Long-Term Potentiation and Depression Induced by a Stochastic Conditioning of a Model Synapse

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ABSTRACT Protracted presynaptic activity can induce long-term potentiation (LTP) or long-term depression (LTD) of the synaptic strength. However, virtually all the experiments testing how LTP and LTD depend on the conditioning input are carried out with trains of stimuli at constant frequencies, whereas neurons in vivo most likely experience a stochastic variation of interstimulus intervals. We used a computational model of synaptic transmission to test if and to what extent the stochastic fluctuations of an input signal could alter the probability to change the state of a synapse. We found that, even if the mean stimulation frequency was maintained constant, the probability to induce LTD and LTP could be a function of the temporal variation of the input activity. This mechanism, which depends only on the statistical properties of the input and not on the onset of additional biochemical mechanisms, is not usually considered in the experiments, but it could have an important role to determine the amount of LTP/LTD induction in vivo. In response to a change in the distribution of the interstimulus intervals, as measured by the coefficient of variation, a synapse could be easily adapted to inputs that might require immediate attention, with a shift of the input thresholds required to elicit LTD or LTP, which are restored to their initial conditions as soon as the input pattern returns to the original temporal distribution.

INTRODUCTION

Synaptic plasticity is currently considered as the first microscopic event leading to macroscopic brain functions such as learning and memory. The long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength are the most studied among the modifications that a synapse can undergo after presynaptic stimulations that significantly depart from the background noise. The experimental induction of LTP and LTD usually requires trains of presynaptic pulses delivered with specific protocols, although a conditioning input consisting of the same number of pulses can reliably induce LTD or LTP if they are simply delivered at a constant low ($\simeq$3 Hz) or high ($\simeq$50 Hz) frequency, respectively (Dudek and Bear, 1992). Thus, if and how much LTD or LTP will be induced seems to depend only on the strength and frequency of the input stimulation.

Neurons in vivo, however, are unlikely to experience the constant frequency stimulation patterns that are usually delivered in the experiments, and highly irregular interstimulus intervals (ISIs) could be expected. Indeed, there is precise experimental evidence, using natural stimulation patterns, suggesting a sensitivity of the neural response to the temporal structure of the input (Dobrunz and Stevens, 1999), and it has been noted that even a single burst of action potentials can induce bidirectional synaptic plasticity (Huerta and Lisman, 1995). It has also been shown that different temporal structures of the stimuli delivered during the conditioning period induced different amount of LTP in hippocampal CA1 neurons (Larson et al., 1986; Larson and Lynch, 1986; Tsukada et al., 1994; Aihara et al., 1997), and that particular timing patterns are more effective than any constant interval conditioning in inducing LTP (Rose and Dundwiddie, 1986). However, it is still unclear what properties a stochastic input pattern should have to influence the LTP or LTD induction characteristics, and their investigation could shed some light on the long-standing effort to figure out if the mean spiking frequency plays an exclusive role in neuronal coding or if higher order statistical measures (variability) are also equally important (Rieke et al., 1997).

A characteristic curve of the net amount of LTD or LTP obtained as a function of the input activity can be drawn (e.g., Dudek and Bear, 1992). Such a curve is usually compared with the prediction based on the theoretical work by Bienenstock et al. (1982) that, to avoid saturation of the synapses and maximize the amount of information that could be stored in a network, the LTP/LTD crossover point, called the LTP threshold, should slide to the left or to the right as a function of the past input activity of the cell. A number of experiments showing that prior conditioning could increase or decrease the amount of LTD or LTP that would otherwise be induced by a given conditioning stimulation (Abraham and Bear, 1996; Kirkwood et al., 1996; Stanton, 1995, 1996), have been interpreted in terms of a sliding threshold.

In this paper, we test in a model synapse whether, and why, different temporal distributions of ISIs, could result in different amounts of LTP and LTD, dynamically shifting the LTP threshold with respect to constant ISIs at the same mean conditioning frequency.

Received for publication 29 January 1999 and in final form 11 May 1999.

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0006-3495/99/09/1234/10 $2.00

METHODS

This work is aimed to study how the temporal structure of the conditioning input changes the probability for a synapse to change its state, using a physiologically reasonable model of synaptic transmission and plasticity. There are very detailed biophysical models of long-term synaptic plasticity (Lisman, 1989, 1994; Lisman and Goldring, 1989; Coomber, 1998). In a complex set of kinetic reactions steps, some of which not yet fully understood (see for example Fig. 4 in Lisman (1994)), these models use the autophosphorylation of the Ca^{2+}/calmodulin-dependent kinase as a molecular switch that, with the appropriate form of the rate constants, leads to LTP and LTD in agreement with experiments. These models have solid bases on the available experimental data about several biochemical steps that are required for LTD/LTP induction and maintenance. Nevertheless, in this paper, we were neither interested to propose an alternative model of LTD/LTP or a specific form of the molecular switch, to model pharmacological manipulations, to reproduce a particular set of experimental data, nor to investigate debatable details of the pre/postsynaptic mechanisms. For this reason, we have chosen not to include all these details, implementing a much simpler empirical model that, however, is able to capture the main experimental characteristics of synaptic transmission and plasticity. From this point of view, the only critical assumptions that we used for our model synapse, and for which there is an ample experimental evidence, were: 1) the maintenance of LTP and LTD is supported by autocatalytic processes, such as the autophosphorylation of the appropriate kinases (Soderling, 1993; Fagnou and Tuchek, 1995), and that 2) these autocatalytic processes are directly or indirectly activated by different levels of presynaptic activity, i.e., the induction of LTP requires a stronger input than for LTD (for a review see Artola and Singer, 1993).

