A unified model of NMDA receptor-dependent bidirectional synaptic plasticity

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Synapses in the brain are bidirectionally modifiable, but the routes of induction are diverse. In various experimental paradigms, N-methyl-D-aspartate receptor-dependent long-term depression and long-term potentiation have been induced selectively by varying the membrane potential of the postsynaptic neurons during presynaptic stimulation of a constant frequency, the rate of presynaptic stimulation, and the timing of pre- and postsynaptic action potentials. In this paper, we present a mathematical embodiment of bidirectional synaptic plasticity that is able to explain diverse induction protocols with a fixed set of parameters. The key assumptions and consequences of the model can be tested experimentally; further, the model provides the foundation for a unified theory of N-methyl-D-aspartate receptor-dependent synaptic plasticity.

Synapses throughout the brain are bidirectionally modifiable. This property, postulated in almost every theoretical description of synaptic plasticity, has been most clearly demonstrated at the Schaffer collateral-CA1 synapse in the hippocampus. Here, it was shown that a low-frequency tetanus induces long-term depression (LTD), whereas high-frequency stimulation produces long-term potentiation (LTP) of the stimulated synapses, and that LTD and LTP are inversely related (1–4). Similar results have been obtained at excitatory synapses throughout the brain.

A considerable body of evidence indicates that the important variable is actually the amount of integrated postsynaptic calcium over what would occur with the EPSP alone. This property, postulated in almost every theoretical description of synaptic plasticity, has been most clearly demonstrated at the Schaffer collateral-CA1 synapse in the hippocampus. Here, it was shown that a low-frequency tetanus induces long-term depression (LTD), whereas high-frequency stimulation produces long-term potentiation (LTP) of the stimulated synapses, and that LTD and LTP are inversely related (1–4). Similar results have been obtained at excitatory synapses throughout the brain.

Ideally, one would like to develop a unified description of the calcium level at synapse \( j \) is below a lower threshold \( \theta_s \), no
modification occurs. If $\theta_d < [Ca_i] < \theta_p$, $W_j$ is depressed, and for $[Ca_i] > \theta_p$, the synaptic strength is potentiated (Fig. 1A).

According to Eq. 1, for a sustained elevated level of calcium, the synaptic weight would either increase or decrease indefinitely—a problem that might be solved, for example, by adding upper and lower bounds to synaptic weight strength. Alternatively, a weight decay term can be added. This term helps stabilize synaptic growth without imposing a saturation limit, and results in the following equation:

$$W_j = \eta[\Omega([Ca_i]) - \lambda W_j],$$  \[2\]

where $\lambda$ represents a decay constant. In contrast to Eq. 1, Eq. 2 has a fixed point for a given calcium level and does not usually converge to the upper or lower saturation bounds.

An unwanted consequence of the decay term, however, is that the synaptic weights rapidly converge back to their initial values when calcium returns to the basal level. In addition, equal learning rates for potentiation and depression can lead to unwanted oscillations in synaptic weight. Both problems can be avoided if the learning rate, $\eta$, is assumed to be calcium dependent and to increase monotonically with calcium levels (Fig. 1B). Thus we write:

$$W_j = \eta([Ca_i]) \Omega([Ca_i]) - W_j.$$  \[3\]

The learning rate $\eta$ is inversely proportional to the learning time constant $\tau$. In Eq. 3, we set $\lambda = 1$ without loss of generality.

Eq. 3 contains a dependence on the total level of calcium through the $\Omega$ function (Fig. 1A) as well as on the temporal pattern of calcium through a variable learning rate (Fig. 1B). This equation also can be derived from a biophysical model that accounts for phosphorylation and dephosphorylation of the $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors in response to NMDAR activation (19, 44). For such a biochemical process, a natural consequence is that $\eta$ is calcium dependent. We designate the principles embodied by Eq. 3 the calcium control hypothesis.

**Assumption 2: NMDARs Are the Primary Source of Calcium.** It has been shown recently that NMDARs are the major source of calcium influx into postsynaptic dendritic spines when presynaptic activity is paired with postsynaptic depolarization (21). This finding is consistent with the large body of evidence showing that NMDAR activation is crucial for synaptic induction of many forms of calcium-dependent LTD and LTP (22).

