

2000-01

Frequency-Dependent Synaptic Potentiation, Depression and Spike Timing Induced by Hebbian Pairing in Cortical Pyramidal Neurons

<https://hdl.handle.net/2144/2251>

"Downloaded from OpenBU. Boston University's institutional repository."

**Frequency-dependent synaptic potentiation, depression
and spike timing induced by Hebbian pairing in cortical
pyramidal neurons**

Murat Okatan and Stephen Grossberg

January, 2000

Technical Report CAS/CNS-2000-003

Permission to copy without fee all or part of this material is granted provided that: 1. The copies are not made or distributed for direct commercial advantage; 2. the report title, author, document number, and release date appear, and notice is given that copying is by permission of the BOSTON UNIVERSITY CENTER FOR ADAPTIVE SYSTEMS AND DEPARTMENT OF COGNITIVE AND NEURAL SYSTEMS. To copy otherwise, or to republish, requires a fee and / or special permission.

Copyright © 2000

Boston University Center for Adaptive Systems
and
Department of Cognitive and Neural Systems
677 Beacon Street
Boston, MA 02215

Frequency-Dependent Synaptic Potentiation, Depression, and Spike Timing Induced by Hebbian Pairing in Cortical Pyramidal Neurons

Murat Okatan and Stephen Grossberg

Department of Cognitive and Neural Systems and Center for Adaptive Systems
Boston University, 677 Beacon St, Boston, MA 02215
Phone: (617) 353-7858 or-7857, FAX: (617) 353-7755
E-mail: okatan@cns.bu.edu, steve@bu.edu

January, 2000

Revised: April, 2000

Technical Report CAS/CNS-2000-003

Abbreviated Title: Frequency-dependent synaptic plasticity in cerebral cortex.

Corresponding Author: Stephen Grossberg, Department of Cognitive and Neural Systems and Center for Adaptive Systems, Boston University, 677 Beacon St, Boston MA 02215.

Phone: (617) 353-9481. Fax: (617) 353-7755. e-mail: steve@bu.edu

Acknowledgements: MO and SG were supported in part by the Defense Advanced Research Projects Agency and the Office of Naval Research (ONR N00014-95-1-0409) and the National Science Foundation (NSF IRI-97-20333).

Abstract—Experiments by Markram and Tsodyks (1996) have suggested that Hebbian pairing in cortical pyramidal neurons potentiates or depresses the transmission of a subsequent presynaptic spike train at steady-state depending on whether the spike train is of low frequency or high frequency, respectively. The frequency above which pairing induced a significant decrease in steady-state synaptic efficacy was as low as about 20 Hz and this value depends on such synaptic properties as probability of release and time constant of recovery from short-term synaptic depression. These characteristics of cortical synapses have not yet been fully explained by neural models, notably the decreased steady-state synaptic efficacy at high presynaptic firing rates. This article suggests that this decrease in synaptic efficacy in cortical synapses was not observed at steady-state, but rather during a transition period preceding it whose duration is frequency-dependent. It is shown that the time taken to reach steady-state may be frequency-dependent, and may take considerably longer to occur at high than low frequencies. As a result, the pairing-induced decrease in synaptic efficacy at high presynaptic firing rates helps to localize the firing of the postsynaptic neuron to a short time interval following the onset of high frequency presynaptic spike trains. This effect may "speed up the time scale" in response to high frequency bursts of spikes, and may contribute to rapid synchronization of spike firing across cortical cells that are bound together by associatively learned connections.

Key Words: synaptic potentiation, synaptic depression, frequency-dependent synaptic plasticity, cortical pyramidal cells, Hebbian pairing, cortical synchronization

1. INTRODUCTION

The simple model of a synapse as a frequency-independent gain element has received wide acceptance and provided the basis for several correlation-based theories and neural models of learning and memory. Experimental evidence has accumulated, however, suggesting that synaptic function requires a more complicated model to account for changes in synaptic efficacy such as short-term synaptic depression (STD) and frequency-dependent synaptic potentiation (FDP). STD refers to the use-dependent short-term decrease in synaptic efficacy that results from axonal transmission and synaptic release events. This decrease in efficacy may be due to factors such as decrease in presynaptic action potential (AP) amplitude and transmission failure of APs at axonal branch points during repetitive stimulation (Brody and Yue, 2000), vesicle depletion (Stevens and Tsujimoto, 1995), inactivation of release machinery (Matveev and Wang, 2000) and postsynaptic receptor desensitization (Markram, 1997; Trussell et al., 1993). FDP is a special form of synaptic potentiation that is induced by Hebbian pairing. It has long been assumed that synaptic potentiation increased the amplitude of the postsynaptic signal regardless of the frequency of the inducing presynaptic spike train. However, recent data have reported that Hebbian pairing increased or decreased the amplitude of the postsynaptic signal depending on the frequency of the inducing presynaptic spike train (Markram and Tsodyks, 1996). Specifically, the data suggested that Hebbian pairing potentiated low frequency stimuli and depressed high frequency stimuli. This article offers a possible explanation and quantitative simulations of these surprising data. Henceforth the term FDP will be restricted to this phenomenon.

STD has been studied and characterized for over five decades in several different neuron types and across species (Abbott et al., 1997; Feng, 1941; Galarreta and Hestrin, 1998; Liley and North, 1953; Markram and Tsodyks, 1996; Parnas and Atwood, 1966; Pinsker et al., 1970; Thomson and Deuchars, 1994; Varela et al., 1997), and has been an integral part of some neural models for over four decades (Abbott et al., 1997; Carpenter and Grossberg, 1981; Chance et al., 1998; Francis et al., 1994; Francis and Grossberg, 1996a, 1996b; Grossberg, 1968, 1969, 1972, 1975, 1984; Liley and North, 1953; Markram et al., 1998a, 1998b, 1998c; gmen, 1993; Tsodyks and Markram, 1997; Varela et al., 1997; Wang, 1999). Recently, neural models featuring synapses that exhibit FDP have been proposed (Carpenter, 1994, 1996, 1997). These models preceded the experimental report of FDP by Markram and Tsodyks (1996) and its modeling by Tsodyks and Markram (1997) and Markram et al. (1998a, 1998b, 1998c), and predicted that FDP should be useful for stable learning of distributed codes.

Markram and Tsodyks (1996) suggested that the effects of Hebbian pairing on the amplitude of the excitatory postsynaptic potentials could be characterized at steady-state ($e.p.s.p_{stat}$). Using their experimental results (Figure 1) they noted that "the increase in the amplitude of... $e.p.s.p_{stat}$ for very low-frequency stimulation..., and the lack of an effect on the amplitude of $e.p.s.p_{stat}$ for a high frequency train, indicates that the potentiation is conditional on the presynaptic spike frequency. The effect of pairing on $e.p.s.p_{stat}$ at several different frequencies was therefore examined." They found that "potentiation of synaptic responses... only occurred when the presynaptic frequency was below 20 Hz" (Figure 2c). In support of this finding they also reported that " $e.p.s.p_{stat}$ is not changed in the 40-Hz trace but is increased in the 5-Hz trace" due to pairing (Figure 2a, b).

Tsodyks and Markram (1997) proposed a phenomenological model of STD and FDP, named the TM model by Markram (1997). Using the TM model, Markram et al. (1998b) concluded that the effect of pairing is to selectively regulate low frequency synaptic transmission (Figure 3). Similarly, Markram et al. (1998a) reported that pairing results in a selective change in low-frequency synaptic transmission, leaving high-frequency transmission unaffected.