The model

In our model, Fig. 1 *A*, the presynaptic machinery was modeled according to the phenomenological model of Markram and Tsodyks (1997) and Abbott et al. (1997). This presynaptic kinetic scheme has been shown to be able to reproduce the synaptic response of interpyramidal cortical neurons to an arbitrary presynaptic spike train (Markram and Tsodyks, 1997). A detailed explanation of all the variables and rate constants used in this scheme can be found in several papers by the same authors. Briefly, x, y, and z are the fractions of resources in the recovered, active, and inactive states, respectively. An input stimulus, I, generated with the appropriate timing according to the ISI distribution chosen, allows a fraction y of the presynaptic resources to generate a synaptic current $I_{syn} = yA_{SE}$, where A_{SE} is the absolute synaptic strength. The postsynaptic membrane potential, v, in response to this current was calculated assuming a passive synapse, with an input resistance R_{in} and membrane time constant τ_m. The postsynaptic depolarization produces (with a rate γ) a second messenger, C, which is degraded with a rate η. C represents all those intermediate processes that, from a postsynaptic depolarization, lead to LTP/LTD induction. In our model, C catalyses, with a rate constant ν, the production of N_P and N_D, that represent all those presynaptic processes that could be involved with LTP and LTD maintenance, such as protein autophosphorylation. N_P and N_D are controlled by two independent autocatalytic processes, governed by g, $\rho_{P,D}$, $M_{P,D}$, and $A_{P,D}$ (for clarity, $M_{P,D}$ and $A_{P,D}$ are not reported in Fig. 1 *A*). They modulate the postsynaptic response with a rate δ, by increasing (LTP) or decreasing (LTD) the net effects of a fraction f of the total synaptic current flowing into the synapse. The operation of the model can be better understood by considering that the autocatalytic processes implement bistable switches (Migliore et al., 1995). Their activation is controlled by the level of the second messenger C and, thus, by the postsynaptic depolarization, v. The temporal structure of the presynaptic stimuli determines which one of the autocatalytic processes is activated. For constant ISI stimulation, it results in the induction of LTD or LTP of the postsynaptic response to a test stimulus as observed in the experiments (e.g., Dudek and Bear, 1992).

The model synapse was implemented with the following system of ordinary differential equations for the presynaptic (PRE) and postsynaptic (POST) sides.

PRE:

$$\frac{dx}{dt} = \frac{z}{\tau_{rec}} - U_{SE}xI \tag{1}$$

$$\frac{dy}{dt} = -\frac{y}{\tau_{in}} + U_{SE}xI \tag{2}$$

$$z = 1 - x - y \tag{3}$$

POST:

$$\frac{dv}{dt} = -\frac{v}{\tau_m} + R_{in}I_{syn}\left(\frac{1}{\tau_m} + f\delta(N_P - N_D)\right) \tag{4}$$

$$\frac{dC}{dt} = \gamma v - \eta C \tag{5}$$

$$\frac{dN_s}{dt} = \nu C - (\rho_s + R_{in}I_{syn}g\delta)N_s + \frac{M_s N_s^2}{A_s + N_s^2} - I\delta N_s, \tag{6}$$

where $s = \{P, D\}$, and $I_{syn} = y \cdot A_{SE}$.

The values of the presynaptic and passive parameters were directly taken from Tsodyks et al. (1998), and an input stimulus was modeled as a 5-ms I pulse with an amplitude adjusted to reproduce their basic results (Fig. 1 of Tsodyks et al., 1998). A refractory period was set at 5 ms, limiting the peak input frequency at 100 Hz. The postsynaptic rate constants were adjusted to reproduce the experimental LTD/LTP frequency dependence (Dudek and Bear, 1992), and to obtain (after the appropriate conditioning) a roughly 50% decrease (LTD) or increase (LTP) in the peak amplitude of the response to a test stimulus. The following numerical values for the rate constants were used for all simulations: $I = 300$, $U_{SE} = 0.5$, $\tau_{in} = 3$ ms, $\tau_{rec} = 0.8$ sec, $A_{SE} = 250$ pA, $R_{in} = 100$ MΩ, $\tau_m = 40$ ms, $\gamma = 200\ s^{-1}$, $\eta = 2\ s^{-1}$, $\nu = 65\ s^{-1}$, $A_P = 1.625\ V^2$, $A_D = 0.55\ V^2$, $M = 3$ V/sec, $\rho_P = 0.95\ s^{-1}$, $\rho_D = 1.9\ s^{-1}$, $\delta = 300\ s^{-1}$, $f = 0.05\ V^{-1}$, $g = 40\ V^{-1}$. All the simulations were carried out in FORTRAN 90, using a standard second-order Runge–Kutta method with a fixed time step of 0.1 ms.

To test for synaptic modifications (no-effects, LTD, or LTP), we compared the peak amplitudes of the membrane potential in response to single presynaptic test pulses delivered before and after a conditioning period. In Fig. 1 *B*, we show the time course of the model variables during a simulation under control conditions, that is using a constant stimulation frequency, ω (i.e., constant ISIs). A single test pulse (P_0) was followed by a 5-sec conditioning period at 5 or 50 Hz. A second test pulse (P_5, P_{50}), was then delivered 30 sec after the end of the conditioning period. Their comparison (Fig. 1 *C*) shows that LTD and LTP were elicited by stimulation at 5 and 50 Hz, respectively. Since the model synapse is implemented as a simple two-state molecular switch, the amount of LTP or LTD obtained after conditioning is all-or-none rather than graded, a feature that has been experimentally confirmed (Petersen et al., 1998). Using a constant ISI conditioning, the model synapse was unchanged, potentiated, or depressed with a 100% probability according to the stimulation frequency, ω, as shown in Fig. 1 *D*. No potentiation or depression was obtained for $\omega <$ 3 Hz, LTD was induced for $3 \leq \omega < 20$ and LTP resulted for $\omega \geq 20$ Hz. For clarity, in the rest of the paper, we will refer to low frequencies or low activity levels as those that, using constant ISIs, were unable to modify the synaptic strength, and to mid or high frequencies (or activity levels) as those that resulted in LTD or LTP, respectively.

Distribution of the presynaptic stimuli

To generate the stochastic patterns that we were interested to test, we assumed that presynaptic stimuli arrive according to a renewal process, i.e., that the intervals separating stimulation pulses are independent and iden-