To calculate the change in postsynaptic calcium concentration caused by NMDAR activation in our model, we use a standard set of assumptions about NMDAR voltage dependence, ligand-binding kinetics, and calcium dynamics. The calcium current through NMDAR is assumed to have the form:

$$I_{NMDAR}(t) = P_dG_{NMDAR}[I_\theta(t)e^{-t/\tau} + I_\theta(t)e^{-t/\tau}]H(V),$$  \[4\]

where $H(V)$ summarizes the voltage dependence as described by Jahr and Stevens (23), $P_d = 0.5$ is the fraction of NMDARs in the closed state that shift to the open state after each presynaptic spike (see Simulation Details and Methods, which is published as supporting information on the PNAS web site, www.pnas.org), and $\theta(t)$ is the zero if $t < 0$ and one if $t \geq 0$. The temporal dynamics are assumed to be the sum of a fast ($\tau = 50$ ms) and a slow ($\tau = 200$ ms) exponential (24). Unless stated otherwise, we assume an equal magnitude for the fast and slow components. Calcium dynamics are described by a first-order linear differential equation of the form:

$$\frac{d[Ca(t)]}{dt} = I_{NMDAR}(t) - (1/\tau_{Ca})[Ca(t)],$$  \[5\]

with a time constant $\tau_{Ca} = 50$ ms, chosen as an intermediate value between different published results (21, 25).

We assume throughout this paper that the primary source of $Ca^{2+}$ is the NMDAR. Although the NMDAR is a major source of $Ca^{2+}$ influx (21), other calcium sources, such as voltage-dependent $Ca^{2+}$ and release from intracellular stores, would add details to our model.

**Assumption 3: Back-Propagating Spikes That Contribute to STDP Have a Slow After-Depolarizing Tail.** STDP produces LTD if a postsynaptic spike occurs within a certain time window after a presynaptic spike (we define this condition as pre-post) and produces LTP if a postsynaptic spike comes before a presynaptic spike (post-pre; refs. 7 and 8). If we accept the calcium control hypothesis (assumption 1), then the post-pre stimulation must produce a modest elevation in calcium (above $\theta_d$), and pre-post stimulation must produce a larger elevation of the calcium level (above $\theta_p$). One way in which information about spiking of the postsynaptic cell can be conveyed back to the synapse is through a BPAP. If we accept assumption 2 above, then the only way the BPAP can influence the sign of synaptic plasticity is by altering the $Ca^{2+}$ influx through the NMDAR, and this must be accomplished by changing the postsynaptic voltage when glutamate is bound to the receptor.

If the BPAP duration is short (say 3 ms; ref. 26), the pre-post procedure would elevate calcium levels to those obtained with presynaptic stimulation alone (Fig. 2A 5 and 6); however, the effect would be small because the short duration of the spike only briefly relieves the $Mg^{2+}$ block of the NMDAR. Worse, the post-pre stimulation procedure (Fig. 2A 3 and 4) would produce calcium levels that are essentially identical to those produced by presynaptic stimulation alone (Fig. 2A 1 and 2).

These problems can be overcome by assuming that the BPAP has a wide after-depolarizing tail in the dendrites. Therefore, we propose a BPAP composed of two components: a fast spike (with time constant $\tau_f = 3$ ms) followed by a slower (and much smaller) after-depolarizing potential (ADP; with a time constant $\tau_{ADP} = 25$ ms). We have chosen the simple functional form:

$$BPAP(t) = 100*[(I_{exp}^{BPAP}exp(-t/\tau_f) + I_{exp}^{BPAP}exp(-t/\tau_{ADP}))],$$  \[6\]

where 100 is the maximal depolarization due to the BPAP, and $I_f$ and $I_{ADP}$ are the relative magnitudes of the fast and slow component of the back spike, respectively, that sum to one. The width and relative magnitude of the ADP component we have assumed is consistent with measurements in dendrites (27, 28). In comparing this assumption with experimental measurement, it should be noted that measurements of half-width at half-height of the full BPAP are nearly independent of the ADP, provided it has a small enough magnitude.

Under this assumption, a post-pre stimulus (Fig. 2B 3 and 4) results in a significantly elevated calcium level when compared with presynaptic stimulation alone (Fig. 2B 1 and 2). Further, the pre-post stimulation results in a much larger calcium increase (Fig. 2B 5 and 6). Notice that because of the form of the calcium transient...
in the pre-post stimulation sequence (Fig. 2B 6), as much time is spent between $\delta_t$ and $\Delta t$ as is spent above $\delta_t$. If learning rates were uniform, all synaptic enhancement above $\delta_t$ would be canceled by synaptic depression between $\delta_t$ and $\Delta t$. This problem is overcome by our proposal that the learning rates increase with increasing calcium levels (Fig. 1B).