Contrary to the above interpretations of the Markram and Tsodyks (1996) data and the predictions of the TM model, the decrease below the 100% level apparent in Figure 2c suggests that paired-activity does have an effect on steady-state synaptic efficacy at high frequencies, and this effect is to further decrease it below the 100% baseline level. We suggest that this decrease in synaptic efficacy was observed not at steady-state but during a transition period preceding it. In addition, our analysis proposes that the frequency-dependent decrease in synaptic efficacy induced by Hebbian pairing may help to localize the firing of the postsynaptic neuron to a short time interval following the onset of high frequency presynaptic spike trains. This localization of firing may help the system to speed up its processing rate under high-frequency conditions. In some neural systems, such as the transduction of light by turtle cones (Baylor, Hodgkin, and Lamb, 1974a, 1974b; Carpenter and Grossberg, 1981), and the rate of key pecking in pigeons (Grossberg and Schmajuk, 1989; Wilkie, 1987), increasing stimulus intensity is observed to speed up the time scale of neural activity and also to time-localize it. Our results suggest that an increase in the level of learning has similar temporal effects in the activity of cortical neurons. We also explain why the TM model prediction in Figure 3, which shows no frequency-dependent decrease below the 100% baseline, differs from the data in Figure 2c. In particular, we show that the time taken to reach steady-state in these systems may also be frequency-dependent. Unless one compensates for this frequency-dependent settling time, important cellular properties, such as frequency-dependent depression, may not be correctly understood.

2. MATERIALS AND METHODS

2.1 STD Experiment

Markram and Tsodyks (1996) characterized STD in fast-depressing excitatory synapses between tufted pyramidal neurons in somatosensory cortical layer 5 of the rat (named TL5 neurons in Markram, 1997). Their results are illustrated in Figure 1. In this experiment they induced a presynaptic TL5 neuron to fire an AP by injecting a 2 nA, 5 ms current pulse into its soma. They administered seven such injections at 23 Hz in each stimulus sweep. A new sweep was started every 5 s. The postsynaptic membrane potential trace (Post V_m) before pairing reflects the average of 58 sweeps and the one after pairing reflects the average of 59 sweeps in the same synaptic connection (Figure 1a).

The pairing method consisted of injecting sustained current pulses of 200 ms duration into visually identified individual presynaptic and postsynaptic TL5 neurons. The current intensity was adjusted to evoke 4—8 spikes and the current pulse in the postsynaptic neuron was delayed (1—5ms) to ensure that the postsynaptic neuron discharged after onset of synaptic input. No attempt was made to control subsequent spikes. The procedure was repeated 30 times every 20 s.

The effect of paired-activity on e.p.s.p amplitudes is illustrated in Figure 1b, where the e.p.s.p amplitudes measured from Figure 1a are plotted. e.p.s.p amplitudes were measured from the voltage immediately before the onset of the e.p.s.p to the peak of the e.p.s.p. Markram and Tsodyks (1996) noted that the presynaptic train of action potentials results in depression of the synaptic response, until a stationary level of e.p.s.p amplitude is reached (defined here as e.p.s.p_{stat}). This definition of e.p.s.p_{stat} implies that it is used to denote the steady-state e.p.s.p amplitude. The e.p.s.p_{stat} was computed as the average of the last 20% of the single exponential fit to the e.p.s.p amplitudes in Figure 1b, and was roughly equivalent to the average of the last 2 e.p.s.ps. (Markram and Tsodyks, 1996). In these responses, Markram and Tsodyks (1996) also distinguished the initial and the transition e.p.s.ps. They noted that ...whereas the amplitude of e.p.s.p_{init} was increased... the average amplitude of e.p.s.p_{stat} was unaffected. In Figure 1b, the amplitude of the transition e.p.s.ps decreases due to pairing. Based on these results they concluded that the effect reported here is not an unconditional potentiation of the efficacy of the synaptic connection; instead, it is a redistribution of the existing efficacy between spikes in a train. Figure 1c illustrates the effect of Ca²⁺ concentration on the differential effect of pairing on the initial and the stationary e.p.s.ps.

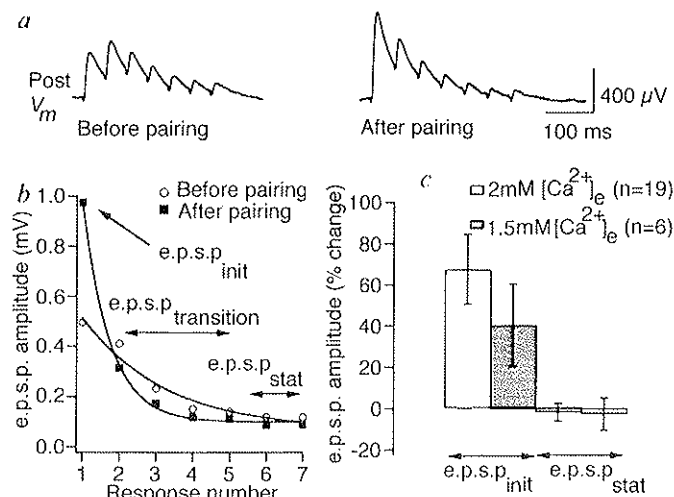


Figure 1. The effect of pairing on postsynaptic responses elicited by 23 Hz test stimuli consisting of seven APs. (a) The average postsynaptic membrane potential (Post V_m) is obtained as the mean of 58 sweeps before pairing (left) and 59 sweeps 20 min after pairing. (b) The amplitudes of the e.p.s.ps in (a) are plotted. The amplitude of an e.p.s.p was computed as the difference between the membrane potential at the peak of an e.p.s.p and the membrane potential at the onset of that e.p.s.p. Fitted curves are single exponentials. The average value of the last 20% of the fitted curves, which was roughly equal to the average of the sixth and seventh e.p.s.p amplitudes, was used as the stationary e.p.s.p amplitude (e.p.s.p_{stat}). Pairing increased the amplitude of the initial e.p.s.p (e.p.s.p_{init}), decreased those of the transition e.p.s.ps (e.p.s.p_{transition}) and left e.p.s.p_{stat} unaffected. (c) Pairing increases the amplitude of the initial e.p.s.p while leaving e.p.s.p_{stat} unaffected, both at experimental level of extracellular Ca²⁺ concentration (2 mM) and at the physiological level for a rat of this age (1.5 mM). (Reprinted with permission from Markram and Tsodyks, 1996).

Based on these results, Markram and Tsodyks (1996) stated that the increase in the amplitude of e.p.s.p_{init}, which actually represents e.p.s.p_{stat} for very low-frequency stimulation (<0.25 Hz), and the lack of an effect on the amplitude of e.p.s.p_{stat} for a high-frequency train, indicates that the potentiation is conditional on the presynaptic spike frequency. The effect of

pairing on $e.p.s.p_{stat}$ at several different frequencies was therefore examined. The next section describes this experiment.

2.2 FDP Experiment

The results of the Markram and Tsodyks (1996) experiment that characterized FDP in TL5 neurons are illustrated in Figure 2.

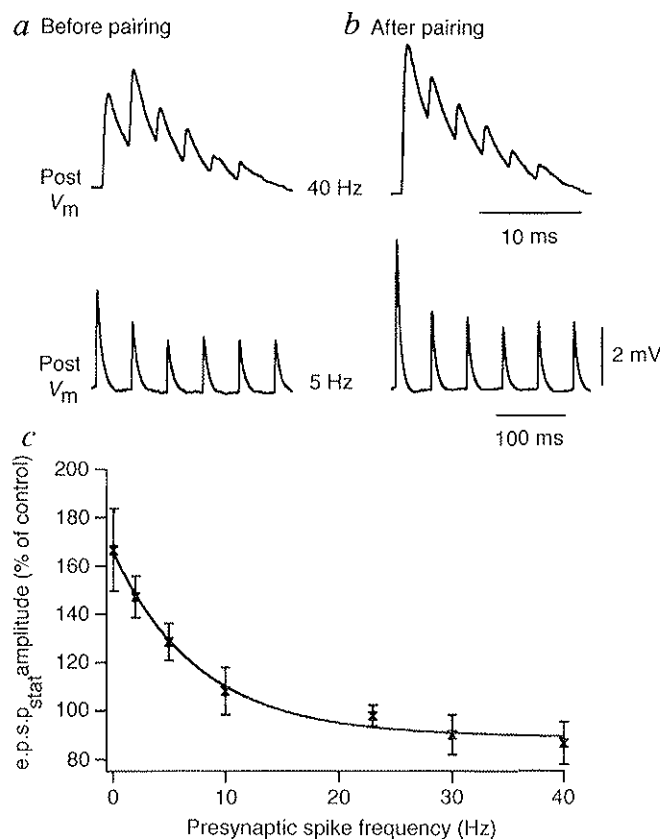


Figure 2. Frequency-dependence of synaptic potentiation in Markram and Tsodyks (1996). The average postsynaptic membrane potential (Post V_m) traces were elicited by using presynaptic spike trains consisting of six APs at 5 Hz and 40 Hz, before (a) and after (b) paired-activity to assess the induced changes in synaptic efficacy. (c) After paired-activity, $e.p.s.p_{stat}$ (See *STD Experiment* in Materials and Methods) is plotted as a function of test frequency. Control refers to the pre-pairing value of $e.p.s.p_{stat}$. Superimposed is a single exponential fit (Henry Markram, personal communication). Data were collected from 33 synaptic connections (1–4 frequencies tested per connection). The leftmost data point represents the average of measurements obtained at 0.067 Hz and 0.25 Hz. All other data points were collected at a single test frequency. Note that pairing increased $e.p.s.p_{stat}$ at low frequencies but decreased it at high frequencies. The article proposes an explanation for this decrease below. (Reprinted with permission from Markram and Tsodyks, 1996).