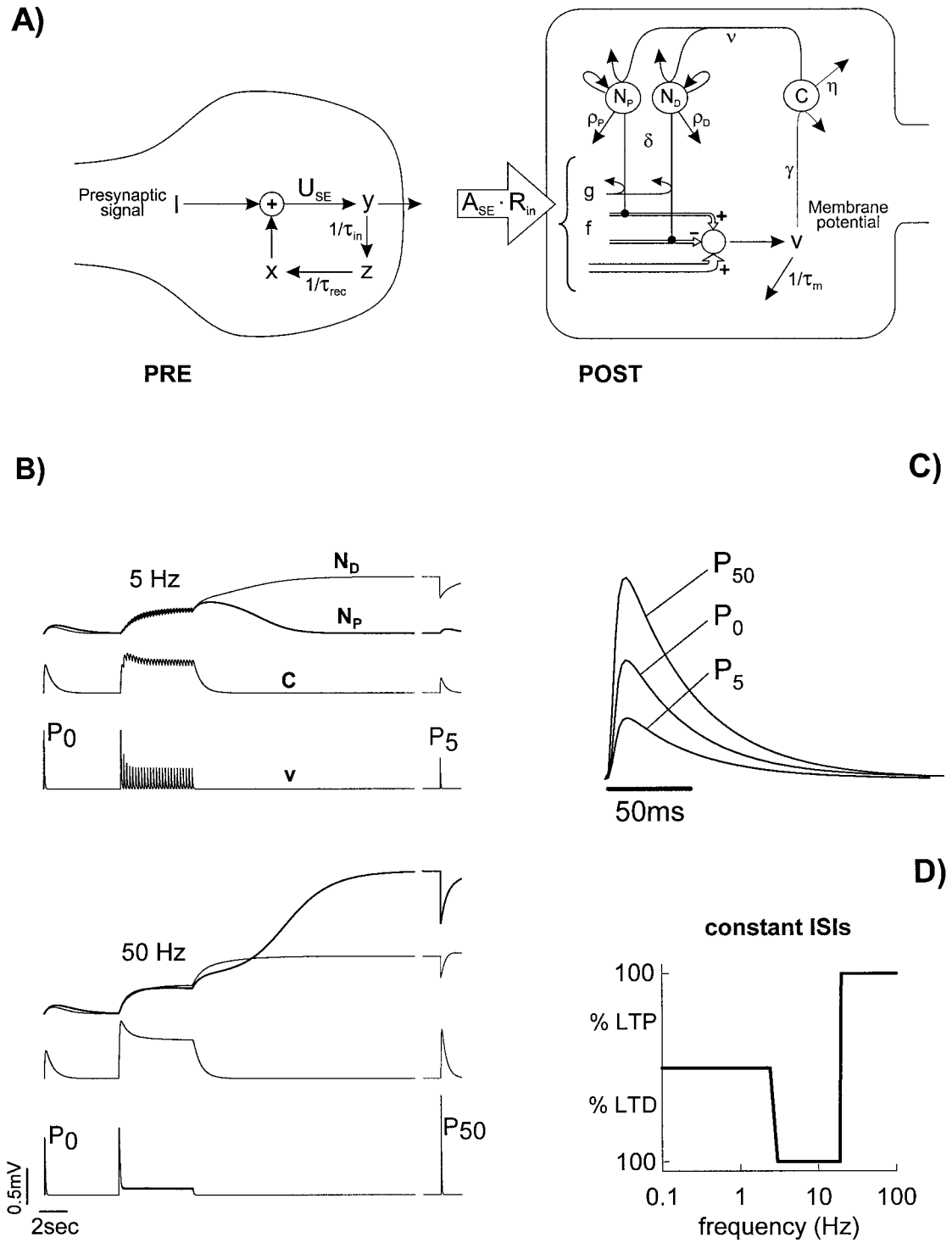

FIGURE 1 (*A*) Schematic representation of the model synapse. See Methods for details. (*B*) Induction of LTP or LTD of the model synapse after a conditioning with constant ISIs. Time course of the postsynaptic depolarization, v, and the postsynaptic model variables C, N_P, and N_D. Test stimuli were delivered before (P_0) and after (P_5, P_{50}) a 5-sec conditioning stimulation at a constant frequency of 5 or 50 Hz. (*C*) Superposition of the postsynaptic response to the test stimuli P_0, P_5, and P_{50} from panel (*B*). (*D*) Probability for the model synapse to change state after a conditioning stimulation at constant frequency.

tically distributed random variables. The stimulation frequency was identified with the reciprocal of the mean ISI (Johnson, 1996). In each simulation (trial) a 20-sec conditioning period consisted of presynaptic pulses with ISIs distributed as described below. The same qualitative results were obtained in a series of preliminary simulations in which, for synaptic conditioning, a fixed number of 900 stimuli (Dudek and Bear, 1992) or a longer (60-sec) period were used. The results (no-effects, LTD, or LTP) from 1000 trials were then averaged for each set of parameters that were

tested. We checked that, in all cases, the calculated statistical properties of the generated ISIs (mean and standard deviation) were in agreement with those expected theoretically. The three following types of stochastic conditioning were used to study the effects of randomness in stimulation on LTD/LTP induction.

Exponential distribution of ISIs (homogeneous Poisson process)

The Poisson process plays its specific role among other abstract descriptions of neuronal activity (Johnson, 1996; Rieke et al., 1997; Tuckwell, 1988). Obviously, its temporal structure is drastically different from the regularly spaced stimuli commonly used in LTP/LTD studies. The generation of ISIs, in this kind of conditioning, follows directly from the cumulative distribution function of an exponentially distributed random variable, $F(t; \omega) = 1 - e^{-\omega t}$, where the reciprocal value of the preselected mean frequency, ω, is the mean ISI. The kth ISI was thus generated as

$$\mathrm{ISI_k} = -\ln(1 - u_k)/\omega, \tag{7}$$

where u_k was a kth independent realization of a random number uniformly distributed over the (0, 1) interval.

Gamma distribution of ISIs

The second type of stimuli was chosen to mimic ISIs forming unimodal and more or less positively skewed histograms. The gamma distribution, or gamma-like histograms, have been commonly found in experimental data when statistical analyses were performed (Tuckwell, 1988). The distribution can be given by its probability density function,

$$f(t; \mu, k) = \mu(\mu t)^{k-1} e^{-\mu t}/k!, \tag{8}$$

where $k > 0$ and $\mu > 0$ are two parameters characterizing its location and shape. The mean ISI of the distribution (Eq. 8) is k/μ and the shapes range from an exponential ($k = 1$ in Eq. 8) to a Gaussian distribution (k large), that can be considered as a generalization of equally spaced stimuli. To test the influence of different gamma distributions of conditioning stimuli on LTP/LTD induction, two different stimulation patterns were tested, with the ISIs sampled from Eq. 8 with $k = \{3, 7\}$ and μ adjusted in such a way to keep the mean ISI equal to $1/\omega$ ($\mu = k\omega$, where ω is the preselected mean frequency). A representative sample of ISIs from these distributions for $\omega = 5$ Hz is shown in Fig. 2 *A*.

