Long-Term Potentiation: effects on synaptic coding*

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1 Introduction

Learning, in the context of individual neurons, is represented in both physiological and Artificial Neural Network (ANN) models by change of synaptic strength. Many of the changes in neural responses as a result of the learning process may be explainable by simple consideration of synaptic strength alteration. For instance, sensitization and habituation of vertebrate and invertebrate neurons are usually interpreted in terms of incrementation and decrementation of synaptic strength [1]. However, there are still many unexplained cases [2]. In the mammalian hippocampus, neurons do not receive one stimulus, but a number of different stimuli from a variety of different locations. So simply looking at the increment and decrement of synaptic strength is insufficient to explain what has been modified by learning.

Neural responses include input and output rate and their *pattern*. By "pattern", we mean the ordered sequence of interspike intervals and cross-intervals.

To study the effect of learning, we use an accepted physiological model: Long-Term Potentiation (LTP), first observed in excitatory synapses of rabbit hippocampal neurons [3]. When a high frequency afferent tetanus is applied to these neurons, postsynaptic potentials are enhanced. Other than the magnitude of postsynaptic potential enhancement, LTP also involves persistent maintenance of this enhancement for minutes or even hours [3]. LTP has also been recorded in invertebrate neurons, for instance in the crayfish opener-excitor neuromuscular synapse.

Similar effects have also been observed in the *inhibitory* synapse of the goldfish, *Carasius auratus* Mauther cell [4]. Thus, though originally investigated in excitatory preparations, there is no *a priori* reason to expect LTP to be an exclusively excitatory phenomenon. One might also consider that cerebellar Purkinje cells, involved in motor learning, are also connected through inhibitory synapses.

LTP aftereffects have been primarily studied in terms of induction as a function of stimulus rate. When a high rate stimulus is applied, LTP duration and PSP strength increase are recorded as the modification of the neural response as a result of learning. However, we can also consider LTP in the context of presynaptic spike temporal pattern, rather than just their rate. There is evidence that this is a better description of LTP dependence on the presynaptic discharge than is presynaptic rate [5]. Tsukada and collaborators showed that the increase in PSP size recorded strongly depends on the correlations among presynaptic interspike intervals [5].

In this report, we consider not only presynaptic pattern, but postsynaptic pattern, too, to describe LTP induction and its effects on neural behavior — the patterns of spikes it produces in response to identical presynaptic spike trains before and after "learning". ¿From our simulation results, we observe that the proportion of synchronization between the neural responses increases after learning, with shorter presynaptic interspike intervals producing a greater proportion of synchronization.

2 Methods

The model used is of the crayfish slowly adapting stretch receptor organ (SAO), the recognized prototype of an inhibitory synapse [6]. This model was chosen because of the level of familiarity with its (and the living preparation's) dynamics in response to stationary [7] and nonstationary [8] inputs, and its convenient representation of synaptic membrane variables. It consists of a single presynaptic inhibitory fiber (IF) and a postsynaptic neuron [9]. Trains of input spikes are presented to the SAO through the IF via their common inhibitory synapse. When the SAO is unperturbed, it fires like a pacemaker with all Action Potentials (APs) separated by a nearly invariant natural interval, N. When inputs are applied, a more complex timing pattern may be produced, either *aperiodic* or *periodic*.

In our model, synaptic strength corresponds to the *maximum permeability* $\bar{P}_{syn}$, of the cell membrane to a charge carrier ion, which is chloride (Cl^-):

$$I_{syn} = A\bar{P}_{syn}\frac{V_m F}{RT}\frac{[Cl^-]_0 - [Cl^-]_i \exp\left(-FV_m/RT\right)}{1-\exp\left(-FV_m/RT\right)} \times \sum_{k=1}^{n}(e^{(s_k-t)/\tau_+} - e^{(s_k-t)/\tau_-}) \tag{1}$$

Though the synapse in our model is an inhibitory synapse, we assume the potentiation is independent of the carrier ion, so modification of $\bar{P}_{syn}$ depends solely on LTP controlling parameters and PSP interspike intervals.