In this experiment, they elicited e.p.s.ps using the same procedure as in the STD experiment, but at several different firing rates ranging from 0.067 Hz to 40 Hz. At all frequencies, they used trains of six APs as test stimuli. Figure 2a shows the postsynaptic potential traces elicited by stimuli of 40 Hz and 5 Hz. Figure 2b shows these traces after pairing. They noted that $e.p.s.p_{init}$ is increased to the same extent for both frequencies, $e.p.s.p_{stat}$ is not changed in the 40-Hz trace but is increased in the 5-Hz trace (compare for example the amplitude of the last 2 e.p.s.ps in the

40-Hz train before and after pairing). Markram and Tsodyks (1996) summarized the change in e.p.s.p_{stat} by computing the ratio of the post-pairing e.p.s.p_{stat} to the pre-pairing e.p.s.p_{stat} at different test frequencies. This ratio is plotted as a function of test frequency in Figure 2c, where the fitted curve is a single exponential (Henry Markram, personal communication). Based on the results shown in Figure 2, they concluded that in the same neuron, e.p.s.p_{init} was found to increase equally for low- and high-frequency trains, whereas e.p.s.p_{stat} was increased only when the frequency was low (Fig. 3a, b; *here Figure 2a, b*). Potentiation of synaptic responses therefore only occurred when the presynaptic frequency was below 20 Hz (Fig. 3c; *here Figure 2c*). They also noted that the physiological implications of redistribution of synaptic efficacy are also entirely different from unconditional potentiation or depression and are partly predicted by the frequency-dependent potentiation seen in Fig.3 (*here Figure 2*). Unlike Figure 1b which shows the data collected from a single synapse, Figure 2c represents the average data obtained from 33 synaptic connections (1—4 frequencies tested per synaptic connection). Note that the e.p.s.p amplitudes corresponding to the 7th response number in Figure 1b would yield an amplitude ratio comparable to the data point shown at 23 Hz in Figure 2c, where pairing-induced decrease in synaptic efficacy below the 100% baseline at high-frequencies is not yet noticeable.

2.3 The TM Model

The TM model, which was proposed by Tsodyks and Markram (1997) and further developed in Markram et al. (1998a, 1998b, 1998c) is a phenomenological model of short-term synaptic plasticity. It applies to both facilitating excitatory synapses from TL5 neurons to bipolar inhibitory interneurons, and to the fast-depressing excitatory synapses between TL5 neurons. It can be used to compute the amplitude of the e.p.s.ps elicited by an arbitrary presynaptic spike train (Tsodyks and Markram, 1997). The equations describing this model in Markram et al. (1998b) are:

$$E_n = A \cdot u_n \cdot R_n, \quad (1)$$

$$u_{n+1} = u_n e^{-\frac{\Delta t}{\tau_{\text{facil}}}} + U \left(1 - u_n e^{-\frac{\Delta t}{\tau_{\text{facil}}}} \right), \quad (2)$$

$$R_{n+1} = R_n (1 - u_{n+1}) e^{-\frac{\Delta t}{\tau_{\text{rec}}}} + 1 - e^{-\frac{\Delta t}{\tau_{\text{rec}}}}. \quad (3)$$

In (1) E_n is the amplitude of the n^{th} e.p.s.p averaged across trials, where the subscript n corresponds to the response number shown in the abscissa of Figure 1b. Function u_n in (1)—(3) denotes the running value of the utilization of synaptic efficacy. Its minimum value is U , and it is transiently elevated following each AP. It then decays to U with the facilitation time constant τ_{facil} . Function R_n in (1) and (3) denotes the fraction of available synaptic efficacy immediately before the n^{th} AP. It is temporarily decreased after each AP and it converges to its maximum value of 1 with recovery time constant τ_{rec} . Parameter A is the absolute synaptic efficacy and denotes the maximal e.p.s.p amplitude that is obtained when R and U are each equal to 1. Δt is the interspike interval and is equal to the inverse of the firing rate for constant frequency stimuli. Markram et al. (1998b) note that synaptic connections displaying depression are characterized by negligible values of τ_{facil} [*3 ms in Tsodyks and Markram (1997)*] and hence $u_n = U$.

Consequently, $u_n = U$ in (1)—(3) for depressing synapses. In short, the equations describing STD in the TM model are:

$$E_n = A \cdot U \cdot R_n, \quad (4)$$

$$R_{n+1} = R_n(1 - U)e^{-\frac{\Delta t}{\tau_{rec}}} + 1 - e^{-\frac{\Delta t}{\tau_{rec}}}. \quad (5)$$

Markram et al. (1998b) proposed that U represents the probability of transmitter release. In their model, the effect of paired-activity is simulated by raising the value of U . U is constrained to lie in $[0, 1]$ and is kept constant during presynaptic activity alone. Markram et al. (1998b) used this hypothesis to simulate FDP. Their prediction for FDP at steady-state is illustrated in Figure 3.

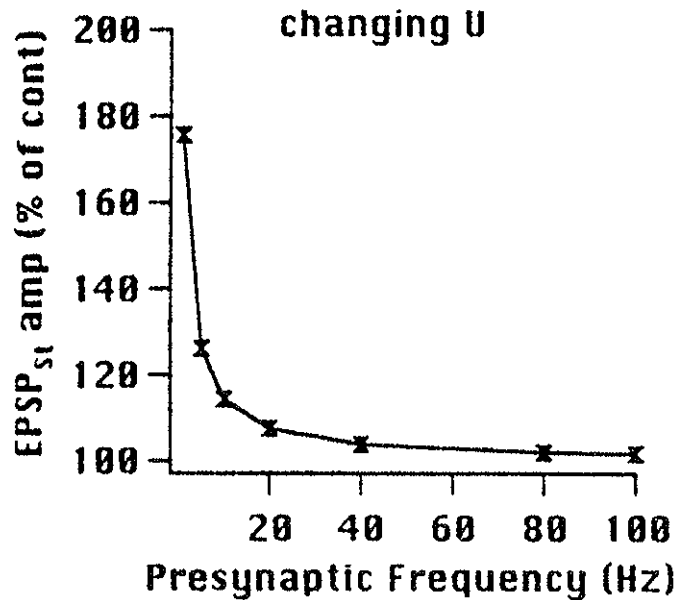


Figure 3. Frequency-dependence of synaptic potentiation predicted by the TM model at theoretical steady-state. Markram et al. (1998b) used the TM model to simulate frequency-dependence of synaptic potentiation (Markram and Tsodyks, 1996). In the TM model of STD (Equations (4)—(5)) the effect of pairing is simulated by increasing the value of the parameter U , which is proposed to represent the probability of release. Here, the steady-state e.p.s.p amplitude (EPSP_{st} amp) is computed using a test stimulus of infinite duration ($n \rightarrow \infty$ in Equation (6)), before ($U = 0.4$, control) and after ($U = 0.8$) pairing. The post-to-pre ratio of EPSP_{st} amplitude is plotted as a function of the test stimulus frequency. The frequency-dependence of this ratio is different from the experimentally determined dependence shown in Figure 2c since it does not exhibit the decrease below the 100% level at high presynaptic firing rates. $A = 1$ and $\tau_{rec} = 800$ ms in Equations (4)—(5). (Reprinted with permission from Markram et al., 1998b).