Bursting Poisson conditioning

To test the effects of a high temporal variability of synaptic activation on the LTP/LTD induction, we defined a bursting Poisson conditioning as a train of stimuli in which two different Poisson processes P_s and P_l, with mean frequencies ω_s and ω_l, respectively, were mixed. Each ISI was generated according to P_s or P_l with probabilities p or $(1 - p)$, respectively. In this way, we were able to transform the structureless distribution of stimuli generated according to a homogeneous Poisson process into a burst-like distribution in which an intraburst and interburst mean frequencies can be identified (ω_s and ω_l, respectively). We have chosen to use ω, ω_s, and p as free parameters, and the two Poisson processes were mixed in such a way that

$$p\omega_s^{-1} + (1 - p)\omega_l^{-1} = \omega^{-1}, \tag{9}$$

ensuring that the resulting mean ISI was equal to $1/\omega$ and $\omega < \omega_s$. Note that, by selecting ω, p, and ω_s, the value of ω_l is determined from Eq. 9. In Fig. 2 *B*, we show a homogeneous Poisson process (*small symbols*, $\omega = 5$ Hz) and a bursting Poisson process with the same mean frequency (*large*

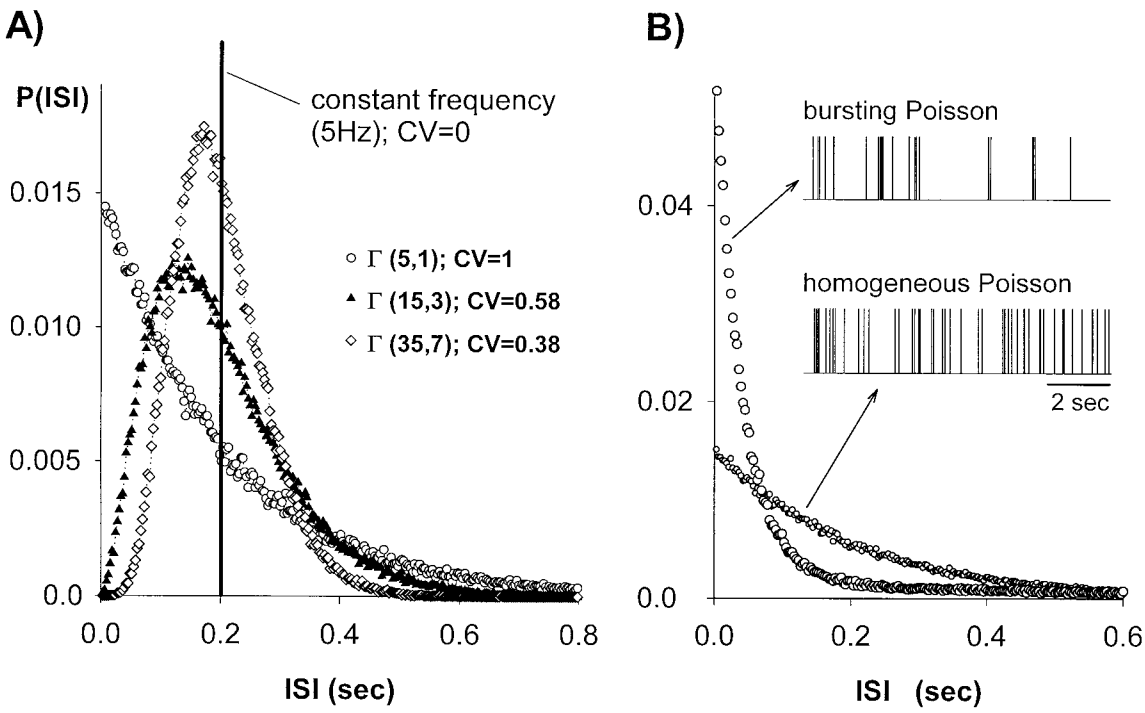

FIGURE 2 (*A*) Example of normalized ISI histograms (bin size 0.003) from the gamma distributions $\Gamma(5, 1)$, $\Gamma(15, 3)$, or $\Gamma(35, 7)$ (*symbols*). The $\Gamma(5, 1)$ corresponds to a Poisson process with mean frequency $\omega = 5$ Hz, and the average ISI is 0.2 sec in all cases. The solid line depicts the position of constant ISIs. (*B*) Examples of normalized histograms of ISIs (bin size 0.003) generated according to a Poisson (*small symbols*, $\omega = 5$ Hz) or a bursting Poisson process (*large symbols*, $\omega = 5$ Hz, $\omega_s = 25$ Hz, $\omega_l = 1.74$ Hz, $p = 0.7$). The insets show a typical temporal distribution of spikes in both cases. The average ISI is 0.2 sec in both cases.

symbols, $\omega = 5$ Hz, $\omega_s = 5\omega$, $p = 0.7$). The insets show typical temporal distributions of stimuli in both cases.

Coefficients of variation

The most common way for quantifying the regularity of a stationary point process is by calculating the coefficient of variation (CV), defined as the standard deviation divided by the mean ISI (CV = σ/m). This holds for description of experimental data as well as for characterization of outputs from model neurons. For constant ISIs, CV = 0, whereas CV = 1 for a Poisson process, and CV = $1/\sqrt{k}$ for the gamma distribution given by Eq. 8. For our bursting Poisson process, the CV can be analytically calculated by considering that the mean for this process is given by Eq. 9 and $\sigma = \sqrt{E(X^2) - m^2}$, where X is a random variable giving the length of an ISI and $E(X^2) = 2(p/\omega_s^2 + (1 - p)/\omega_f^2)$ is its second moment. It can be shown that, for $p > 0$ and $\omega_s \neq \omega$ is always CV > 1. A CV ≈ 1 has been found in cortical neurons in vivo (Softky and Koch, 1993), and a higher CV could be expected in bursting cells such as hippocampal CA3 pyramidal neurons. Possible sources of large values of CV were investigated theoretically (Wilbur and Rinzel, 1983; Bugmann et al., 1997).

RESULTS

Unless otherwise noted, in all simulations, a 20-sec conditioning period was used, and only the distribution of ISIs was changed (see Methods). First of all, we tested if conditioning stimuli delivered according to a gamma distribution (that includes the Poissonian case) result in different amounts of LTD or LTP with respect to the constant ISI case. The ISIs were sampled according to Eq. 8. The results are shown in Fig. 3 in terms of the net amount of LTD/LTP induced as a function of the average input frequency. The findings for a constant interval stimulation (*solid line*) are compared with the results obtained by using gamma distributions (*dotted lines*). They showed that already these simple (and more physiological) departures from the constant frequency case resulted in a shift of the LTD/LTP threshold, that was more and more pronounced as the distribution approached the Poissonian case (Fig. 3, *circles*). Often, however, typical in vivo recordings are not Poissonian, but show an extremely variable firing activity (e.g., Fenton and Muller, 1998), with short bursts of action potentials at high frequency (~100 Hz) separated by longer intervals with little or no activity. With our bursting Poisson generation scheme, we thus considered several different combinations of intraburst frequency ω_s and probability of bursting p, to study if and to what extent the induction of LTD or LTP was affected. The main findings are summarized in Fig. 4 *A*, where ω_s was fixed and the probability to have a burst, p, increased. The results for a homogeneous Poisson distribution of ISIs is shown for comparison (Figs. 4 *A*, *solid line*).

