Long-Term Potentiation and Neural Coding as a Single Dynamical Process*

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***Abstract*— Because we think of learning and computation in terms of separate *a priori* categories, we naturally consider them as separate processes in neural networks. Our preconceptions do not translate into imperatives for Nature, however. We present an overview of work carried out by the HKUST Biocomputing Group which shows that some learning mechanisms must be considered as inseparable parts of the synaptic coding process, leading to the consideration of coding in the presence of learning-mediated changes.**

1 Introduction

Modification of neural networks in response to life experience is of central importance in living organisms. Without such a capability, they would be forced to react to their changing environment using only hard-wired reflexes. In higher organisms, this adaptation or learning process extends to the construction of basic architectural components for sensory input processing, as has been shown in the development of visual cortex in kittens, for example [1]. It is certainly what enables what at a high level we call "learning" and "memory".

Artificial neural network research presupposes experience-mediated synaptic modification occurs according to some *learning algorithm*, and much effort is spent in developing and analyzing the relative strengths and weaknesses of various algorithms from practical performance and theoretical computational points of view. One assumption underlying all such work is that the learning algorithm, while coupled to the network which it modifies, can be treated as an independent module of the overall system: in other words, its operation can be understood without reference to the details of the network.

Candidate physiological mechanisms have been identified only relatively recently. Notable among these are long-term potentiation (LTP) [2] and inhibitory LTP (ILTP) [3]. These involve changes in excitatory and inhibitory synapses, respectively, in response to stereotypical stimuli. These changes cause subsequent postsynaptic potentials' amplitudes to be increased, and this can extend for a significant period of time.

An important question is: what effect does a learning mechanism have on the information processing function of a single neuron or network? In the case of ANNs, this is a well-posed problem *by design*. One of the major contributions of such work has been the rigorous and precise explication of the computational properties of networks of simple processing elements coupled to certain classes of learning algorithms. Results are usually interpretable in terms of the parameters of the network transfer function being adjusted to minimize some error metric computed from the data used during the learning process.

The HKUST Biocomputing Group has been concerned recently with the issue of the meaning of learning in terms of *synaptic coding*: the transformation of presynaptic spike trains into postsynaptic spike trains across a single synapse. Because neurons are nonlinear dynamical systems, their responses to even simply-described spike trains (for example, *pacemaker* inputs where all spikes are separated by an invariant interval I) are complex [4]. This has important consequences for any learning algorithm which might be applied [5].

This is one consequence of the *bifurcation behavior* of such a nonlinear dynamical system [6]. In such systems, as some parameter is gradually changed (in the case of a neuron in the presence of a pacemaker presynaptic discharge, the presynaptic rate or the synapse strength), the output may change by either a small or a large amount. Large changes in postsynaptic discharge generally occur at discrete values of the parameter — *bifurcation points*, so-called because they are parameter values at which two distinct dynamical behaviors come together. Such behavior has been illustrated in terms of synaptic coding by our collaborators and ourselves in both living preparations and simulations [4, 7, 8, 9, 10, 11, 12]. Our current work has included analysis of coding across a single synapse in the presence of a synaptic potentiation process; this can be undertaken by extension from the observed coding in the absence of LTP [13].