Based on Figure 3, Markram et al. (1998b) stated that The phenomenon produced when Pr changes is readily distinguished from virtually all other types of synaptic changes since changing Pr is a mechanism to selectively regulate low frequency synaptic transmission. Here, Pr means probability of release, which is denoted by U in Equations (4)—(5) and other types of synaptic changes include changes in the absolute synaptic efficacy, A , or the recovery time constant, τ_{rec} . Also, Markram et al. (1998a) noted that ...changes in U ... result in changes in the frequency dependence of transmission, also referred to as redistribution of synaptic efficacy (Markram & Tsodyks, 1996). Specifically, changing U results in a selective change in low-frequency synaptic transmission, leaving high-frequency transmission unaffected.

Figure 3

To simplify the computation of the trial-averaged e.p.s.p amplitude E_n at a given response number, a non-iterative expression for E_n was obtained from the iterative equations in (4) and (5) (see Appendix):

$$E_n = \frac{AU}{1-\Lambda} \left[1 - \Lambda^n - (1 - \Lambda^{n-1}) e^{-\frac{\Delta t}{\tau_{\text{rec}}}} \right], \quad (6)$$

where

$$\Lambda = (1-U) e^{-\frac{\Delta t}{\tau_{\text{rec}}}}. \quad (7)$$

We used Equations (6) and (7) to simulate the STD and FDP data of Markram and Tsodyks (1996) and to explain the pairing-induced decrease in synaptic efficacy below the 100% baseline in Figure 2c. Below we describe the computational procedures employed to fit the data. The implications of the fits are explained in the Results section.

2.4 Determination of Parameter Values

STD data We determined the optimal parameter values in (6)–(7) by minimizing the root-mean-squared-error (rmse) from the data:

$$\varepsilon = \sqrt{\frac{1}{N} \sum_{n=1}^N \varepsilon_n^2}, \quad (8)$$

where ε_n denotes the difference between $E_{n\text{-experiment}}$ and $E_{n\text{-predicted}}$. The parameters that minimize (8) can be determined by generating the error surface $\varepsilon(U, \tau_{\text{rec}})$ and finding its global minimum.

For the STD experiment, $E_{n\text{-experiment}}$ is measured from Figure 1b for each of the seven e.p.s.ps before and after pairing. The pre-pairing and post-pairing data are pooled to compute the rmse in (8). To remove the dependency on A in Equation (6), all e.p.s.ps are then divided by the amplitude of the initial e.p.s.p measured after pairing. According to the TM model, $E_1 = AU$, as can be obtained from Equation (6). Thus, the ratio of the initial e.p.s.p amplitudes after and before pairing yields the ratio of the after pairing to before pairing values of U . This ratio is computed to be 1.956 in Figure 1b, and constrains the parameter search.

Markram (1997) reported that the values of U and τ_{rec} were observed to lie in the ranges 0.5 s—1.5s and 0.1—0.95, respectively. Equation (6) is used to compute the error surface for values of τ_{rec} ranging from 0.2 s to 2 s with steps of 10 ms, and with U in the range from 0.1 to 0.95 with steps of 0.01. The global minimum of $\varepsilon(U, \tau_{\text{rec}})$ was found in the region of the parameter space defined by these ranges. The optimal parameters and fits are shown in the Results section.

FDP data The experimentally determined amplitude ratios that characterize FDP can be measured from Figure 2c. Since the test stimuli consisted of only six APs at each test frequency and since $e.p.s.p_{\text{stat}}$ was roughly equivalent to the average of the sixth and seventh e.p.s.ps in Figure 1b, in the current article the simulated amplitude ratios were computed based on the amplitude of the sixth e.p.s.p. Thus, Equation (6) was used to compute $E_6(U_{\text{post}}, \tau_{\text{rec}})/E_6(U_{\text{pre}}, \tau_{\text{rec}})$ at each test frequency and the root-mean-squared-error from the experimental data of Figure

2c was computed. Markram and Tsodyks (1996) reported that the leftmost data point in Figure 2c represents the average measurement from two different low-frequency test stimuli at 0.067 Hz and 0.25 Hz. All other data points were measured at a single test frequency. Accordingly, the simulated leftmost data point was computed as the average of the e.p.s.p ratios computed at 0.067 Hz and 0.25 Hz.

As discussed in the previous section, according to the TM model, the amplitude ratio at the initial e.p.s.p reflects the ratio of the post-pairing to pre-pairing values of U . At very low frequencies, the synapse recovers almost completely between consecutive spikes and thus the amplitude of the sixth e.p.s.p can be considered equal to that of the initial e.p.s.p. Thus the amplitude ratio at the sixth e.p.s.p also reflects the ratio of the post-pairing to pre-pairing values of U at very low firing rates. Markram and Tsodyks (1996) reported that this ratio is found to be 1.665 in Figure 2c. This ratio constrains the parameter search, as in the previous section.

3. RESULTS

3.1 Optimal parameters and fits

STD data We have conducted an exhaustive search, as described in the Methods section, to find the optimal parameters in the physiologically plausible intervals for U and τ_{rec} . This method differs from the method of Markram et al. (1998b) who iteratively changed the model parameters A , U , and τ_{rec} , to minimize Equation (8). Although different optimal parameter values may be found by the two methods, this does not affect any of our conclusions about the impact of Hebbian pairing on synaptic transmission at high frequencies.

The parameter search revealed that a global minimum exists at the point $(U_{pre}, \tau_{rec}) = (0.363, 0.65 \text{ s})$. The post-pairing value of U is found to be $0.71 = 0.363 \times 1.956$. These parameter values lie in the range of experimentally observed values reported by Markram (1997). The curves in Figure 4 illustrate the prediction of the TM model using the optimal parameters. The data points represent the experimentally determined e.p.s.p amplitudes measured from Figure 1b and normalized to the post-pairing amplitude of the initial e.p.s.p.

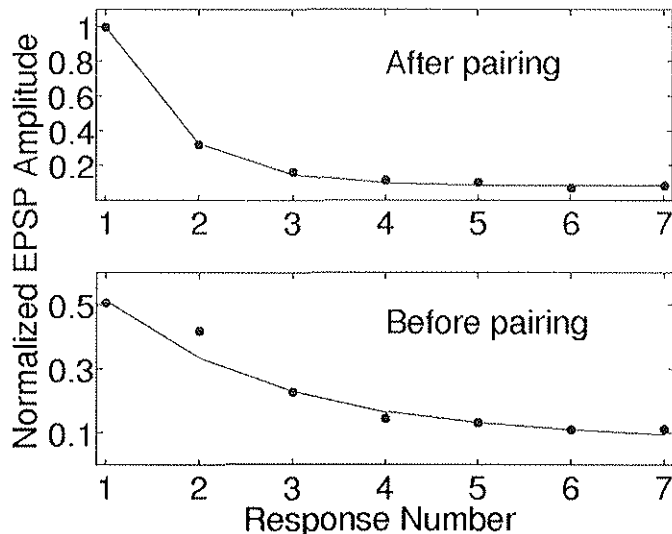


Figure 4. Simulation of short-term synaptic depression using the TM model. The mean-squared-error between the TM model's prediction and the experimental data provided in Figure 1b was at a global minimum for the parameter values $U = 0.363$ and $\tau_{rec} = 0.65 \text{ s}$. The curves in the top and bottom panels illustrate the simulation results using these parameter values. The data points represent the experimental results shown in Figure 1b after normalization to the post-pairing amplitude of the initial e.p.s.p.