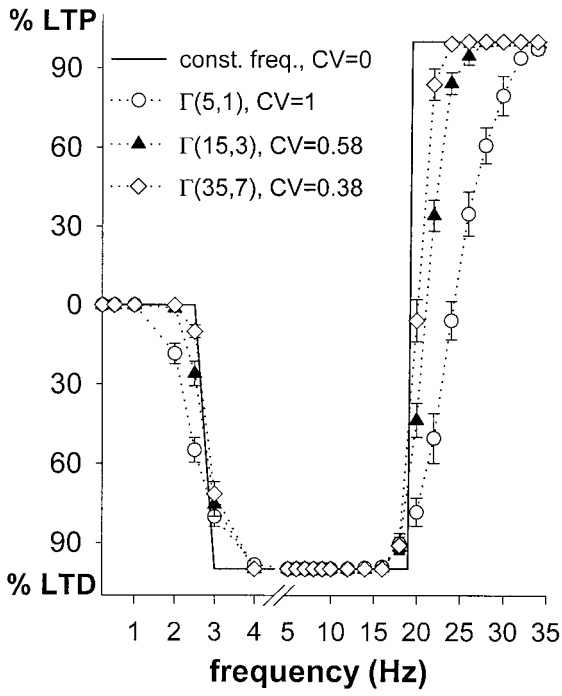

FIGURE 3 Probability of LTD and LTP induction for constant (*solid line*) or gamma distributed ISIs (*dotted lines*).

An increase of p at low levels of input activity resulted in an increase in the amount of LTD induced (compare black circles and open diamonds in Fig. 4 *A*). A different effect was observed for mid frequencies (Fig. 4 *A*, $\omega \sim 4$), where a decrease in the net amount of LTD resulted when the probability to have a burst was increased. Finally, a substantial reduction in the net amount of LTP was observed increasing p at higher frequencies ($\omega \sim 30$ Hz), resulting in a marked shift to the right, toward higher frequencies, of the LTD/LTP threshold. Since these were net changes, they could, in general, be caused by independent changes in the individual probabilities for LTD or LTP, a characteristic that cannot be easily tested in the experiments. For this reason, we show, as separate curves (Fig. 4 *A*, *lower panel*), the relative contribution of LTD and LTP. As can be seen, an increase in the burst probability, p, resulted in an earlier induction of LTD at low frequencies, where no effects were induced by a constant or a Poissonian ISI distribution. A significant amount of LTP was induced in the midfrequency range ($3 < \omega < 5$), where only LTD can be induced by a homogeneous stimulation (Fig. 4 *A*, *solid line*). At higher frequencies, the relative contributions of LTP and LTD suggest that the decrease in the net LTP induction, increasing the bursting probability, was caused by both an actual reduction in the probability to induce LTP and a significant increase in LTD (compare the open and close symbols in Figs. 4 *A* for $\omega \sim 30$ Hz). As shown in Fig. 4 *B*, essentially the same results were obtained increasing ω_s rather than p, suggesting that it is the bursting behavior that plays a significant role, not a particular characteristic. Thus, whenever an occasional clustering of spikes at the appropriate frequency is delivered to the synapse, LTD or LTP could be induced, even if a homogeneous (or constant) ISI distribution at the same average input frequency would give a different result.

The effects caused by an increase in the bursting behavior are illustrated in Fig. 5, where we show the membrane potential in two simulations using a 20-sec conditioning