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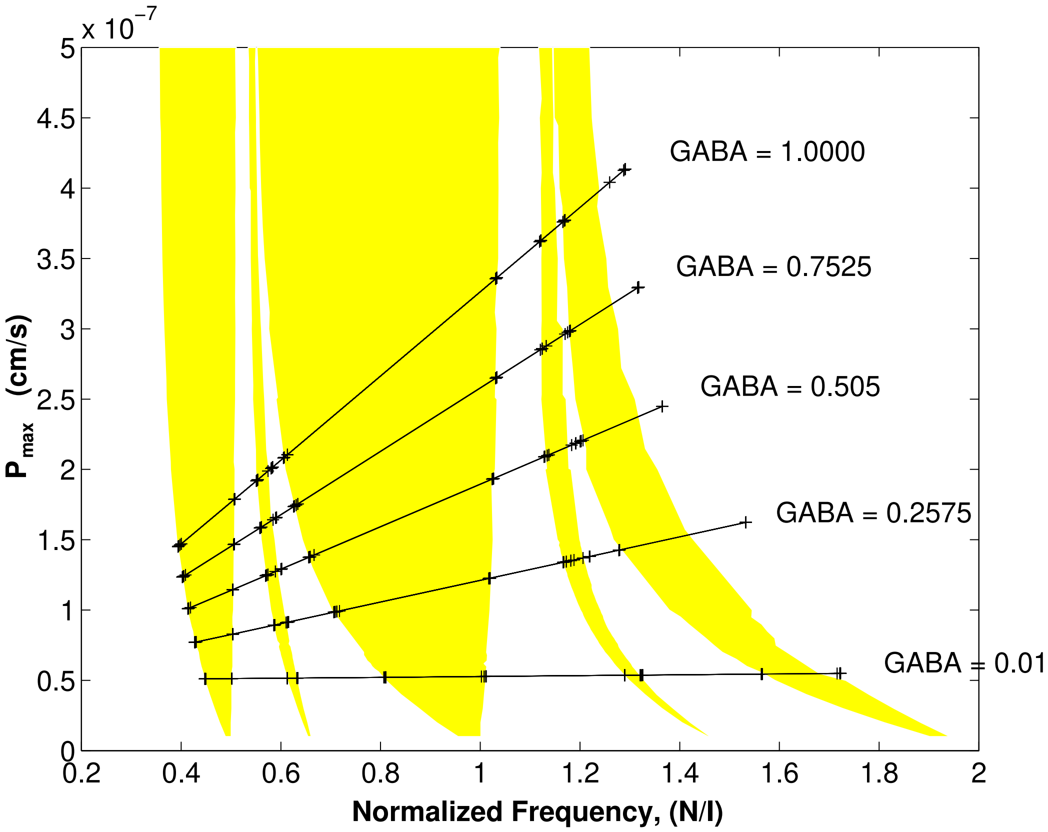

Figure 1: Comparison of behaviors produced by the simulation for both constant synaptic strength and ILTP. Gray regions correspond to lockings at ratios 1:2, 2:3, 1:1, 3:2, and 2:1 for constant synaptic strength. Each ILTP simulation's asymptotic synaptic strength is labeled with a '+'; simulations that involved release of equal amounts of neurotransmitter are connected by lines.

2 Methods

The living preparation includes the recognized prototype of an inhibitory synapse: the crayfish slowly adapting stretch receptor organ or SAO [4]. A Hodgkin-Huxley-like model was adapted for duplication of experiments on the SAO [14, 8, 9, 12]; its basic equations are presented in Appendix A.

Presynaptic spike trains were delivered to both the SAO and the model and the times of each presynaptic and postsynaptic spike was recorded: s_k and t_i for spikes numbered k and i ($k, i = 0, 1, \ldots$), respectively. From these, certain time intervals and cross intervals were computed, the most relevant here being the presynaptic intervals $I_k = s_k - s_{k-1}$ (identically equal to a fixed I for pacemaker driving), postsynaptic intervals $T_i = t_i - t_{i-1}$, and *phases* $\phi_i = t_i - s_*$ (the cross interval from a postsynaptic spike back to the most recent presynaptic spike). This assimilation of the spike trains to a point process [15] has proven sufficient for analysis of the dynamical behaviors of this system.

It will be sufficient for the purposes of this paper to distinguish between two broad classes of dynamical responses displayed by the neuron: *phase locking* and non-locked behaviors. In phase locking (or simply "locking"), a fixed, repeating temporal relationship exists between the postsynaptic discharge and the pacemaker input. p presynaptic spikes occur in the same period of time as q postsynaptic ones, and a locking is thus said to occur at a *p:q ratio*. Intervals $\langle T_i, T_{i+1}, \ldots, T_{i+q-1}\rangle$ and phases $\langle \phi_i, \phi_{i+1}, \ldots, \phi_{i+q-1}\rangle$ repeat in exactly the time taken up by p inputs, pI.

A variety of non-locked behaviors are also exhibited; we can lump them all together in one category here without affecting our conclusions (this is some indication of the very early stage of the work of incorporation of ILTP into the dynamical coding model).