FDP data The analysis revealed that there is one global minimum and one local minimum in the domain defined by the intervals $[0.1, 0.95]$ for U and $[0.2 \text{ s}, 2 \text{ s}]$ for τ_{rec} . The global minimum was found at the point $(U_{\text{pre}}, \tau_{\text{rec}}) = (0.18, 0.87 \text{ s})$ and the local minimum was found at $(U_{\text{pre}}, \tau_{\text{rec}}) = (0.5, 0.44 \text{ s})$. As mentioned before, the data in Figure 2c were collected from 33 synaptic connections (1—4 frequencies tested per connection). Thus the optimal values of U and τ_{rec} do not necessarily belong to any particular synapse. The rmse at the local minimum was 17% larger than the one at the global minimum. In either case, the post-pairing value of U is obtained by multiplying the pre-pairing value by 1.665. The globally optimal parameter values lie in the range reported by Markram (1997). But the locally optimal value of 0.44 s is slightly smaller than the lower bound of 0.5 s of the range of observed values of τ_{rec} .

The curve in Figure 5 illustrates the prediction of the TM model using the globally optimal parameter set. The data points and error bars represent the experimental results that are measured from Figure 2c.

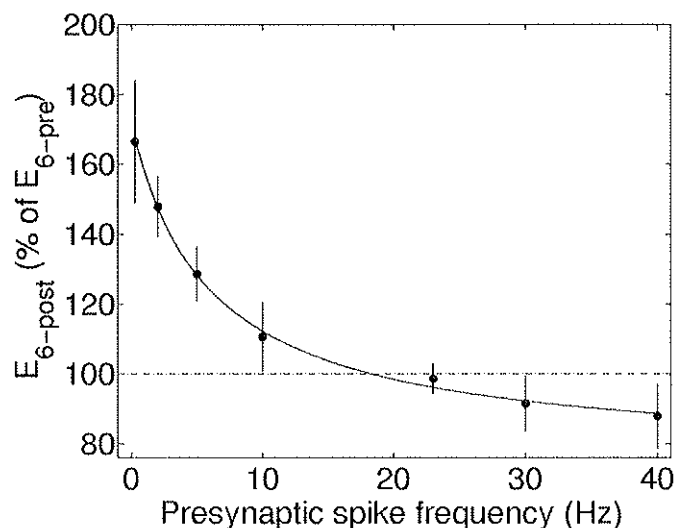


Figure 5. Simulation of frequency-dependent synaptic plasticity using the TM model. The mean-squared-error between the TM model's prediction and the experimental data provided in Figure 2c was at a global minimum for the parameter values $U = 0.18$ and $\tau_{\text{rec}} = 0.87 \text{ s}$. The curve represents the TM model's prediction using these parameter values and it shows the post-pairing amplitude of the sixth e.p.s.p ($E_{6\text{-post}}$) in percents of the pre-pairing amplitude of the sixth e.p.s.p ($E_{6\text{-pre}}$). The data points and the error bars were measured from Figure 2c. The simulation fits the experimental results successfully and predicts the pairing-induced decrease apparent at high-frequencies. E_6 is computed using Equation (6).

3.2 Computing e.p.s.p ratios at the sixth e.p.s.p explains pairing-induced decrease in synaptic efficacy

How can the discrepancy be explained between the high-frequency depression that is shown in the data of Figure 2c (Markram and Tsodyks, 1996) and the theoretical curve of Markram et al. (1998b) that is shown in Figure 3, which does not include this depression? In Figure 2c, Markram and Tsodyks (1996) estimated $e.p.s.p_{\text{stat}}$ from the sixth e.p.s.p in the data; see the Methods section for the details. However, to derive the curve in Figure 3, Markram et al. (1998b) estimated this value using the theoretical steady-state, which they derived by letting $n \rightarrow \infty$ in Equation (6). By so doing, Markram et al. (1998b) assumed that the steady-state was essentially

reached by the 6th e.p.s.p in Figure 2. It is, however, shown below that the theoretical steady state is *not* achieved at the 6th spike at *high frequencies*. In fact, as frequency increases, it takes more and more spikes for the theoretical steady-state to be reached. On the other hand, if one computes Figure 5 directly from Equation (6), evaluated at the 6th spike, rather than as $n \rightarrow \infty$, then the pairing-induced decrease in synaptic efficacy that is seen in the data above 20 Hz is predicted by the TM model.

The fact that more spikes are needed to reach the steady-state at high frequencies can be shown by using Equation (6) to determine the minimum number of APs that is needed for the e.p.s.p amplitudes to reach a criterion fraction of the theoretical steady-state level. Since E_n converges to the steady-state level from above as $n \rightarrow \infty$ in Equation (6), the smallest number n for which E_n/E_∞ is less than or equal to the criterion fraction must be found. For the synaptic parameters used in Figure 5, this number is shown as a function of test frequency in Figure 6 for an arbitrarily chosen criterion fraction of 105%.

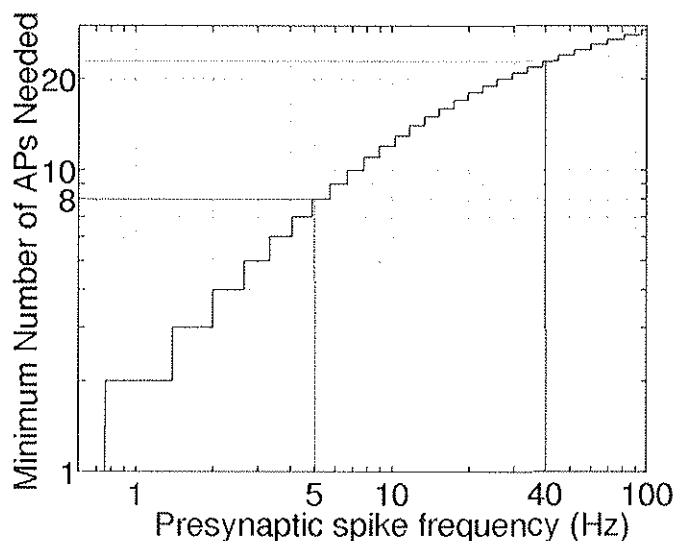


Figure 6. Minimum number of action potentials needed for the e.p.s.p amplitude to reach a criterion fraction of the theoretical steady-state level. Equation (6) is used to compute the minimum value of the response number n at which E_n enters the range $[1.05E_\infty, E_\infty]$. The criterion fraction of 105% was chosen arbitrarily. E_∞ denotes the e.p.s.p amplitude at theoretical steady-state. E_n converges to E_∞ from above. n is seen to increase with presynaptic spike frequency. The curve shows that for the synaptic parameters used in Figure 5, $n = 8$ at 5 Hz and $n = 23$ at 40 Hz.

According to Figure 6, for these values of U and τ_{rec} , it takes at least eight APs for the e.p.s.p amplitude to be less than or equal to 105% of the theoretical-steady state level at 5 Hz, while this number is 23 at 40 Hz. Thus, if test stimuli consisting of a constant number of APs are used at different test frequencies, changes in synaptic efficacy may be compared at different phases of the postsynaptic response, unless a test stimulus of very long duration is used. Note that in Figure 2c, stimuli of six APs were used at all firing rates, which apparently was not enough to reach the steady-state at high frequencies.

3.3 Pairing-induced decrease in synaptic efficacy is a significant synaptic property

The previous section suggested that a common ground to compare synaptic responses of different frequencies may be to compare e.p.s.p amplitudes that are within a criterion fraction of the theoretical steady-state level. As shown in Figure 6, however, the test stimuli need to be longer at high frequencies for the e.p.s.p amplitude to reach a criterion level. The required stimulus duration may even be longer than the duration of a physiological spike train of a given frequency at high firing rates. In such a case, the frequency of the presynaptic firing might change before the postsynaptic response has reached the criterion-level. In other words steady-state may not be a functionally relevant phase at high frequencies. This fact was also pointed out by Markram and Tsodyks (1996): Under *in vivo* conditions, neurons tend to discharge irregularly, which effectively represents a multitude of spike frequencies persisting for different time periods, indicating that the effect of pairing on synaptic input generated by an irregular presynaptic spike train would be complex if redistribution of synaptic efficacy was to occur (Fig. 4; *not shown here*). The effect cannot be predicted as most synaptic responses during such a train have not reached a stationary level for the given frequency and hence are all transition e.p.s.ps (see Fig. 2b; *here Figure 1b*). As discussed, transition e.p.s.ps could be enhanced, depressed or unchanged after pairing. Redistribution of synaptic efficacy may therefore serve as a powerful mechanism to alter the dynamics of synaptic transmission in subtle ways and hence to alter the content rather than the gain of signals conveyed between neurons.