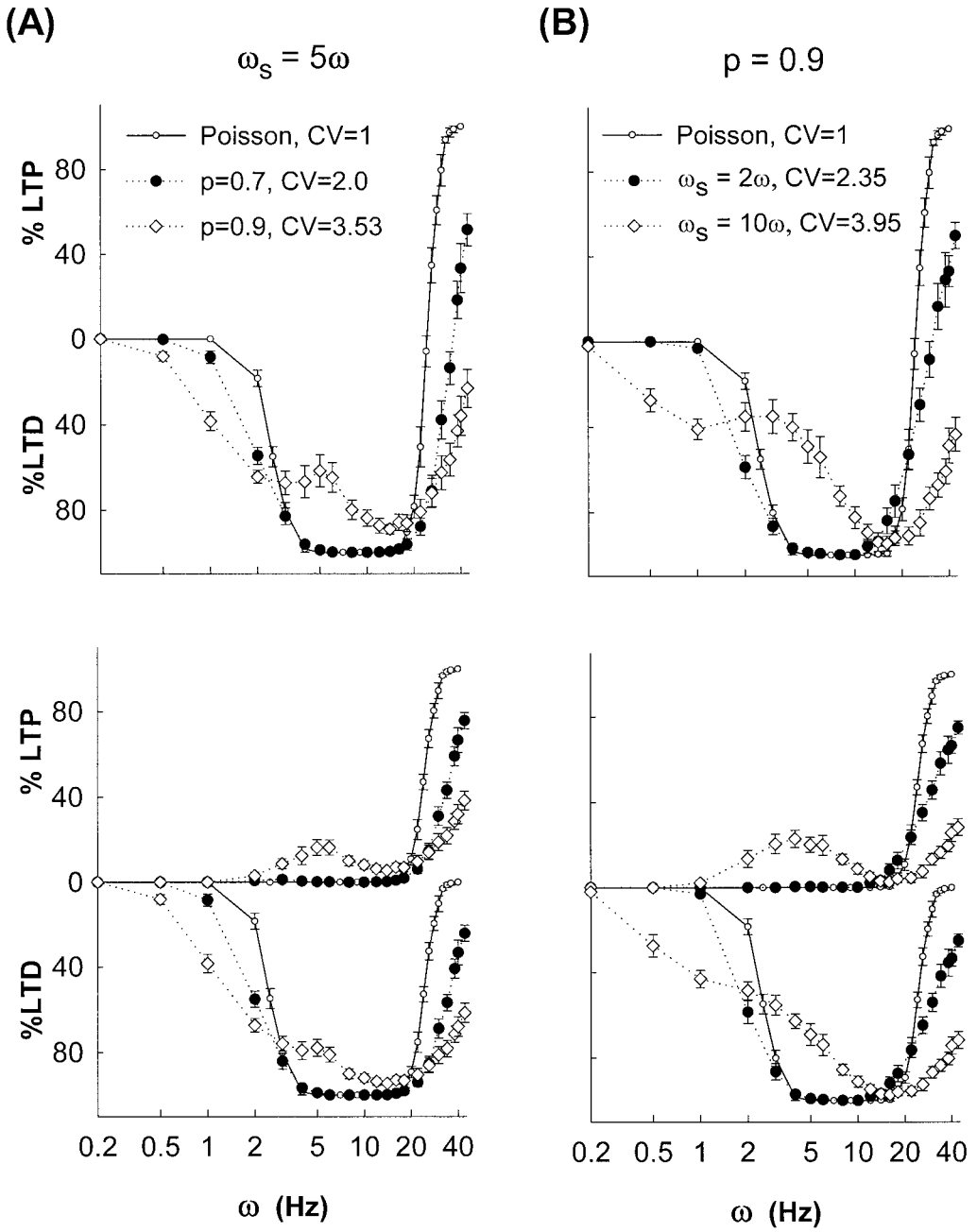

FIGURE 4 (*A*) (*Upper)* Net probability of LTD or LTP induction versus mean input activity (ω) for a homogeneous (*solid line*) or bursting Poisson processes (*dotted lines*) with the same intraburst frequency ($\omega_s = 5\omega$) but different probabilities (p) to burst. (*Lower*) Relative contribution of LTD and LTP. (*B*) (*Upper*) Net probability of LTD or LTP induction for homogeneous and bursting Poisson processes with the same probability to have a bursting behavior ($p = 0.9$) but different intraburst frequency (ω_s). (*Lower*) Relative contribution of LTD and LTP. Symbols as in (*A*).

period at a mean frequency $\omega = 1$ Hz in both cases. The conditioning stimuli were delivered according to a homogeneous (Fig. 5, *left*) or a bursting (Fig. 5, *right*) Poisson process, at the same average frequency. The bottom panels show typical temporal distributions of stimuli in both cases. The CV_{ISI} values are actual CV from each simulation. The distribution of ISIs had a much higher CV for the bursting case, $CV_{ISI} = 0.8$ versus $CV_{ISI} = 3.3$. In fact, the clustering of stimuli at higher frequency occurring in a bursting Poisson process ($\omega_s = 10\omega = 10$ Hz) resulted in net LTD being induced in ~40% of the cases, whereas LTD was never obtained with a homogeneous process (see solid lines in Fig. 4). Similar findings, the CV_{ISI} for the bursting case being much higher than for the homogeneous one, were obtained for higher levels of input activity, as shown in Fig. 6 for $\omega = 30$ Hz. In this case, however, the relatively steady input activity that induced LTP during the homogeneous Poisson conditioning was broken by the longer intraburst intervals in the bursting case, inducing LTD rather than LTP in most cases (~80%, see lower panels of Fig. 4 *B*).

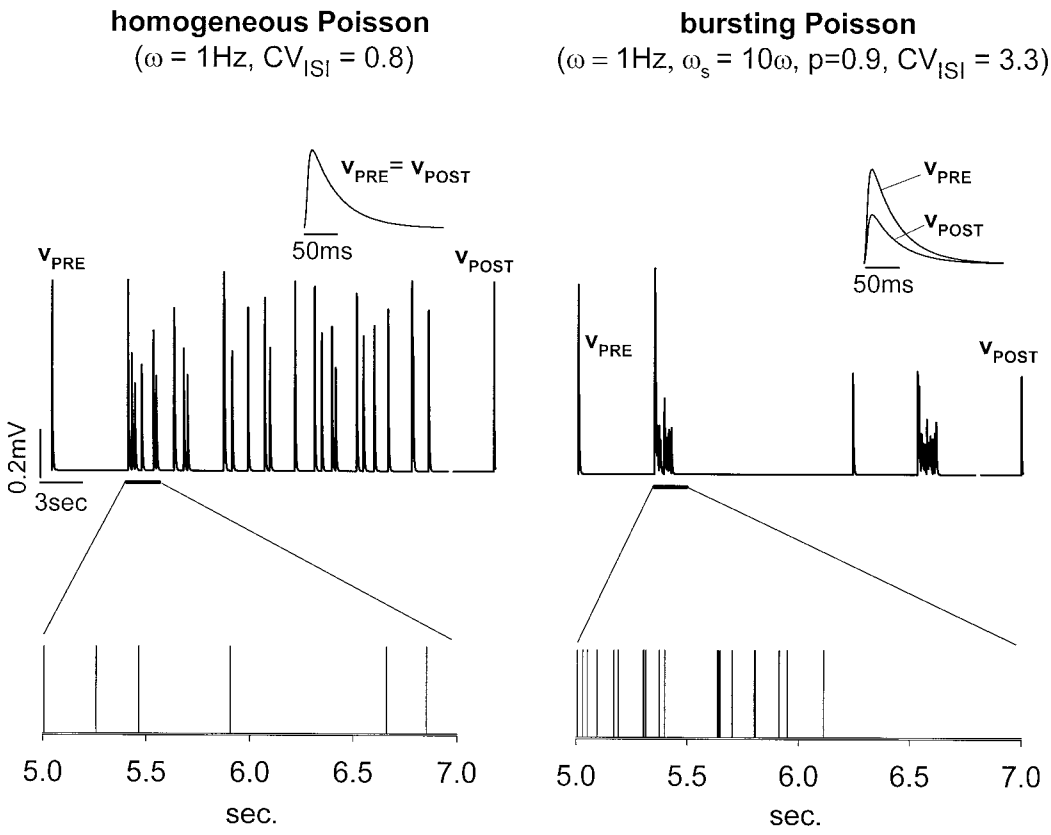

FIGURE 5 Postsynaptic depolarization during a 20-sec conditioning period at a mean frequency of $\omega = 1$ Hz using a homogeneous (*left*) or a bursting Poisson process (*right*). In the bursting case, two homogeneous Poisson processes were mixed in such a way to obtain bursts of stimuli with an average intraburst frequency of $\omega_s = 10\omega$ and probability $p = 0.9$ (see Eq. 9). The insets show a superposition of the postsynaptic response to test stimuli delivered before (v_{pre}) and after (v_{post}) conditioning. The bottom panels show typical temporal distributions of stimuli in both cases. The CV_{ISI} values are the actual CV calculated from each simulation.