Table 1: Typical values for model time constants.

m	0.3ms	r	2s
h	5ms	τ_+	0.25ms
n	6ms	τ_-	0.5ms
l	1.7s	α	0.5s

3 An Example: Pacemaker Inhibition

Figure 1 presents results of 2800 simulations: 1550 performed without ILTP and 1250 with. In all cases, pacemaker input was used. The figure is an *Arnol'd map* or *two-dimensional bifurcation diagram*: a plot of some measure of system behavior versus two parameters. In this case, the parameters are presynaptic rate (normalized as N/I) and synaptic strength. The measure used is computed from the recorded phases and intervals, with locations in the plane corresponding to parameter combinations that produced ratio 1:2, 2:3, 1:1, 3:2, and 2:1 lockings identified and colored gray for the non-ILTP simulations (white regions correspond to non-locked behaviors and lockings at other ratios). The result is a group of 5 vertical *tongues*, "anchored" at the X-axis (zero synaptic strength) at $N/I = p/q$, and broader (occupying a nonzero range of the rate domain) for physiologically meaningful values of synaptic strength. These tongues show that contiguous regions of the parameter plane produced lockings at particular ratios, a familiar result from the periodically-driven pacemaker literature [16].

3.1 ILTP Effects

For any combination of parameters, under pacemaker driving, the ILTP simulation will approach an asymptotic value of synaptic strength after some time. ILTP simulations were performed and the resultant behaviors analyzed within the epochs for which synaptic strength had become acceptably stationary. These simulations were used to locate presynaptic rates which were bifurcation points bounding one of the five locking ratios previously mentioned. Each ILTP simulation is indicated by a '+' in the figure, located at the coordinates corresponding to its presynaptic rate and asymptotic synaptic strength. Parameter settings were combinations of $\mathcal{G} = \{0.01, 0.2575, 0.505, 0.7525, 1.0\}$ and $\gamma = \{1, 25.75, 50.5, 75.25, 100.00\}$; for all, $\bar{P}_{\mathrm{syn,f}} = 5 \times 10^{-6}$cm/s and $\alpha = 0.505$s (see Appendix A for a discussion of model parameters). Simulations corresponding to equal amounts of neurotransmitter release are connected by solid lines.

These preliminary results suggest that, for fixed parameters and presynaptic pacemaker rate, the effects of presynaptic-discharge-only induced ILTP are equivalent to a rotation and scaling of the non-ILTP Arnol'd map, with angle of rotation determined primarily by the amount of neurotransmitter released. In the new coordinate system, widths of locking tongues are increased for simpler ratios above (and including) 1:1. Thus, LTP causes an increase of simple synchronization *in a rate-dependent manner.*

4 Discussion

Understanding the physiological and molecular mechanisms which underly synaptic modification requires an experimental paradigm in which one can reliably induce a potentiating response at desired times and test the results of such potentiation while minimizing disturbance of it. Figure 2(A) illustrates this approach, in which LTP is treated as a binary action produced only by a stereotypical, discrete potentiating stimulus and unaffected by other, test stimuli. This is fine as far as it goes, but it would be unrealistic to expect nervous systems to perform learning as such a discrete behavior. We therefore must be careful not to confuse an experimental setup developed to dissect LTP into understandable parts with the action of LTP *in vivo.*

An alternative approach is taken in the ANN community, shown in (B), where the learning mechanism does indeed receive the same inputs as the neural network and operate while the network is. However, it is typically assumed that the system can be decomposed into two parts: the network (feedforward or recurrent) and the learning method (supervised or unsupervised). Even given this decomposition, network dynamics (including bifurcation behavior) complicate learning algorithm design [17].

