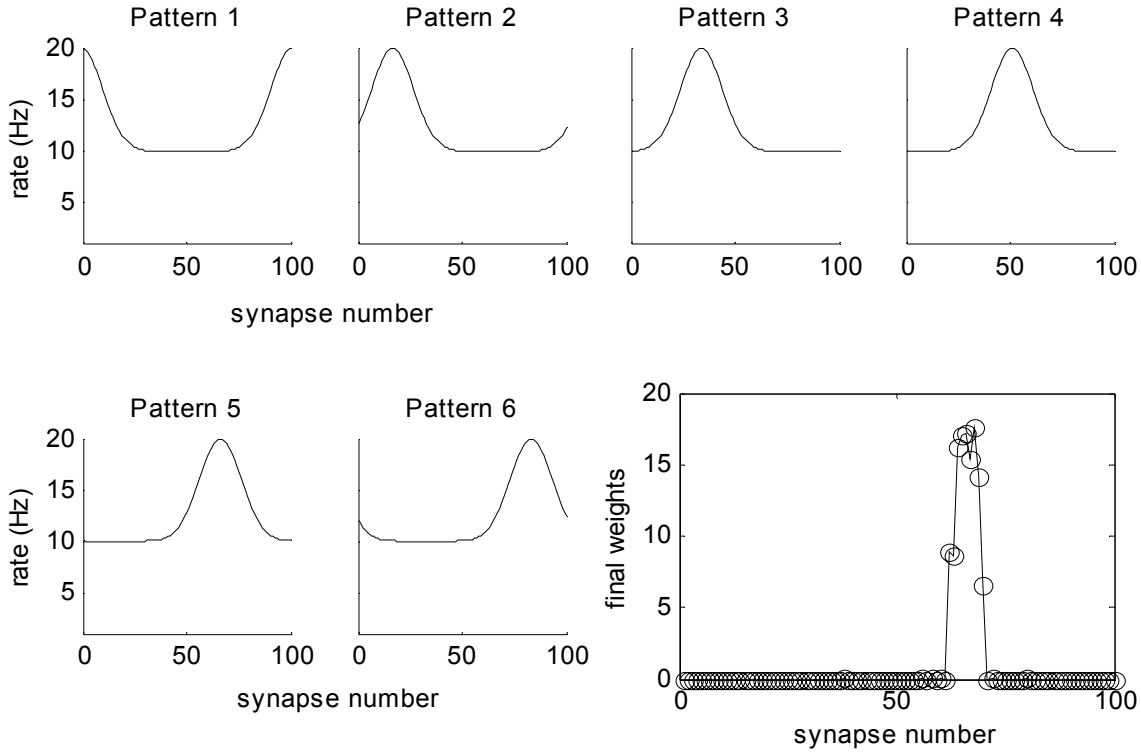

Figure 3: 6 overlapping Gaussian patterns of input rate-distribution across 100 synapses and the final values of the synaptic weights after a typical run. The final configuration of this particular run is selective to pattern 5.

4. Discussion

Neuronal selectivity has been shown to be experience dependent (Frégnac and Imbert, 1978; Chapman et al., 1996) and prevented when NMDA receptors are blocked (Kleinschimidt et al., 1987; Ramoa et al., 2001). It is likely, therefore, that receptive field formation relies on the same type of NMDA dependent synaptic plasticity observed *in vitro* (Dudek and Bear 1992; Bliss and Collingridge 1993; Bi and Poo, 1998). Previous work has shown that these *in vitro* rate and spike time-induced plasticity can be accounted for by the biologically inspired UCM. In this work, we have shown that the same model can lead to the experience-dependent development of neuronal selectivity.

Metaplasticity adds robustness to the system and reinforces competition indirectly, by controlled scaling of NMDAR currents. Direct and indirect competition can both account for the formation of ocular dominance, but in different ways that can be distinguished experimentally (Miller et al., 1989; Blais et al., 1999). We have shown here that even in very simple input environments there is segregation among the synaptic strengths, depending on the spatiotemporal statistics of different channels. This is analogous to what occurs in ocular dominance plasticity and is likely to generalize to more realistic assumptions.

Because UCM is responsive to input rates, in addition to spike-timing, we are able to achieve selectivity to rate-distribution patterns in spiking neurons that is comparable to the selectivity obtained in simplified, continuous-valued systems (Clothiaux et al., 1991). This result suggests that the coexistence and complementarity of rate- and spike time-dependent plasticities, previously demonstrated for a one-dimensional neuron (Shouval et al., 2002a), can be extended to multi-dimensional input environments. We are currently investigating the formation of receptive fields in more realistic scenarios, such as natural stimuli; and examine how the their statistical properties can be translated into a physiological mechanism for emergence of selectivity to input patterns.

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