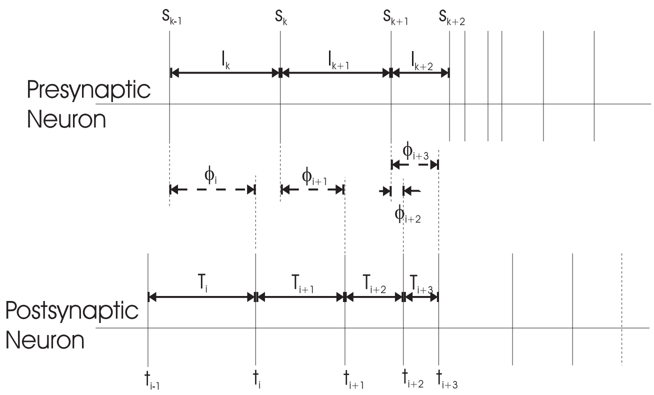

Figure 1: The presynaptic stimulus, s_k, the postsynaptic response, t_i, the phase, ϕ_i, the presynaptic interval, I_k and the postsynaptic interval, T_i.

As shown in Fig. 1, we record the time of occurrence of each pre- or post- synaptic spike (s_k or t_i, respectively, $i, k = 0, 1, 2\ldots$) thus assimilating both trains to point processes. Based on these times, certain interspike intervals are calculated, including postsynaptic, $T_i = t_i - t_{i-1}$, and presynaptic, $I_k = s_k - s_{k-1}$. Cross intervals or *phases*, $\phi_i = t_i - s_*$, were also computed from an AP back to the most recent preceding PSP.

Pacemaker inputs, with $I_k = I$ (typically normalized as N/I), were applied to the model SAO as the simplest stationary presynaptic pattern, and to duplicate the most common LTP experiments.

We incorporated a general mathematical model of LTP into the SAO model, rather than one specific to pyramidal neurons with uniquely mammalian messengers [5]. The modifiable component of permeability, $\bar{P}_{syn,m}$ in the model after the k^{th} PSP is:

$$\begin{aligned}\bar{P}_{syn,m}(I_k) &= (1-\frac{1}{\gamma})\bar{P}_{syn,m}(I_{k-1}) + \frac{A\bar{P}_{syn,f}}{\gamma} \\ &\quad \times \left(e^{-\alpha(I_k+I_{k-1}+\ldots+I_1)} + e^{-\alpha(I_k+I_{k-1}+\ldots+I_2)} + \cdots + e^{-\alpha I_k}\right) \end{aligned} \tag{2}$$

where γ is the LTP growth rate, A is the LTP glutamate transmitter amount, α is the LTP decay time constant and $\bar{P}_{syn,f}$ is the fixed component of the maximum permeability $\bar{P}_{syn} = \bar{P}_{syn,f} + \bar{P}_{syn,m}$. It causes the maximum synaptic permeability of our simulation to vary along time. These changes are compared with the unpotentiated value to compute the magnification ratio,

$$M = \frac{\bar{P}_{syn,m}}{\bar{P}_{syn,f}} \tag{3}$$

Magnification ratio plots were produced by recording the magnification ratio at presynaptic spike arrival times for multiple simulations with different N/I. Additionally, *bifurcation diagrams* are used to show the change in neural response due to LTP. These plot a measure of neural *behavior*, here ϕ_i, verses normalized presynaptic rate N/I. These behaviors include *locked* and *non-locked* behaviors. *p:q* locked behaviors are stationary, periodic behaviors where q postsynaptic spikes appear for every p presynaptic spikes in a repeating sequence of T_i and ϕ_i. Non-locked behaviors include a variety of aperiodic behaviors. In bifurcation diagrams, locked behaviors produce ranges of N/I with few, discrete categories of ϕ_i, while non-locked ones produce a vertically dense distribution of points within a range of ϕ_i.

3 Results

Magnification ratios obtained from the LTP simulation, shown in Fig. 2, mimic those found in living preparations [3, 10, 5]. They increase continuously from their unpotentiated values to their asymptotic

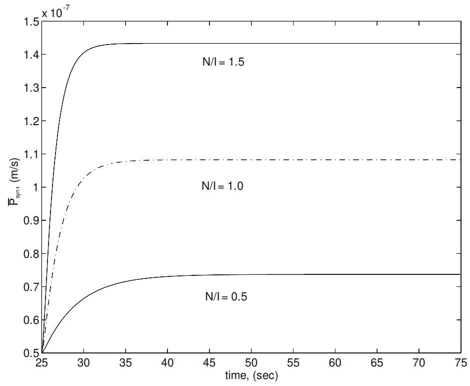

Figure 2: Magnification Ratio versus simulation time for $N/I = 0.5, 1.0, 1.5$.

