Alternating dominance of NMDA and AMPA for learning and recall: a computer model

Joshua Chover, Lewis B. Haberly[1] and William W. Lytton[2,CA]

Departments of Mathematics and [1]Anatomy, University of Wisconsin; [2]Departments of Physiology/Pharmacology and Neurology, SUNY, Downstate 450 Clarkson Ave., Box 31 Brooklyn, NY 11203, USA

[CA]Corresponding Author

Physiological studies reveal a dichotomy in biological Hebbian learning: NMDA receptors are utilized for induction of long term potentiation (LTP) whereas AMPA is used for LTP expression. We propose that this dichotomy would have functional value: preventing previously stored memories from interfering with the storage of new memories. A previous hypothesis reduces this interference by temporarily reducing associative weights during learning. Complementary to this model, we propose a dual transmission algorithm in which one set of synaptic weights are used primarily for learning and another primarily for recall. This algorithm shows good performance in a simple neural network model. Biologically, the model could be mediated by a cholinergic switch from dominance of learning-insensitive NMDA receptors to dominance of learning-modifiable AMPA receptors. *NeuroReport* 12:2503–2507 © 2001 Lippincott Williams & Wilkins.

Key words: Acetylcholine; Long-term potentiation; Memory; Simulation

INTRODUCTION

The Hebb synapse was described biologically with the discovery of long-term potentiation (LTP), a mechanism whereby coincident pre- and postsynaptic activity produces a long-lasting increase in synaptic efficacy. Although there is considerable diversity in neuronal mechanisms for LTP, a large number of studies have now confirmed that the form originally demonstrated in hippocampus where different glutamate receptors are involved in induction and expression, occurs at most excitatory synapses in the cerebral cortex under appropriate conditions [1,2]. Although both NMDA and AMPA receptors are activated during both induction and expression of this ubiquitous form of LTP, NMDA receptors play the critical permissive role in permitting LTP induction while change in AMPA-mediated excitatory postsynaptic conductances (EPSCs) is the primary outcome [3]. In Hebbian terms, the NMDA-receptor serves as the monitor of pre- and postsynaptic coincidence while AMPA-mediated conductances express the changes in connection strength. In this study we consider the significance of this functional separation in the LTP process in the context of the sparse connectivity of the central nervous system. After the occurrence of learning-related changes, AMPA activation can express the new learned Hebb assemblies, while NMDA activation will maintain the old hardwired assemblies.

In most recurrent neural network algorithms, memory traces are stored without regard to arrival order, since outer-product matrices are either added [4,5] or are determined by extensive training [6]. In biological networks, however, real-life memories arrive consecutively in time, and often must be learned quickly. With such serial presentation, previously constituted sets of preferentially connected neurons (cell assemblies) tend to activate as subsequent patterns are presented, interfering with new learning. One approach that has been shown to reduce this effect involves reduction in synaptic strength during learning, which can be accomplished through presynaptic inhibition by ACh [7,8]. In this paper, we examine the consequences of dual AMPA-NMDA transmission and demonstrate that dual transmission, like presynaptic inhibition, can decrease interference from prior learning. Additionally, dual transmission provides improved performance by making greater use of the sparse connectivity of cortex.

We have previously approached these issues analytically, using information theoretical and probabilistic techniques [9]. We found that these analyses could not easily be extended to address the biological issues we wished to understand. Therefore, we developed a highly simplified bottom-up model which incorporates basic biological features such as sparse connectivity, LTP- and LTD-like synaptic plasticity, and dual transmission capabilities. In order to rapidly run multiple simulations, we use binary units [10]. In this network, we wish to produce learning and recall after only a small number of firing iterations, insufficient for the attractor dynamics typical of the Hopfield network [5]. Thus, although firing coincidences are

registered by increasing synaptic strength, there is no global energy function involved.