Fig. 2. Consequences of changing the duration of the BPAP. (A) Narrow BPAP. Presynaptic stimulation alone (A1) results in the binding of glutamate to NMDAR (blue) and a small postsynaptic depolarization (red; not visible at this scale), which produces moderate calcium influx (A2). Post-pre stimulation ($\Delta t = -10$ ms) (A3) results in a large but brief postsynaptic depolarization that is nearly over before the opening of the NMDARs, which produces calcium influx (A4) nearly identical to that produced by pre alone (A2). Pre-post stimulation ($\Delta t = -10$ ms) (A5) results in a strong but brief depolarization shortly after NMDAR open, which results in slightly larger calcium transients (A6). (B) Consequences of a BPAP with a long repolarization tail. Presynaptic stimulation alone (B1, B2) is identical to the previous case described above with narrow BPAP (A1, A2). Post-pre stimulation ($\Delta t = -10$ ms) (B3) results in a strong postsynaptic depolarization that partially overlaps the onset of glutamate binding to NMDAR. Therefore, the calcium influx in this case (B4) is significantly larger than for pre alone (B2). Pre-post stimulation ($\Delta t = -10$ ms) (B5) results in a strong depolarization (red) shortly after NMDARs open (blue). This stimulation protocol results in calcium transients (B6) that are larger than the calcium transients in the pre-post condition. Therefore, with the wider back spike, two thresholds (dashed green lines) can be set for LTD and LTP.
A detailed description of the methods and equations used can be found in Simulation Details and Methods.

Results

We now show that the various induction protocols can be simulated with our model by using a single set of parameters. These parameters were chosen to yield STDP consistent with what was reported by Bi and Poo (8); however, qualitatively different results can be obtained with different parameter choices.

Induction of Synaptic Plasticity by Pairing Presynaptic Stimulation with Postsynaptic Voltage Clamp. The control calculation hypothesis is formulated with the aid of a thought experiment in which the calcium level is controlled directly for a sustained period. This experiment, although conceptually simple, is practically difficult to implement (17). A more common approach is the induction of plasticity by "pairing," in which the postsynaptic voltage is clamped to a fixed value and low-frequency pulses are delivered to the presynaptic pathway (5, 29–31).

Pairing was simulated with 100 presynaptic pulses at low frequency (1 Hz), whereas the postsynaptic cell was held at a constant voltage. The fixed point of the synaptic weight, \( W \), varied continuously with the level of the postsynaptic potential during pairing (Fig. 3A). No plasticity was induced below \(-65\) mV, LTD was induced between \(-60\) mV and \(-52.5\) mV, and LTP was induced at higher postsynaptic potentials. This result is reminiscent of the \( \Phi \) function of the Bienenstock, Cooper, Munro (BCM) theory (32), and is a direct consequence of the form of \( \Phi \) in assumption I.

Because of the calcium-dependent learning rate, induction of LTD is more rapid than the induction of LTP, and because of the decay term, the rate of plasticity depends on the initial synaptic strength. Both of these results are consistent with experimental observations, and are described further in Figs. 6 and 7, which are published as supporting information on the PNAS web site.

Induction of Synaptic Plasticity by Varying the Rate of Presynaptic Stimulation. Most synaptic plasticity experiments have been performed by using extracellular field potential recording. Such procedures do not allow as much control of postsynaptic depolarization and action potentials as does the induction paradigm described above. When using extracellular methods, LTP is attained by high-frequency stimulation of presynaptic afferents, and LTD is attained by low-frequency stimulation (1, 3). The frequency and intensity of the stimulus is used to indirectly control the postsynaptic depolarization and magnitude of intracellular calcium.