The effect of pairing may be studied not at a particular criterion level but as a function of stimulus duration. Figure 7 illustrates FDP as a function of both stimulus duration in number of APs and stimulus frequency, for the synaptic parameters used in Figure 5.

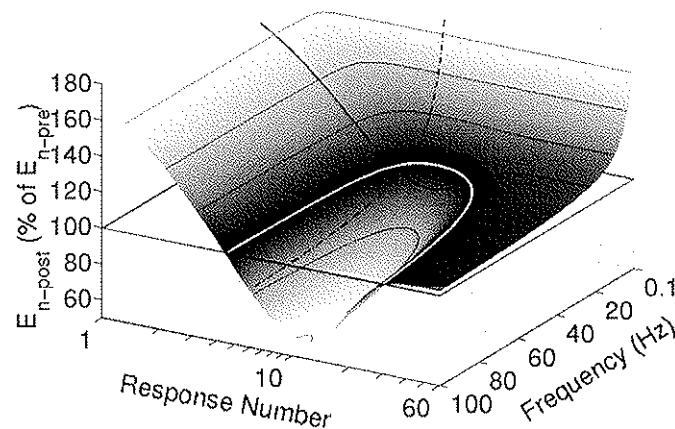


Figure 7. Dependence of pairing-induced changes in synaptic efficacy on test stimulus frequency and response number. The ratio of post-pairing to pre-pairing values of E_n (Equation (6)) is shown for response number $n = 1-60$ and test frequencies of 0.1 Hz to 100 Hz for the synaptic parameter values used in Figure 5. The black contour lines denote the 60%-160% levels in steps of 20%. The white contour line denotes the 100% level. The dashed line at $n = 6$ is the TM model's prediction shown in Figure 5. The solid line illustrates the dependence of the ratio on response number at $F = 23$ Hz. Around 20 Hz, the ratio passes through the 100% level at the sixth AP. At higher frequencies, this transition occurs at earlier response numbers, thereby causing the ratio to be lower than 100% at the sixth AP.

Figure 7 shows that redistribution of synaptic efficacy (RSE) translates into a prominent decrease in synaptic efficacy that sets in soon after the onset of moderate to high frequency spike trains. The white contour line denotes the 100% level on the surface. The decreased efficacy lasts for 9 APs (~ 390 ms), 17 APs (~ 420 ms) and 27 APs (~ 270 ms) at 23 Hz, 40 Hz and 100 Hz, respectively. Note that at the end of trains of 60 APs, the frequency-dependence of synaptic potentiation has the same form as in Figure 3. This is because the postsynaptic response is close to theoretical-steady state level at all frequencies by the 60th AP. The continuous curve at 23 Hz illustrates the e.p.s.p ratios at that frequency. The dashed curve at response number $n = 6$ is the curve shown in Figure 5. Note that it enters the region of decreased efficacy at about 20 Hz.

In addition to lasting long, pairing-induced decrease in synaptic efficacy may also reach significant levels. For instance, pairing decreases the amplitude of the 11th e.p.s.p to 58% of the pre-pairing level at 100 Hz. The timing and extent of the decrease in efficacy is seen to depend on the presynaptic firing rate. It also depends on the parameters U and τ_{rec} . Figures 8 and 9 illustrate this dependence at 40 Hz while the ratio $U_{\text{post}}/U_{\text{pre}}$ is held constant at 1.665.

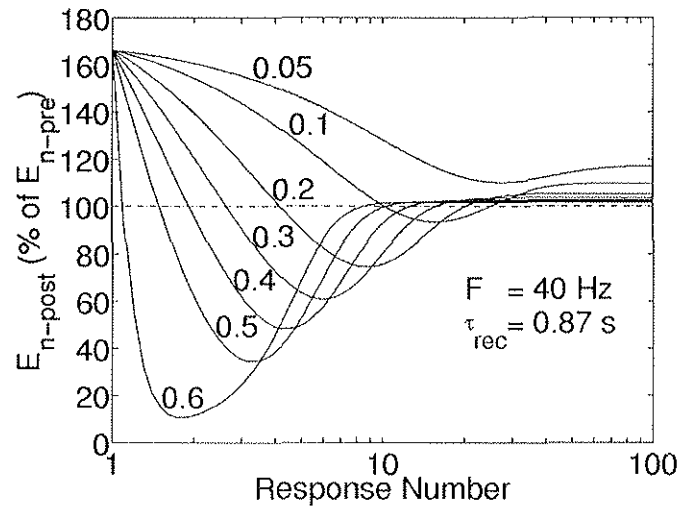


Figure 8. Dependence of pairing-induced changes in synaptic efficacy on the pre-pairing value of the parameter U . The ratio $E_{n\text{-post}}/E_{n\text{-pre}}$ (%) was computed using Equation (6) at 40 Hz for different pre-pairing values of the parameter U . These values are shown next to the corresponding curves. $\tau_{\text{rec}} = 0.87$ s and $U_{\text{post}}/U_{\text{pre}} = 1.665$ for each curve.

It can be seen in Figure 8 that the same proportional increase in U results in a larger decrease in efficacy that also sets in sooner and lasts longer if the pre-pairing value of U is high. However, pairing induces a less defined decrease in efficacy or no decrease at all in synapses with very low release probability to begin with. It should be noted that the same amount of pairing may result in different increases in U depending on the pre-pairing value of the latter. In other words, a given amount of pairing results in an increase in U that is dependent on U_{pre} . Thus, Figure 8 does not characterize the effect of a fixed amount of pairing for different pre-pairing values of U .

The dependence of pairing-induced decrease in synaptic efficacy on the recovery time constant is illustrated in Figure 9. In synapses that recover slowly, pairing induces a more pronounced and longer-lasting decrease in synaptic efficacy.

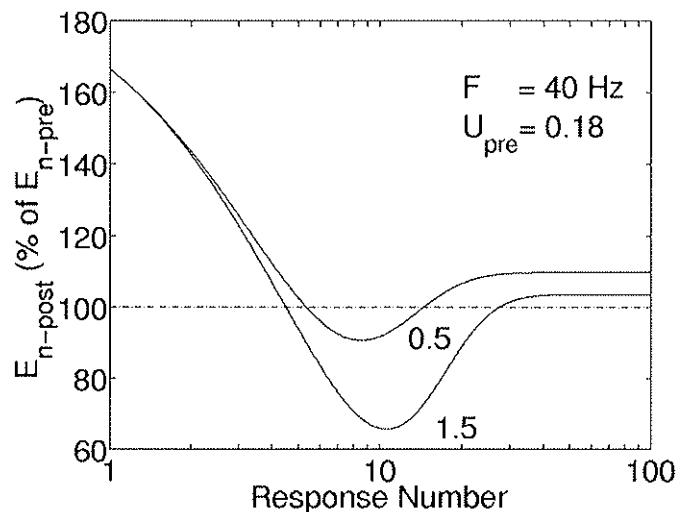


Figure 9. Dependence of pairing-induced changes in synaptic efficacy on recovery time constant τ_{rec} . The ratio E_{n-post}/E_{n-pre} (%) was computed using Equation (6) at 40 Hz for $\tau_{rec} = 0.5$ s and 1.5 s. These values are shown next to the corresponding curves. $U_{pre} = 0.18$ and $U_{post}/U_{pre} = 1.665$ for each curve.

3.4 Pairing localizes postsynaptic firing to a short time interval following the onset of moderate to high frequency presynaptic spike trains

The dependence of synaptic potentiation on the stimulus duration that is illustrated in Figure 7 suggests that the overall effect of pairing is to selectively enhance the transmission of early APs in a train. As a result, presynaptic activity increases postsynaptic firing probability preferentially near the onset of stimulation. Pairing hereby decreases the average delay between the onset of presynaptic spike train and the occurrence of the postsynaptic APs elicited in response. This trend is observable at all stimulation frequencies except below about 1 Hz.