MATERIALS AND METHODS

Simulations were done in Mathematica 3.0.1. Figure 1a took ~16 h to run on a Power Macintosh G4 computer. Copies of the simulation program are available from the authors.

A 2000 binary-unit associative processing layer (correlation or C-layer) received projections from a 1000 binary-unit virtual input layer (sensory or S-layer). Each C-layer unit had random non-plastic convergence from 140 S-layer units and random plastic convergence from 160 C-layer units. We assessed values from 100–200 for convergence parameters and obtained similar results. C-layer weights were initialized to 1 before learning; S-C weights were fixed at 2. Both the size of the network and the divergence numbers were varied and gave qualitatively similar results. We can also obtain similar results when we combine S and C layers into a single homogeneous layer. However, the S/C design gives conceptual clarity. It also offers technical advantages by reducing noise during the dot-product identification of the recalled patterns.

Bit patterns of size 100 were learned. Learning involved

feedforward activation from the S-layer to C-layer followed by recurrent activation within the C-layer, for 5–10 iterations. Instead of using a unit update rule, k-winner-take-all (kwta) competition was used to determine unit state. At each iteration, the 85 C-units with the greatest input were set to 1, with all other units set to 0. Use of kwta instead of a threshold selection function allowed us to avoid having to impose explicit inhibition or normalization to prevent runaway firing. Our use of this algorithm as a computational shortcut was validated by replicating the basic functionality of the network using a model using inhibition instead of kwta.

C-layer input was integrated during the 5–10 iterations; these values were used with the kwta competition rule to determine which cells would be active for learning ($a = 1$). For active postsynaptic cells, weights were altered according to the following rule:

$$w = w + \gamma, \quad \text{when} \, a_{pre} = 1 \, (\text{LTP}) \tag{1a}$$

$$w = d \times w + (1 - d) \times q, \quad \text{when} \, a_{pre} = 0 \, \text{and} \, a_{post} = 1 \, (\text{LTD}) \tag{1b}$$

where w = weight; a = activation state; $d = 0.5$; $q = 1$ if $w > 1$, otherwise $q = 0.2$; $\gamma = 5$.

The additive LTP rule of Barkai and Hasselmo [11] was adopted; an LTD rule reduced weights of currently unused synapses while keeping enhanced weights (w_1) above naive level and unenhanced weights still positive.

To compare the effects of suppression via presynaptic *vs* dual-transmission mechanisms, we introduced a suppression parameter s that was varied from 0 (no suppression) to 1 (complete suppression); C-layer weights were temporarily set to w_1 as follows:

$$w_1 = w \times (1 - s) \quad \text{Presynaptic suppression model,} \tag{2a}$$

$$w_1 = w \times (1 - s) + w_{NMDA} \times s \quad \text{Dual transmission model,} \tag{2b}$$

where $w_{NMDA} = 2$ to match the afferent inputs, except for depressed synapses ($w \leqslant 1$) where $w_{NMDA} = 2 \times w$. For a given simulation, the NMDA component of the weight matrix during learning remained unmodified.

During recall, prompts consisted of a portion (35%) of a learned pattern in S plus noise. S-C feedforward activation and subsequent C-C recurrent activation were similar to that during learning but without suppression. Here the kwta algorithm activated 95 C units for firing. No synaptic weight change took place during recall.

Pattern completion was assessed by feeding back the C-layer pattern through the transpose of the S-C matrix (with unused connections deleted), providing a virtual backprojection for each S-C forward projection. This feedback step was used solely for pattern checking and was not part of recall dynamics. The kwta competition rule allowed the 100 units with greatest activation to be set to 1 (125 units for Fig. 2). Activation in the S-layer (the response) was compared using inner product with each known pattern. Recall completion was measured in Fig. 1a and for primary target in Fig. 2 as the largest fraction by which the response overlapped the part of the target pattern not in the prompt, during six iterations of the recall algorithm.