Applying the calcium control hypothesis to rate-based induction paradigms requires a mathematical description of a cortical cell. Neuronal responses to tectonic stimulation are complex and depend on physiological properties of cells and synapses that can vary substantially. As a first approximation, we implemented a simple statistical model of the postsynaptic neuron for generating postsynaptic spikes (see Simulation Details and Methods); in addition, to simplify the analysis further, we also simulated synaptic plasticity in the absence of postsynaptic action potentials. The latter situation is easier to simulate and requires fewer additional assumptions about neuronal excitability. Such simulations are further justified by the fact that most LTD (and many LTP) experiments are carried out in the low-intensity regime where few postsynaptic spikes are generated. In the absence of spikes, we assume that local temporal and spatial integration of excitatory postsynaptic potentials are the sole source for the postsynaptic depolarization, which we take into account by using a spatial integration parameter (see Simulation Details and Methods).

To induce frequency-dependent synaptic plasticity, we simulate an induction paradigm composed of 900 extracellular stimuli at different frequencies from 0.5–20 Hz. Simulations of rate-induced plasticity with and without postsynaptic spikes result in a complete LTD/LTP curve similar to those observed experimentally (Fig. 3B). We also find that the generation of spikes during low-frequency stimulation reduces the magnitude of LTD and lowers the LTP threshold.

Induction of Synaptic Plasticity by Varying Spike Timing. To simulate STDP, we evoke pre- and postsynaptic action potentials with different time lags between them. We denote by \( \Delta t = t_{\text{pre}} - t_{\text{post}} \) the time lag between the post- and presynaptic action potentials; negative numbers imply that the postsynaptic action potential precedes the presynaptic action potential. Pairs of presynaptic and postsynaptic stimuli were repeated 100 times at 1 Hz. In Fig. 3C, we display the full STDP plot as a function of \( \Delta t \). The y axis represents the value of the synaptic weight after 100 pairs of pre- and postsynaptic stimulation. For \(-30\) ms < \( \Delta t \) < \(-5\) ms, we obtain LTD; for \( 0 \) < \( \Delta t \) < \( 45\) ms, we obtain LTP. This finding is consistent with experimental results (7, 8).

Pre-Post LTD. In addition to the expected results displayed in Fig. 3C, however, we also obtain an unexpected LTD region at values of \( \Delta t \) > 50 ms. This LTD occurs because the fraction of NMDARs in the open state decays continuously (although in a stochastic manner) after the initial binding of glutamate, and the concentration of
calcium that produces LTD, according to Eq. 3, is at an intermediate value between the concentration that produces no change and the concentration that produces LTP. If a postsynaptic spike arriving at a short time interval ($\Delta t_1$) after a presynaptic event causes LTP, and if a postsynaptic spike arriving at a very long interval ($\Delta t_2$) after the presynaptic spike elicits no change, then there must be an intermediate time ($\Delta t_3$) such that $\Delta t_1 > \Delta t_3 > \Delta t_2$ which, on average, produces LTD. Although the existence of this LTD region is a robust prediction of our model, we show below (Figs. 4 and 5 and Figs. 8 and 9, which are published as supporting information on the PNAS web site) that the width of this region depends on the model parameters and, primarily, on the NMDAR time constants. In addition, we expect considerable variability in producing LTD at any single delay because of large fluctuations in the relative number of NMDAR in the open state in this time window.

If experiments show that the pre-post form of LTD does not exist, they would necessitate the alteration of one of our key assumptions. Because it likely that calcium levels vary continuously as a function of $\Delta t$, whether their primary source is NMDAR (assumption 2) or another calcium source, a failure to find pre-post LTD would indicate that the calcium control hypothesis must be altered.

Existing data are relatively sparse at pre-post delays greater than 20 ms (7, 8, 10), and we hope our model will encourage greater scrutiny of longer $\Delta t$. However, Nishiyama et al. (ref. 33; Fig. 2) reported LTD at pre-post delays greater than those effective for LTP, consistent with the prediction of our model.

**Necessary Properties of the BPAP.** To account for STDP under the assumption that NMDARs are the primary source of calcium, we additionally assume that the BPAP has a slow after-depolarizing tail (Fig. 2A). It is not surprising, therefore, that the shape of the STDP curve has a strong dependence on the form of the BPAP. Changing the width of the ADP from 25 ms to 15 and 50 ms, for example, significantly alters the STDP function, particularly the width of the post-pre LTD window (Fig. 4A). A strong prediction of our model is that in the absence of a broad BPAP there will be no post-pre form of LTD. We also predict that regulation of this property, e.g., by those in modulation of dendritic potassium conductances, will have a profound effect on the properties of synaptic plasticity.