At moderate and high frequencies (above about 20 Hz in Figure 7), the additional feature of pairing-induced decrease in synaptic efficacy emerges. The exact frequency at which this feature emerges is dependent on the values of the synaptic parameters U and τ_{rec} and also on the extent of pairing-induced increase in U . Hebbian pairing accentuates the synaptic depression through RSE, and this results in the exclusive enhancement of the transmission of the first few APs in a train, while the transmission of subsequent APs is depressed until steady-state is reached. Thus, pairing sharpens the time window during which presynaptic stimulation is likely to induce postsynaptic firing. The end of this window is sharply defined at moderate and high firing rates by the decrease in synaptic efficacy to below pre-pairing levels, but not at low firing rates.

4. DISCUSSION

The characterization of FDP by Markram and Tsodyks (1996) has important implications for neural models. Their results suggested that pairing-induced synaptic potentiation is not a frequency-independent process in excitatory synapses between TL5 neurons. The phenomenological model that Tsodyks and Markram (1997) proposed for depressing synapses is reminiscent of the Liley and North (1953) model, which also predicts FDP in a similar way, even

though this was not explicitly shown by Liley and North (1953). Grossberg and colleagues (Fiala, Grossberg, and Bullock, 1996; Grossberg, 1987; Grossberg and Merrill, 1992, 1996; Grossberg and Schmajuk, 1989) have also developed a synaptic model wherein a depressing variable, like R in (4), multiplies an associative variable that is influenced by Hebbian pairing, like U in (4). Unlike in Equation (5), in their model the rate of depression does not depend on the associative variable, but the associative variable does depend on the rate of depression. This model was used to explain data about adaptively timed learning processes.

The Markram and Tsodyks (1996) data about FDP showed that paired-activity induces a decrease in steady-state synaptic efficacy at high frequencies, as shown in Figure 2c. However, this decrease was not further analyzed and was treated in Markram and Tsodyks (1996) and in later studies (Markram et al., 1998a, 1998b, 1998c) as consistent with no change at all. The current results suggest that the observed decrease was significant and that it was due to the fact that FDP was not characterized at a phase close to steady-state at high frequencies. This is because the duration of the test stimuli, which consisted of six APs in Figure 2, was apparently not long enough for the e.p.s.p amplitude to reach the same criterion fraction of the steady-state level that was reached at low frequencies. These results also explain why the Markram et al. (1998b) simulation of FDP (Figure 3) at theoretical steady-state using the TM model deviates from the experimental results of Markram and Tsodyks (1996) at high frequencies (Figure 2c). It is also shown that steady-state may take a long time to settle at high frequencies (Figure 6), raising the possibility that the change in steady-state synaptic efficacy may not be a functionally relevant descriptive feature of FDP at those frequencies.

An alternative characterization of FDP is proposed in Figure 7, where the change in synaptic efficacy is illustrated as a function of stimulus duration in number of APs and stimulus frequency. Figure 7 illustrates the consequences of RSE as a function of presynaptic firing rate. Since both potentiation and depression are observable in Figure 7, it may be more appropriate to use the abbreviation FDP to mean frequency-dependent synaptic plasticity instead of potentiation. The characterization of FDP shown in Figure 7 reasserts the existence of the trend suggested in Figures 1 and 2 that pairing selectively enhances the transmission of early APs in a train. Such an enhancement may decrease the average delay between the onset of a presynaptic spike train and the occurrence of the postsynaptic APs elicited in response, by decreasing the scattering of the induced postsynaptic spikes in time. This trend is observable at all stimulation frequencies except below about 1 Hz in Figure 7.

The pairing-induced decrease in synaptic efficacy that is observable at high frequencies is part of the same trend and furthermore results in the exclusive enhancement of the transmission of the first few APs in a train, while depressing the transmission of subsequent APs during a frequency-dependent time interval. Thus, pairing sharpens and narrows down the time window during which presynaptic activity is likely to induce postsynaptic firing. Consequently, further increase in release probability, which requires paired-activity, is less likely to be triggered outside a time interval that immediately follows presynaptic activity. The length of this time interval becomes progressively shorter after each pairing, as suggested by Figure 8.

The findings of Markram and Tsodyks (1996) and the current analysis of their results suggest that the excitatory synapses between TL5 neurons directly participate in temporal signal processing in cortical networks instead of acting as frequency-independent gain elements. Current analysis suggest that paired-activity regulates synaptic transmission not only at low frequencies

but also at high frequencies. Pairing-induced decrease in synaptic efficacy, which is a consequence of RSE, appears to have an important role in controlling the timing of postsynaptic spiking driven by presynaptic activity. These results encourage investigating neural models in which global functional properties are obtained as a result of the frequency-dependence of pairing-induced changes in synaptic efficacy. In particular, the present results may clarify how certain cortical circuits can rapidly synchronize their firing across spatially disjoint cell populations (Brecht et al., 1998; Eckhorn et al., 1988, Gray and Singer, 1989; Grossberg and Grunewald, 1997; Grossberg and Somers, 1991), including populations that may be linked together by associative learning.

REFERENCES

- Abbott, L. F., Varela, J. A., Sen, K., & Nelson, S. B. (1997). Synaptic depression and cortical gain control. *Science*, **275**, 220-224.
- Baylor, D. A., Hodgkin, A. L. and Lamb, T. D. (1974a). The electrical response of turtle cones to flashes and steps of light. *Journal of Physiology*, **242**, 685-727.
- Baylor, D. A., Hodgkin, A. L. and Lamb, T. D. (1974b). Reconstruction of the electrical responses of turtle cones to flashes and steps of light. *Journal of Physiology*, **242**, 759-791.
- Brecht, M., Singer, W., & Engel, A. K. (1998) Correlation analysis of corticotectal interactions in the cat visual system. *Journal of Neurophysiology*, **79**, 2394-2407.
- Brody, D. L., & Yue, D. T. (2000). Release-independent short-term synaptic depression in cultured hippocampal neurons. *Journal of Neuroscience*, **20**, 2480-2494.
- Carpenter, G. A. (1994) A distributed outstar network for spatial pattern learning. *Neural Networks*, **7**, 159-168.
- Carpenter, G. A. (1996). Distributed activation, search, and learning by ART and ARTMAP neural networks. In *Proceedings of the International Conference on Neural Networks (ICNN 96): Plenary, Panel and Special Sessions* (pp. 244-249). Piscataway, New Jersey: IEEE.
- Carpenter, G. A. (1997) Distributed learning, recognition, and prediction by ART and ARTMAP neural networks. *Neural Networks*, **10**, 1473-1494.
- Carpenter, G. A., & Grossberg, S. (1981). Adaptation and transmitter gating in vertebrate photoreceptors. *Journal of Theoretical Neurobiology*, **1**, 1-42. Reprinted in Grossberg, S. (1987). *The Adaptive Brain*, Vol. II. Amsterdam: Elsevier/North-Holland.
- Chance, F. S., Nelson, S. B., & Abbott, L. F. (1998). Synaptic depression and the temporal response characteristics of VI cells. *Journal of Neuroscience*, **18**, 4785-4799.
- Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M., & Reitboeck, H. J. (1988) Coherent oscillations: a mechanism of feature linking in the visual cortex? *Biological Cybernetics*, **60**, 121-130. (From Grossberg and Grunewald, 1997).
- Feng, T. P. (1941). Studies on the neuromuscular junction. XXVI. The changes of the end-plate potential during and after prolonged stimulation. *Chinese Journal of Physiology*, **16**, 341-372. (From Markram et al., 1998a).
- Fiala, J. C., Grossberg, S., & Bullock, D. (1996) Metabotropic glutamate receptor activation in cerebellar Purkinje cells as substrate for adaptive timing of the classically conditioned eye blink response. *Journal of Neuroscience*, **16**, 3760-3774.
- Francis, G., & Grossberg, S. (1996a) Cortical dynamics of boundary segmentation and reset: Persistence, afterimages, and residual traces. *Perception*, **35**, 543-567.
- Francis, G., & Grossberg, S. (1996b) Cortical dynamics of form and motion integration: Persistence, apparent motion, and illusory contours. *Vision Research*, **36**, 149-173.
- Francis, G., Grossberg, S., & Mingolla, E. (1994) Cortical dynamics of feature binding and reset: Control of visual persistence. *Vision Research*, **34**, 1089-1104.
- Galarreta, M., & Hestrin, S. (1998). Frequency-dependent synaptic depression and the balance of excitation and inhibition in the neocortex. *Nature Neuroscience*, **1**, 587-594.
- Gray, C. M., & Singer, M. (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proceedings of the National Academy of Sciences of USA*, **86**, 1698-1702.