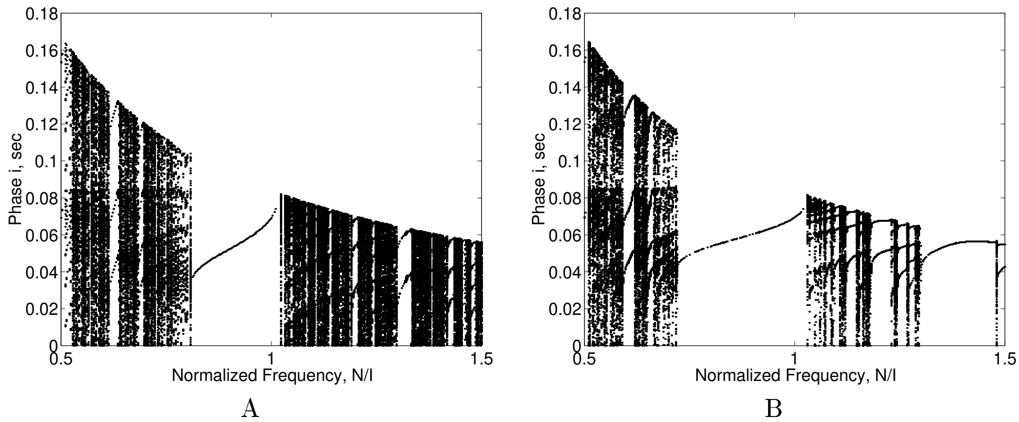

Figure 3: Comparison of two bifurcation diagrams for constant PSP simulation and LTP enhanced PSP simulation. (A) Constant PSP simulation with $\bar{P}_{syn} = 5 \times 10^{-6}$ cm/s. (B) LTP enhanced PSP simulation with $\bar{P}_{syn,f} = 5 \times 10^{-6}$ cm/s, LTP glutamate transmitter amount, $A = 0.533$, LTP decay time constant, $\alpha = 1/223\ \mathrm{msec}^{-1}$ and LTP growth rate, $\gamma = 25$.

values which depend directly on presynaptic rate for pacemaker input. This has also been reported in other experiments [10].

This increase in synaptic permeability modifies the global behavior of the neuron. From the bifurcation diagrams in Fig. 3, one can see the increase in locked responses as a result of LTP. Without LTP enhancement, 62% of the neural responses were locked. However, with LTP, 84% of input rates in the identical range produced locking.

Additionally, the widths of the input rate domains within which certain locking ratios occurred increased with LTP. Although not all the locking domains increased in width, the major ones, such as 1:1, 2:3 and 3:2, widened dramatically. Responses were still ordered along N/I in the same sequence with and without LTP.

Locked responses in the high rate region ($N/I > 1.0$, $p{:}q > 1{:}1$) increased more rapidly than the low rate region ($N/I < 1.0$, $p{:}q < 1{:}1$). For low rates, locking domains increased by 6.1%; for high rates, 81.3% of the responses were locked with LTP — a 34.7% increases.

4 Conclusions

Application of a general model of LTP causes a time-varying increase in maximum synaptic permeability in response to pacemaker input, with a concomitant increase in the dynamical postsynaptic aftereffects of IPSPs. Because the potentiating effect of PSPs decay over time, shorter interspike intervals result in greater accumulated potentiation [5]. Therefore, maximum permeability increases as interspike interval decreases.

LTP enhancement clearly changes the neuron's behavior. The abundance of locked responses increases. The lower rate boundary of the 1:1 locked response has been shifted towards the low rate region after "learning". However, the changes were not uniformly distributed along the inhibitor rate scale, being concentrated in the high rate region. Higher input rates produce greater potentiation, hence higher maximum permeability. So more higher locked responses (p:q > 1:1) reside in the identical simulation range ($N/I > 1.0$) after LTP enhancement.

We can summarize that the neuron synchronizes more readily with the input stimulus with LTP. Shorter input intervals produce more periodic neural responses. Therefore, the responses and the dynamics of the neuron depend on the effects of LTP. How each individual LTP parameter affects this synchronization is still an issue to be determined.

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