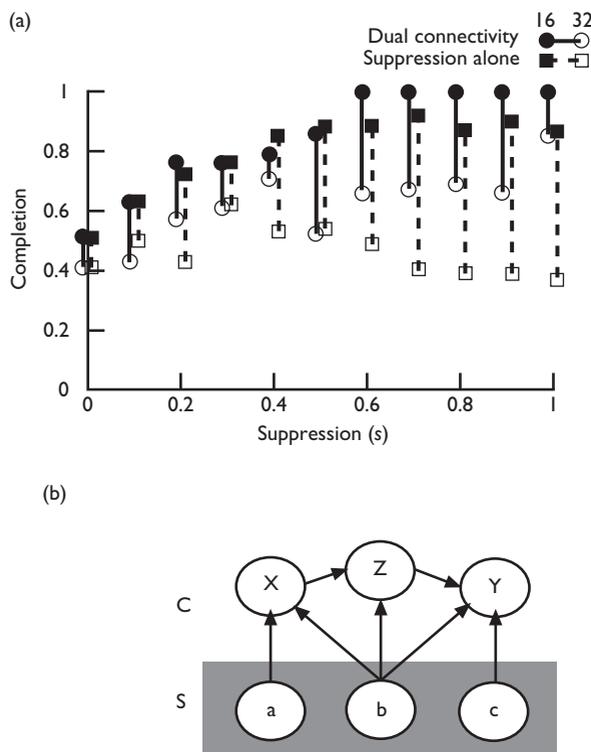The specific parameter choices were selected to have

Fig. 1. (a) Recall of patterns with different degrees of suppression using presynaptic suppression and dual transmission algorithms. Performance dropped off as number of patterns learned was increased from 16 (solid symbols) to 32 (open symbols). Recall was prompted with 35% of an individual pattern plus noise. Results represent averages over four independent prompts. (b) Schematic illustrating additional associative information utilized during learning with the dual transmission algorithm; see text for details.
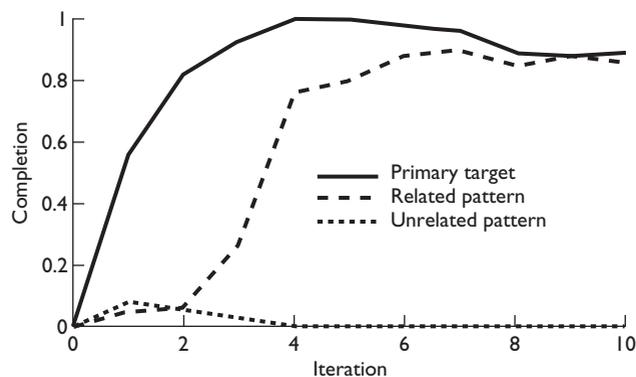
Fig. 2. Recall completion (see Materials and Methods) of patterns at intermediate level of suppression (s = 0.5) using the dual transmission algorithm. 18 patterns were learned of which 10 were paired doublets with 50% homology. Prompting was done using 35% of a primary target that was a member of one of the doublets (plus noise). During 10 iterations of operation of the C network, primary target completion occurred first followed by partial completion of the related pattern. Completion of an unrelated pattern was not significant. (In order to study completion of other patterns, the k-winner-take-all competition in the S-layer was increased to k = 125, as described in Materials and Methods). Completion of a non-primary target was measured as the fraction by which that target overlapped the set of response cells which were neither in the primary target nor in the prompt as noise.

realistic orders of magnitude, comparable to hippocampal observations. These were generally either based on Hasslemo's model [7] or Traub's model [12], on which Hasslemo's model is partially based.

RESULTS

Explorations with the dual transmission algorithm were carried out in a simple neural network model. Biological considerations motivated three major model design specifics that differed from classical cell assembly models such as that of Hopfield [5]. These were (1) sparse random interconnectivity and (2) input from a sensory layer by way of sparse, divergent connections rather than a direct clamping of input onto the processing matrix; and (3) transient dynamics: short learning and recall sessions without relaxation to an attractor.