Decomposing a dynamical system into independent subparts is a reasonable approximation if a sufficient difference exists among the time constants of these parts. We typically break such a system into two parts: a *slow subsystem* and a *fast subsystem*, though in principle one is not limited to two. From the

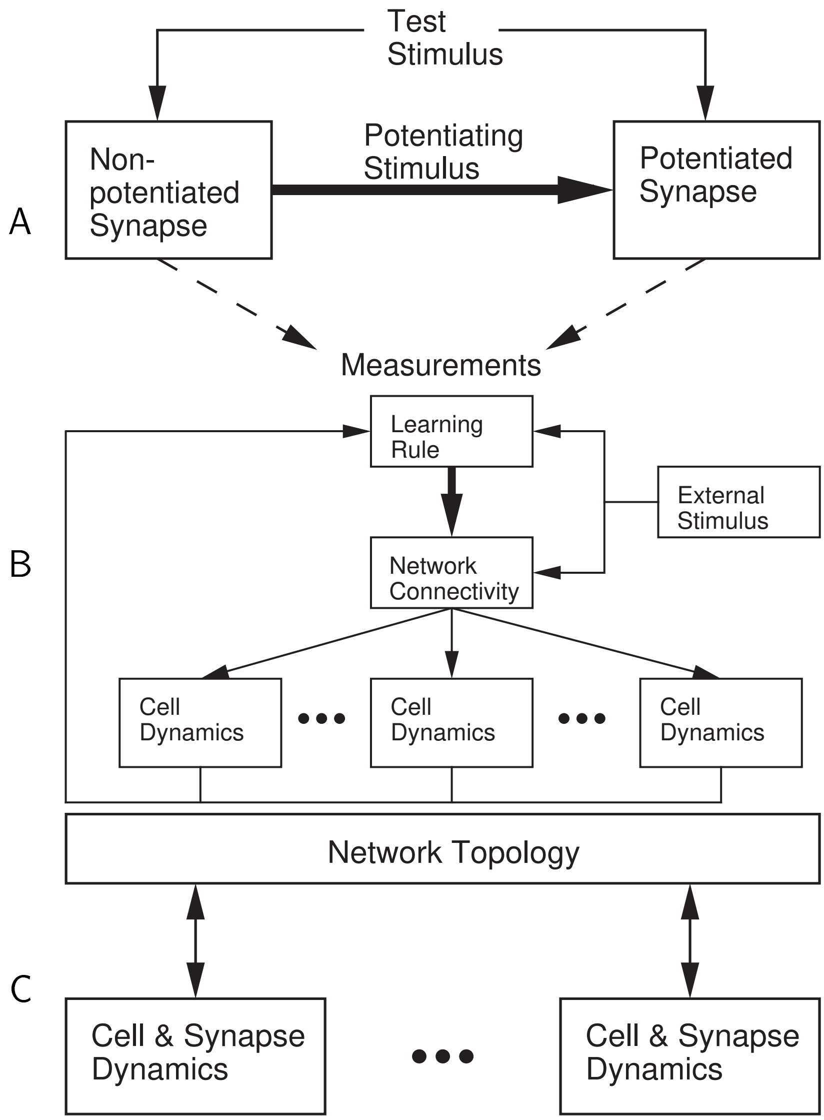

Figure 2: Schematic block diagram showing three approaches to analyzing learning in neural networks: physiological mechanisms (A), ANN (B), and dynamical coding (C).

point of view of the fast subsystem, the slow variables are treated as constants (since over the time scale of change in the fast subsystem, they change little). Decomposing a neural network into a slow learning subsystem and a fast network processing system presupposes that the time scale of change in the learning algorithm is much different than that in the neurons themselves. However, this is not the case in real neurons or physiological models. Table 1 lists typical values for various time constants in our model.

The time that the cell produces its next spike depends not only on the time of arrival of the last IPSP, but also on the times of arrival of a few previous ones, for a length of time which can be considered its dynamical memory. As can be inferred from the table (and from previous results with time-varying inputs [18, 19, 20, 21]), this dynamical memory is at least as long the time constant α associated with ILTP, which is on the order of 2–5 times I. We cannot separate out the ILTP equations as a separate, slow learning subsystem. Instead, we must consider the process of input pattern coding into output pattern via the intact synapse/cell system, as schematized in Figure 2. In this approach, LTP is an inseparable part of coding.