**Rate Dependence of STDP.** Another fundamental consequence of our model is that the STDP function varies with the frequency of stimulation (Fig. 4B). The form of the STDP curve changes at 5 Hz, and LTP is induced at all values of $\Delta t$ at 10 Hz. This result is because of temporal integration of calcium transients. It is important to stress that the detailed frequency dependence will depend on the choice of parameters. However, regardless of the specific parameters used, there is a frequency at which potentiation is induced at all $\Delta t$. We note that the qualitative form of the frequency dependence of STDP, which is a consequence of our theoretical model, has very recently received some initial experimental support (34).

Unlike hippocampal neurons in culture (8), pre-post LTP in some neocortical slices have been shown to require high rates of stimulation (7), yielding a frequency dependence different from that displayed in Fig. 4B. These findings can be reproduced by varying some of the parameters of the model (see Fig. 10, which is published as supporting information on the PNAS web site). In other neocortical preparations, STDP has been induced with low-frequency stimulation (10, 34) but requires more robust extracellular stimulation. It is important to emphasize that, just as the properties of neurons vary significantly from one preparation to another, it is to be expected that parameter values also vary. Such variation can reproduce different manifestations of STDP.

Stability in previous models of STDP has required the assumption that LTD predominates over LTP (35). Thus, the saturation of STDP at higher frequencies poses a potential problem for our theory. Therefore, an additional mechanism for stabilizing plasticity should be assumed. Possible mechanisms that have experimental support are changes in NMDAR excitatory postsynaptic potential amplitude and duration that occur as a function of the history of cortical activity (24, 36–38). In the next section we describe the effect changing the temporal dynamics of the NMDAR.

**Effect of Varying NMDAR-Binding Kinetics.** The magnitude and the kinetics of the calcium influx through NMDARs affect the functional form of synaptic plasticity in all of the induction protocols we
aptic plasticity based on three key assumptions: (i) postsynaptic Ca$^{2+}$ controls the rate and sign of synaptic plasticity, according to the calcium control hypothesis; (ii) NMDARs are the relevant sources of Ca$^{2+}$; and (iii) the BPAP has a long-lasting depolarization. This model accounts for forms of synaptic plasticity induction as diverse as STDp, pairing-induced plasticity, and rate-dependent plasticity. It also accounts for the frequency dependence of STDp. However, a model based solely on these three assumptions is likely to be unstable—like many other Hebbian models. Therefore, we propose an additional assumption (iv), that metaplasticity, through activity-dependent regulation of NMDAR properties, is required for stability. In this paper, we show that plasticity can be achieved by plasticity of NMDAR but do not show that it is required for stability or specify a dynamic equation governing the plasticity of NMDAR. In another paper (44), we propose a specific dynamical equation. Further investigation of the implications of these coupled dynamical equations for receptive field plasticity is needed.

In the past, a common description of synaptic plasticity was based on the rates of pre- and postsynaptic firing (45). Recent results have shown that plasticity can also depend on the precise timing of pre- and postsynaptic spikes. These new findings have led to the suggestions that rate- and pairing-based induction protocols are artificial, whereas spike-time induction protocols are more similar to those occurring naturally, and that naturally occurring forms of plasticity can be accounted for on the basis of STDp. Indeed, some theoretical studies have shown how rate-based plasticity can be derived from STDp (45–47). However, in vitro (5, 29) and in vivo (48, 49) plasticity can occur in the absence of postsynaptic spikes. Moreover, naturally occurring plasticity, even when postsynaptic spikes are present, cannot be accounted for solely by linearly superimposing STDp curves obtained at a single frequency, because this will not account for the frequency dependence of STDp.

Other models that attempt to account theoretically for various forms of induction on the basis of a common mechanism have been put forward (20, 50, 51). Although these attempts are conceptually similar to ours, they differ in the specific mechanisms assumed, as well as in the resulting consequences, and therefore can be distinguished experimentally from our proposal.

Our model of NMDAR-dependent synaptic plasticity is based on a common, low-level, physiological mechanism that can account both for the various induction protocols and naturally occurring plasticity. The structure we have presented here, with its clear connections between assumptions and consequences (expected as well as previously uncharacterized), can and should be tested experimentally. If it passes the experimental test, it can serve as a basis for a unified theory of synaptic plasticity.

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