- Grossberg, S. (1968). Some physiological and biochemical consequences of psychological postulates. *Proceedings of the National Academy of Sciences of USA*, **60**, 758-765.
- Grossberg, S. (1969). On the production and release of chemical transmitters and related topics in cellular control. *Journal of Theoretical Biology*, **22**, 325-364.
- Grossberg, S. (1972). A neural theory of punishment and avoidance. II. Quantitative theory. *Mathematical Biosciences*, **15**, 253-285. (Reprinted in Grossberg S. (1982). *Studies of Mind and Brain*, D. Reidel Publishing Company, Boston.)
- Grossberg, S. (1975). A neural model of attention, reinforcement, and discrimination learning. *International Review of Neurobiology*, **18**, 263-327. (Reprinted in Grossberg S. (1982) *Studies of Mind and Brain*, D. Reidel Publishing Company, Boston.)
- Grossberg, S. (1984) Some normal and abnormal behavioral syndromes due to transmitter gating of opponent processes. *Biological Psychiatry*, **19**, 1075-1118.
- Grossberg, S. (1987) Cortical dynamics of three-dimensional form, color, and brightness perception, II: Binocular theory. *Perception and Psychophysics*, **41**, 117-158.
- Grossberg, S., & Grunewald, A. (1997) Cortical synchronization and perceptual framing. *Journal of Cognitive Neuroscience*, **9**, 117-132.
- Grossberg, S., & Merrill, J. W. L. (1992) A neural network model of adaptively timed reinforcement learning and hippocampal dynamics. *Cognitive Brain Research*, **1**, 3-38.
- Grossberg, S., & Merrill, J. W. L. (1996) The hippocampus and cerebellum in adaptively timed learning, recognition, and movement. *Journal of Cognitive Neuroscience*, **8**, 257-277.
- Grossberg, S., & Schmajuk, S. (1989). Neural dynamics of adaptive timing and temporal discrimination during associative learning. *Neural Networks*, **2**, 79-102.
- Grossberg, S., & Somers, D. (1991) Synchronized oscillations during cooperative feature linking in a cortical model of visual perception. *Neural Networks*, **4**, 453-466.
- Liley, A. W., & North, K. A. K. (1953). An electrical investigation of effects of repetitive stimulation on mammalian neuromuscular junction. *Journal of Neurophysiology*, **16**, 509-527.
- Markram, H. (1997). A network of tufted layer 5 pyramidal neurons. *Cerebral Cortex*, **7**, 523-533.
- Markram, H., Gupta, A., Uziel, A., Wang, Y., & Tsodyks, M. (1998a). Information processing with frequency-dependent synaptic connections. *Neurobiology of Learning and Memory*, **70**, 101-112.
- Markram, H., Pikus, D., Gupta, A., & Tsodyks, M. (1998b). Potential for multiple mechanisms, phenomena and algorithms for synaptic plasticity at single synapses. *Neuropharmacology*, **37**, 489-500.
- Markram, H., & Tsodyks, M. (1996). Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature*, **382**, 807-810.
- Markram, H., Wang, Y., & Tsodyks, M. (1998c). Differential signaling via the same axon of neocortical pyramidal neurons. *Proceedings of the National Academy of Sciences of USA*, **95**, 5323-5328.
- Matveev, V., & Wang, X. (2000). Implications of all-or-none synaptic transmission and short-term depression beyond vesicle depletion: a computational study. *Journal of Neuroscience*, **20**, 1575-1588.
- gmen, H (1993). A neural theory of retino-cortical dynamics. *Neural Networks*, **6**, 254-273.

- Parnas, I., Atwood, H. L. (1966). Phasic and tonic neuromuscular systems in the abdominal extensor muscles of the crayfish and rock lobster. *Computational Biochemistry and Physiology*, **18**, 701-723. (From Markram et al., 1998a)
- Pinsker, H., Kandel, E. R., Castellucci, V., & Kupfermann, I. (1970). An analysis of habituation and dishabituation in *Aplysia*. *Advances in Biochemical Psychopharmacology*, **2**, 351-373. (From Markram et al., 1998a)
- Stevens, C. F., & Tsujimoto, T. (1995). Estimates for the pool size of releasable quanta at a single central synapse and for the time required to refill the pool. *Proceedings of the National Academy of Sciences of USA*, **92**, 846-849.
- Thomson, A. M., & Deuchars, J. (1994). Temporal and spatial properties of local circuits in neocortex. *Trends in Neurosciences*, **17**, 119-126.
- Trussell, L. O., Zhang, S., & Raman, I. M. (1993). Desensitization of AMPA receptors upon multiquantal neurotransmitter release. *Neuron*, **10**, 1185-1196.
- Tsodyks, M., & Markram, H. (1997). The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. *Proceedings of the National Academy of Sciences of USA*, **94**, 719-723.
- Varela, J. A., Sen, K., Gibson, J., Fost, J., Abbott, L. F., & Nelson, S. B. (1997). A quantitative description of short-term plasticity at excitatory synapses in layer 2/3 of rat primary visual cortex. *Journal of Neuroscience*, **17**, 7926-7940.
- Wang, X. J (1999). Fast burst firing and short-term synaptic plasticity: a model of neocortical chattering neurons. *Neuroscience*, **89**, 347-362.
- Wilkie, D.M. (1987). Stimulus intensity affects pigeons' timing behavior: Implications for an internal clock model. *Animal Learning and Behavior*, **15**, 35-39.

Appendix

Derivation of Equation (6) from Equations (4) and (5):

Equation (5) is repeated as Equation (A.1):

$$R_{n+1} = R_n(1-U)e^{-\frac{\Delta t}{\tau_{\text{rec}}}} + 1 - e^{-\frac{\Delta t}{\tau_{\text{rec}}}}. \quad (\text{A.1})$$

This equation is simplified by using the following notation:

$$R_{n+1} = R_n \Lambda + \Gamma \quad (\text{A.2})$$

where

$$\Lambda = (1-U)e^{-\frac{\Delta t}{\tau_{\text{rec}}}}, \quad (\text{A.3})$$

$$\Gamma = 1 - e^{-\frac{\Delta t}{\tau_{\text{rec}}}}. \quad (\text{A.4})$$

The first AP occurs after the synapse has been at rest for a while. Therefore immediately before the first AP, $R = R_1 = 1$. Iterating (A.2) yields:

$$\begin{aligned} R_2 &= \Lambda + \Gamma, \\ R_3 &= \Lambda^2 + \Gamma\Lambda + \Gamma, \\ &\dots \\ R_n &= \Lambda^{n-1} + \Gamma(\Lambda^{n-2} + \dots + \Lambda + 1). \end{aligned} \quad (\text{A.5})$$

Thus R_n can be written as:

$$R_n = \Lambda^{n-1} + \Gamma \frac{1 - \Lambda^{n-1}}{1 - \Lambda} = \frac{\Lambda^{n-1}(1 - \Lambda) + \Gamma(1 - \Lambda^{n-1})}{1 - \Lambda}. \quad (\text{A.6})$$

(A.6) is then simplified using the expressions for Λ and Γ given in (A.3) and (A.4) to obtain (A.7):

$$R_n = \frac{1}{1 - \Lambda} \left[1 - \Lambda^n - (1 - \Lambda^{n-1})e^{-\frac{\Delta t}{\tau_{\text{rec}}}} \right]. \quad (\text{A.7})$$

$E_n = AUR_n$ is obtained by multiplying (A.7) by AU.