A The Model

A physiological model was modified from the lobster SAO model developed by Edman and collaborators [14, 12]. The lumped membrane model has two voltage-dependent permeabilities, P_{Na} and P_{K}, three leakage permeabilities, $P_{\mathrm{L,Na}}$, $P_{\mathrm{L,K}}$, and $P_{\mathrm{L,Cl}}$, two active pumping pathways, $I_{\mathrm{p,Na}}$ and $I_{\mathrm{p,K}}$, a fixed bias I_{bias}, and the membrane capacitance, C_m, and voltage, V_m. Inputs cause fixed-duration changes in the synaptic permeability, P_{syn}, to Cl^- [22]. Equations (1–5) describe the basics of all currents except the synaptic one, and also their summation to produce variation in the membrane potential, with A the cell membrane area, I_{X} the ionic current for ion X, $\bar{P}_{\mathrm{X}}$ its maximum permeability, F the Faraday constant, R the universal gas constant, T absolute temperature, and m, h, l, n, and r gating variables. The pumping mechanism exchanges 3 Na^+ ions for 2 K^+ in (5), where $\bar{J}_{\mathrm{p,Na}}$ is the maximum Na^+ pump capacity, K_m a constant, and the factor of 1/3 is the net effect of the 3:2 pump ratio.

$$
\begin{aligned}
\frac{dV_m}{dt} &= -(I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{L,Na}} + I_{\mathrm{L,K}} + I_{\mathrm{L,Cl}} + I_{\mathrm{p}} + I_{\mathrm{bias}} + I_{\mathrm{syn}})/C_m && (1)\\
I_{\mathrm{Na}} &= A\bar{P}_{\mathrm{Na}} m^2 hl \frac{V_m F^2}{RT} \frac{[\mathrm{Na}^+]_o - [\mathrm{Na}^+]_i \exp\left(FV_m/RT\right)}{1 - \exp\left(FV_m/RT\right)} && (2)\\
I_{\mathrm{K}} &= A\bar{P}_{\mathrm{K}} n^2 r \frac{V_m F^2}{RT} \frac{[\mathrm{K}^+]_o - [\mathrm{K}^+]_i \exp\left(FV_m/RT\right)}{1 - \exp\left(FV_m/RT\right)} && (3)\\
I_{\mathrm{L,X}} &= AP_{\mathrm{L,X}} \frac{V_m F^2}{RT} \frac{[X]_o - [X]_i \exp(FV_m/RT)}{1 - \exp(FV_m/RT)} && (4)\\
I_{\mathrm{p}} &= \frac{AF}{3} \frac{\bar{J}_{\mathrm{p,Na}}}{\left(1 + \frac{K_m}{[\mathrm{Na}^+]_i}\right)^3} && (5)
\end{aligned}
$$

The synapse contributes current in response to each presynaptic arrival at time s_k according to equations (6–8), after Tsukada and collaborators [23]. In this model, potentiation depends solely on the arrival times of the presynaptic discharge. Each IPSP has associated with it a permeability composed of a fixed part, $\bar{P}_{\mathrm{syn,f}}$, and a modifiable part, $P_{\mathrm{syn,m}}$, that varies based on previous IPSP arrival times. The latter is set to zero for simulations without ILTP; it varies along time for ILTP-inclusive simulations, asymptotically reaching a maximum for pacemaker inputs [13]. ILTP parameters also include a growth rate, γ, amount of transmitter released, $\mathcal{G}$, and a decay time constant, α.

$$
\begin{aligned}
I_{\mathrm{syn}} &= A\frac{V_m F^2}{RT} \frac{[\mathrm{Cl}^-]_o - [\mathrm{Cl}^-]_i \exp(FV_m/RT)}{1 - \exp(FV_m/RT)} \times \sum_{k=1}^{n} P_{\mathrm{syn}}(s_k) \left(e^{(s_k - t)/\tau_+} - e^{(s_k - t)/\tau_-}\right) && (6)\\
P_{\mathrm{syn}}(s_k) &= \bar{P}_{\mathrm{syn,f}} + P_{\mathrm{syn,m}}(s_k) && (7)\\
P_{\mathrm{syn,m}}(s_k) &= \left(1 - \frac{1}{\gamma}\right) P_{\mathrm{syn,m}}(s_{k-1}) + \frac{\mathcal{G}\bar{P}_{\mathrm{syn,f}}}{\gamma} \times \sum_{\ell=0}^{k-1} e^{(s_\ell - s_k)/\alpha} && (8)
\end{aligned}
$$

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