The CV of the ISIs can be a useful indicator of the bursting behavior of the input pattern. In Fig. 7, we show the amount of LTD or LTP induced as a function of the effective CV_{ISI} calculated from all the simulations at 1 and 30 Hz. As can be seen, in this model, an increase of the bursting properties of the input increased the probability to induce LTD at both low and high activity levels. More generally, this figure clearly illustrates one of the main results of this work, explaining why first-order statistics (such as the mean average stimulation frequency) are not sufficient to characterize the plasticity of a synapse in response to a train of stimuli. Second-order measures of the input, such as the variability of its temporal structure, should also be taken into account.

DISCUSSION

The main purpose of this work was to show, in a simple but physiologically reasonable model, if and to what extent the temporal distributions of ISIs could modify the probability of LTD and LTP induction. Qualitative differences in the amount of LTD/LTP induced were already observed increasing the CV from 0 to 1, that is, when a conditioning input was delivered with constant ISIs, or according to a Gamma distribution or a simple (homogeneous) Poisson (Fig. 4). The model suggested that the differences with the constant ISIs case could further increase, when more irregular input patterns (higher CV) are delivered to the synapse. Both the no-effects/LTD and LTD/LTP thresholds could be significantly shifted by increasing the bursting behavior of the input ISIs, even if the average frequency is maintained constant.

It easy to see that our qualitative results depend only on our assumptions that LTD and LTP are selectively induced by different levels of synaptic activity (as unquestionably shown by experiments), and could be explained by the increased variability in the input ISIs caused by a presynaptic bursting behavior. The occasional clustering of presynaptic spikes at the appropriate frequency and duration, most likely to occur in a bursting Poisson process, was able to significantly alter the probability to induce LTD/LTP in the synapse, with respect to a homogeneous process. The use of a more detailed set of kinetics, of an analog synapse or a different set of parameters, may result in quantitatively different results (in the direction and amount of the threshold shift). However, the main qualitative result that the net amount of LTD/LTP (and, thus, the LTD/LTP threshold) could dynamically change according to the temporal distri-

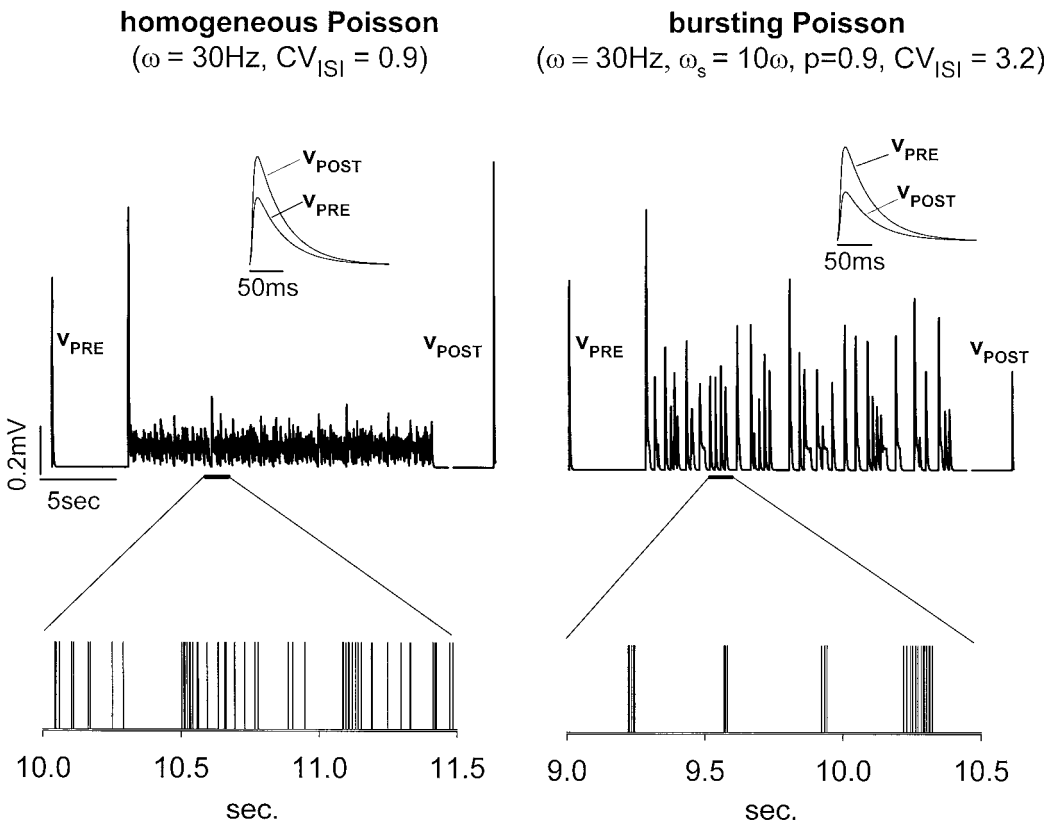

FIGURE 6 Postsynaptic depolarization during a 20-sec conditioning period at a mean frequency of $\omega = 30$ Hz using a homogeneous (*left*) or a bursting Poisson process (*right*). In the bursting case, two homogeneous Poisson processes were mixed in such a way to obtain bursts of stimuli with an average intraburst frequency of $\omega_s = 10\omega$ and probability $p = 0.9$ (see Eq. 9). The insets show a superposition of the postsynaptic response to test stimuli delivered before (ν_{pre}) and after (ν_{post}) conditioning. The bottom panels show typical temporal distributions of stimuli in both cases.

bution of the conditioning stimuli is rather general, and it is consistent with the theoretical view (Lisman, 1997) and the experimental evidence (Hajos and Sharp, 1997), suggesting that bursts are more effective than constant frequency in inducing synaptic plasticity and, thus, may be a useful way to encode information. Our findings in the present work, where we used the presynaptic model from Markram and Tsodyks (1997) and Abbott et al. (1997), are in agreement with the BCM theory (Bienenstock et al., 1982) predicting that, to avoid saturation of the synapses and maximize the amount of information that could be stored in a network, the LTD/LTP threshold should slide to the right (LTD should increase and LTP decrease) increasing the input activity levels. They are also consistent with the experimental findings in layer 2/3 of rat primary visual cortex (Varela et al., 1997), where an extensive depression was induced using a random mixture of frequencies as conditioning stimulation. Furthermore, depression was preferentially induced in hippocampal CA1 region, using stimulation patterns derived from in vivo recordings (Dobrunz and Stevens, 1999). However, in a series of in vitro experiments in the CA1 region (Tsukada et al., 1994; Aihara et al., 1997), using a Markov chain to increase the statistical correlation between successive ISIs (Tsukada et al., 1983), the LTD/LTP threshold was shifted to the left, with respect to a constant stimulation (i.e., the amount of LTP increased using a bursting stimulation). In this latter case, we have previously shown (Migliore and Lansky, 1999) that the use of a nondepressing synapse may result in a threshold shift consistent with the experiments.