Our major measure of network function was accuracy in pattern completion. This can be likened to accurate recall following alterations in stimulus prompts, as when faces are recognized despite age-related changes. Secondarily, we assessed network capacity by noting the rate at which accuracy of recall dropped off as new memories were added. We focused on pattern completion since the basic problem with synaptic interference is contamination of learning by recall, strengthening synapses between, rather than just within, cell assemblies. Thus, the interference problem can be viewed as causing crosstalk where cells that are part of pattern A connect to cells that form pattern B, recalling this separate memory as well.

We compared the performance of associative presynaptic suppression alone with the dual transmission algorithm (Fig. 1a). We assessed both models with varying degrees of suppression (s) during learning. In the presynaptic suppression model, the s-parameter reduced all associative connections. In the dual transmission model the s-para-

meter augmented the NMDA connectivity matrix to the same degree as it suppressed the effect of the AMPA connectivity matrix. We incorporated long-term depression (LTD) in both models whereby synaptic strength was weakened when postsynaptic activity was not accompanied by presynaptic activity during learning [13].

Dual transmission improved pattern completion (Fig. 1a). Performance improved with higher s in either model as less crosstalk with other patterns was noted in the recall. Performance declined with increasing numbers of patterns learned, with less drop-off for the dual transmission model.

The performance advantage of dual transmission was consequent to the retention of activity in associative (C-C) pathways during learning. This is important in networks with sparse connectivity because correlations often cannot be recorded directly: coincident activity will not result in local synaptic potentiation if the two cells involved are not anatomically connected. The preservation of active connections during learning in the dual transmission model permitted these correlations to be registered indirectly. Dual transmission selectively increased the degree of transmission via NMDA receptors relative to AMPA receptors, thereby suppressing previously enhanced weights (AMPA suppression) while retaining the efficacy of underlying hardwired associative connectivity (NMDA augmentation). Thus many more routes through the network were active and contributed to learning.

Divergence in connectivity of the sensory (S) net to the correlational (C) net reorganized the input patterns. This allowed the network to compute higher order correlations, as synaptic augmentation reflected input from multiple sensory inputs rather than just from input pairs. This recoding allowed information to be stored via alternate routes when direct correlation storage was not possible due to the lack of a connection between units. Consider the simplified connectivity diagram of Fig. 1b, wherein three sensory (S) units (a-c) project to three correlational (C) units (x-z). A pattern is presented that would activate all of the S-units shown. Assume that activation of two presynaptic units is necessary to reach threshold (determined by competition in our simulations; see Materials and Methods). With preservation of associative wiring between C-units during learning in the dual transmission model, connections from x to y via z are augmented. Note that activation of z by b is required to produce sufficient activation to propagate the activity through the C-layer. Thus the x→z→y connections effectively encode the higher order correlation of the 3 S-units shown. With presynaptic suppression alone, the x→z→y connections are suppressed during learning and z is never sufficiently activated to produce potentiation. With dual transmission, preserved activity mediated by intact intrinsic network connections allows the associational connections to register additional correlation information. Information spread increases the likelihood that correlated activity will coincide with the location of synaptic connections.

Although reducing synaptic interference is generally desirable, limited retention of synaptic interference can actually be helpful for certain learning tasks. Synaptic interference is detrimental for pattern completion because it tends to bring up older memories. However, such

interference can potentially improve the learning of familiar patterns by effectively predicting a pattern through its similarity to other previously learned patterns. Additionally, the resulting overlap in recall, which is generally viewed as undesirable crosstalk, can instead be viewed in a positive light as providing a mechanism for contributing to heteroassociative learning of relationships between different learned patterns. Consequently, there is a trade-off between accurate recall and heteroassociative synthesis that can be controlled by varying the degree of suppression. We explored the ability of our model to demonstrate heteroassociative recall with varying degrees of suppression during learning. As expected, high suppression values did not permit much bleed-over to related patterns. Low suppression, on the other hand, produced competing completion in all directions at once, obscuring specific relationships between patterns. At intermediate values, both the primary target pattern and a related secondary target could be elicited from a prompt made up of a portion of the primary target (Fig. 2). Both presynaptic suppression and dual transmission approaches performed similarly at these intermediate levels of suppression.