Beyond the quantitative aspects discussed above, however, our results pointed out a new operational mode for a synapse that could be easily masked by the typical stimulation protocols widely used in the experiments. In response to a change in the ISIs distribution, a synapse could be easily adapted to inputs that might require immediate attention with a shift of the input thresholds required to elicit LTD or LTP, which are restored to their initial conditions as soon as the input pattern returns to the original temporal distribution. An experimental verification of our model's prediction has been recently obtained by Dobrunz and Stevens (1999), who have shown how rapidly synapses change their state in response to natural stimuli in a brain area where this faster mode may be the most useful way to process synaptic inputs, such as the hippocampal place cells region. In our model, such relatively rapid metaplasticity depends on the rapid increase in the level of C, roughly corresponding to Ca^{2+}/calmodulin, and on how fast the autocatalytic variables, N_P and N_D, reach their equilibrium values during a stimulation. The γ and δ rate constants in our model control these properties. In fact, during a stimu-

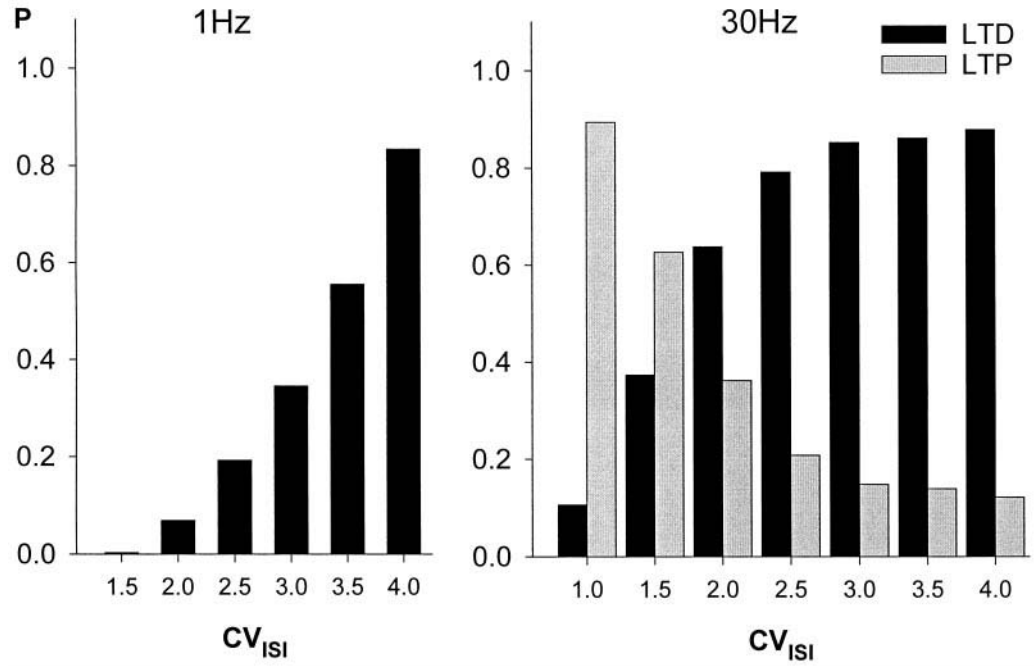

FIGURE 7 Probability to induce LTD or LTP at an average stimulation frequency of 1 or 30 Hz as a function of the CV of the input ISIs, CV_{ISI}.

lation, the previous stable state (nothing, LTP, or LTD) must be eventually changed to reflect the current features of the input. High values of γ provide the appropriate level of C needed to activate the autocatalytic processes for N_P and N_D. High values for δ, representing the Ca^{2+}-dependent phosphatase responsible for the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) dephosphorylation (Lisman, 1994; Coomber, 1998), allow N_P and N_D to reach, with a faster kinetics, the appropriate equilibrium value for a given stimulation. Low values for γ and/or δ would make it more difficult for the synapse to change its state.

It should be stressed that this kind of metaplasticity, as the plasticity of synaptic plasticity that results in the sliding threshold has been termed (Bear, 1995; Abraham and Bear, 1996), is a rather different mode of operation than the conventional long-term shift. Different biochemical/biophysical mechanisms, such as regulations of Ca^{2+} buffering in the spine (Gold and Bear, 1994) and alterations in the autophosphorylation characteristics of the CaMKII (Bear, 1995), have been proposed to explain metaplasticity. A number of experimental results have also showed that purely biochemical stimuli can result in threshold shifts (Stanton, 1995; Cohen and Abraham, 1996; Coussens et al., 1997). However, the recruitment of other biochemical processes or steps, in addition to those already involved with LTP and LTD induction and maintenance, produce modifications of the input level required for LTD/LTP induction that, once established, cannot be easily cleared by an input pattern and can last for up to one hour (Abraham and Bear, 1996; Abraham and Huggett, 1997). This kind of mechanism could be most useful at those synaptic locations where a long-term storage turns out to be the most appropriate computational function at that time and at that point, or region, of the network. In our case, the threshold of the model synapse itself did not change. In fact, we were not acting on the synaptic environment with a preconditioning priming, as in Abraham and Bear (1996), in the CA1 area of the hippocampus or with something like light deprivation, as in the work by Kirkwood et al. (1996), in visual cortex. Instead, we manipulated the temporal distribution of the ISIs within the conditioning period with no change in the average level of input activity. The consequent shifts in the input activity thresholds for LTD and LTP depended only on the temporal distribution of ISIs, and did not require the onset of any additional biochemical mechanisms, which is equivalent to a modification of the model equations, with a consequent change in the threshold of the model synapse itself.

The short-term mode of operation that our model suggested, together with the long-term mode triggered by a priming stimulation (Abraham and Bear, 1996; Kirkwood et al., 1996), might be important steps to control how the massive amount of information that flows within the brain is transformed in a robust and reliable neural code. Although they influence the same processes (LTD and LTP) and have essentially the same effects (both change the amount of LTD and LTP that is induced by a given conditioning), there are no physiological reasons that prevent their implementation at the same time and location, adding functional flexibility and computational complexity to a synapse.

Partial support from Academy of Sciences grant No. A7011712/1997 and Consiglio Nazionale della Ricerche-Istituto per le Applicazioni Interdisci-

plinari della Fisica is acknowledged. M.M. thanks S. Pappalardo for technical assistance.

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