DISCUSSION

NMDA receptors participate in learning by producing changes in synaptic strength in response to simultaneous presynaptic activity (glutamate release) and postsynaptic activity (membrane depolarization). The dual transmission hypothesis suggests a second role, that of propagating activity through sparsely connected networks, thereby improving pattern completion and storage capacity. Early studies reported that a selective alteration in AMPA receptors underlies long-term potentiation (LTP) [14,15]; recent studies have revealed conditions and experimental preparations in which alterations occur in NMDA as well as AMPA receptors [16]. These NMDA alterations would modify patterning of activity propagation through intrinsic connections during learning, an additional possibility that remains to be explored.

Since the time courses of NMDA- and AMPA-mediated synaptic conductances differ in cortical neurons [17], an important question is the extent to which a switch from AMPA to NMDA dominance during learning would alter the flow and processing of information in the cortex. Although this issue cannot be resolved from available data, there are many factors that would minimize changes in timing from such a switch during normal brain function: (1) The timecourse of natural stimuli is typically long in comparison to the timecourse of excitatory synaptic processes. (2) Delays of tens to hundreds of milliseconds are introduced by the multisynaptic relays that occur before information reaches most cortical areas. (3) The dendritic placement of most excitatory synapses and the actions of voltage-dependent channels slow the rise times of excitatory inputs to cortical neurons. (4) Inhibitory processes tend to convert excitatory inputs into transient responses, regardless of their durations.

A number of known biological processes could contribute to a switch from AMPA to NMDA dominance during learning. Feedback inhibitory processes maintain neuronal systems in their optimal dynamic range and would be expected to normalize EPSP amplitudes. Therefore, an increase in NMDA conductance during learning, mediated by either direct [18] or indirect [19] processes, would secondarily decrease the effective amplitude of the AMPA component. Of particular interest with regard to our dual transmission hypothesis are the neuromodulatory actions of ACh. ACh would not only decrease interference by suppressing transmitter release [7], but could also have two complementary actions contributing to a shift from AMPA to NMDA dominance: ACh has been shown to produce greater suppression of previously potentiated associational synapses, and to augment NMDA conductance [20].

A key prediction from our dual transmission hypothesis is that increases in NMDA conductance during learning are sufficiently large to not only admit the Ca that triggers changes in synaptic strength, but also to substantially increase the extent to which this conductance generates EPSPs. It can also be proposed that an increase in NMDA dominance resulting, for example, from an alteration in expression or subunit composition [21], would improve memory function not only by increasing the strength of synaptic potentiation, but also by altering network dynamics so as to improve the ability to keep learned patterns distinct from one another.

CONCLUSION

The combinatorics of nervous system transmitters and receptors matching is complex, with synapses featuring multiple transmitters and modulators for the same receptor and multiple receptors for the same transmitter. The dual transmission algorithm offers a preliminary explanation for the common colocalization of AMPA and NMDA glutamatergic receptors, suggesting that dual transmission in this case permits the dual use of synapses in learning and recall. This duality allows information intrinsic to anatomical connectivity to be preserved, while minimizing degradation in learning performance as a result of accumulated alterations in synaptic strength. This would be particularly important in settings where the underlying architecture has meaning. Adaptive, activity-related shaping of afferent and intrinsic axonal connections in cerebral cortex has been well-documented during development, and to a more limited extent throughout life [22,23]. Although it is possible that in some cases neuronal connections are entirely random and pluripotential [24], we regard it as more likely that the connectivity of most networks is crafted to optimize their performance.

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