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Converging evidence for a simplified biophysical model of synaptic plasticity

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Abstract. Different mechanisms that could form the molecular basis for bi-directional synaptic plasticity have been identified experimentally and corresponding biophysical models can be constructed. However, such models are complex and therefore it is hard to deduce their consequences to compare them to existing abstract models of synaptic plasticity. In this paper we examine two such models: a phenomenological one inspired by the phenomena of AMPA receptor insertion, and a more complex biophysical model based on the phenomena of AMPA receptor phosphorylation. We show that under certain approximations both these models can be mapped on to an equivalent, calcium-dependent, differential equation. Intracellular calcium concentration varies locally in each postsynaptic compartment, thus the plasticity rule we extract is a single-synapse rule. We convert this single synapse plasticity equation to a multi-synapse rule by incorporating a model of the NMDA receptor. Finally we suggest a mathematical embodiment of metaplasticity, which is consistent with observations on NMDA receptor properties and dependence on cellular activity. These results, in combination with some of our previous results, produce converging evidence for the calcium control hypothesis including a dependence of synaptic plasticity on the level of intercellular calcium as well as on the temporal pattern of calcium transients.

1 Introduction

Bi-directional changes in the strength of synaptic efficacy are thought to underlie information storage in neural networks. In many regions of the brain, long-term potentiation (LTP) (Bliss and Lømo 1973), a long-lasting increase in synaptic efficacy, is produced by high frequency stimulation (HFS) of presynaptic afferent or by pairing presynaptic stimulation with robust postsynaptic depolarization (Wigstrom and Gustafsson 1986). Long-term depression (LTD) (Dudek and Bear 1992), a long-lasting decrease in the strength of synaptic transmission, is produced by low frequency stimulation (LFS) of presynaptic afferent. Not only are LTP and LTD expressed in many brain regions of numerous species, but also the majority of synapses that express LTP also express LTD, which is the reason it is known as bi-directional plasticity.

The AMPA subtype of ionotropic glutamate receptor (AMPAR) provides the majority of inward, depolarizing current at excitatory synapses. As such, changes in the response properties of glutamatergic synapses will profoundly affect synaptic strength. Experimental support for the following three major, non-mutually exclusive hypotheses, have been put forward as molecular bases of bi-directional activity-dependent synaptic plasticity: 1) change in the probability of glutamate release (Stevens and Wang 1994) 2) insertion/removal of postsynaptic AMPAR's (Liao et al. 1995; Isaac et al. 1996) 3) Phosphorylation and dephosphorylation induced change of AMPAR conductance (Lee et al. 2000; Barria et al. 1997).

In this paper we address the postsynaptic mechanisms (hypotheses 2 and 3 above). The model we develop of AMPAR insertion is phenomenological, and is based on experimental observations (Sect. 2), while the phosphorylation models we examine are based on our previous complex biophysical approach (Castellani et al. 2001) (Sect. 3). A fundamental assumption shared by both of these approaches is that calcium influx through NMDA receptors is the trigger for a signal transduction cascade that controls the sign and magnitude of synaptic plasticity (Bear et al. 1987; Lisman 1989; Yang et al. 1999; Cormier et al. 2001).

Both approaches produce the same equation for calcium dependent synaptic plasticity. This equation, which we denote the *calcium control hypothesis*, has also been hypothesized as a possible mechanism to explain various forms of plasticity (Shouval et al. 2002). Thus there is converging evidence for this calcium control hypothesis.

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The calcium-dependent synaptic plasticity equation that we derive here depends on the local level of calcium at each synapse. In contrast, most abstract learning rules (von der Malsburg 1973; Oja 1982; Bienenstock et al. 1982; Linsker 1986) depend on a local presynaptic variable and a global postsynaptic variable. We use a known model of NMDA receptor calcium influx (Jahr and Stevens 1990) to obtain a model that depends on presynaptic glutamate release and postsynaptic depolarization. In addition we use temporal averaging to obtain a rate based model. These steps convert the original single-synapse, calcium dependent rule to a multi-synapse rule that depends on a local, rate dependent, presynaptic variable (glutamate binding) and a global postsynaptic variable (postsynaptic depolarization).

Like many Hebbian rules, this plasticity equation is not stable. Additional assumptions must be made in order to stabilize learning. We show how metaplasticity (Abraham and Bear 1996; Bienenstock et al. 1982) can be added to this rule by assuming plasticity of NMDA receptors' conductance (Carmignoto and Vicini 1992; Quinlan et al. 1999; Philpot et al. 2001; Watt et al. 2000). This type of metaplasticity is analogous to the sliding modification threshold of the BCM rule. We derive an explicit equation for the plasticity of NMDA receptors that leads to BCM-like metaplasticity. The consequences of this approach are consistent with experimental observations (Kirkwood et al. 1996; Wang and Wagner 1999).

2 A phenomenological model of AMPAR insertion

Exocytosis and endocytosis of AMPAR's have been suggested as mechanisms for LTP and LTD. There is significant evidence that the induction of LTP causes AMPAR's to be inserted into the postsynaptic membrane (Liao et al. 1995; Isaac et al. 1996). It has also been shown that LTD correlates with physical *removal* of AMPAR's from dendritic spines (Kandler et al. 1998; Carroll et al. 1999) and that LTP correlates with *delivery* of AMPAR's to dendritic spines (Shi et al. 1999; Hayashi et al. 2000). In addition it has been demonstrated in vivo that LTP results in an *increased* number of AMPA receptors in the postsynaptic density and that LTD results in a *decrease* in their number (Heynen et al. 2000).

Further, there is strong evidence that calcium levels are the primary trigger for the induction of synaptic
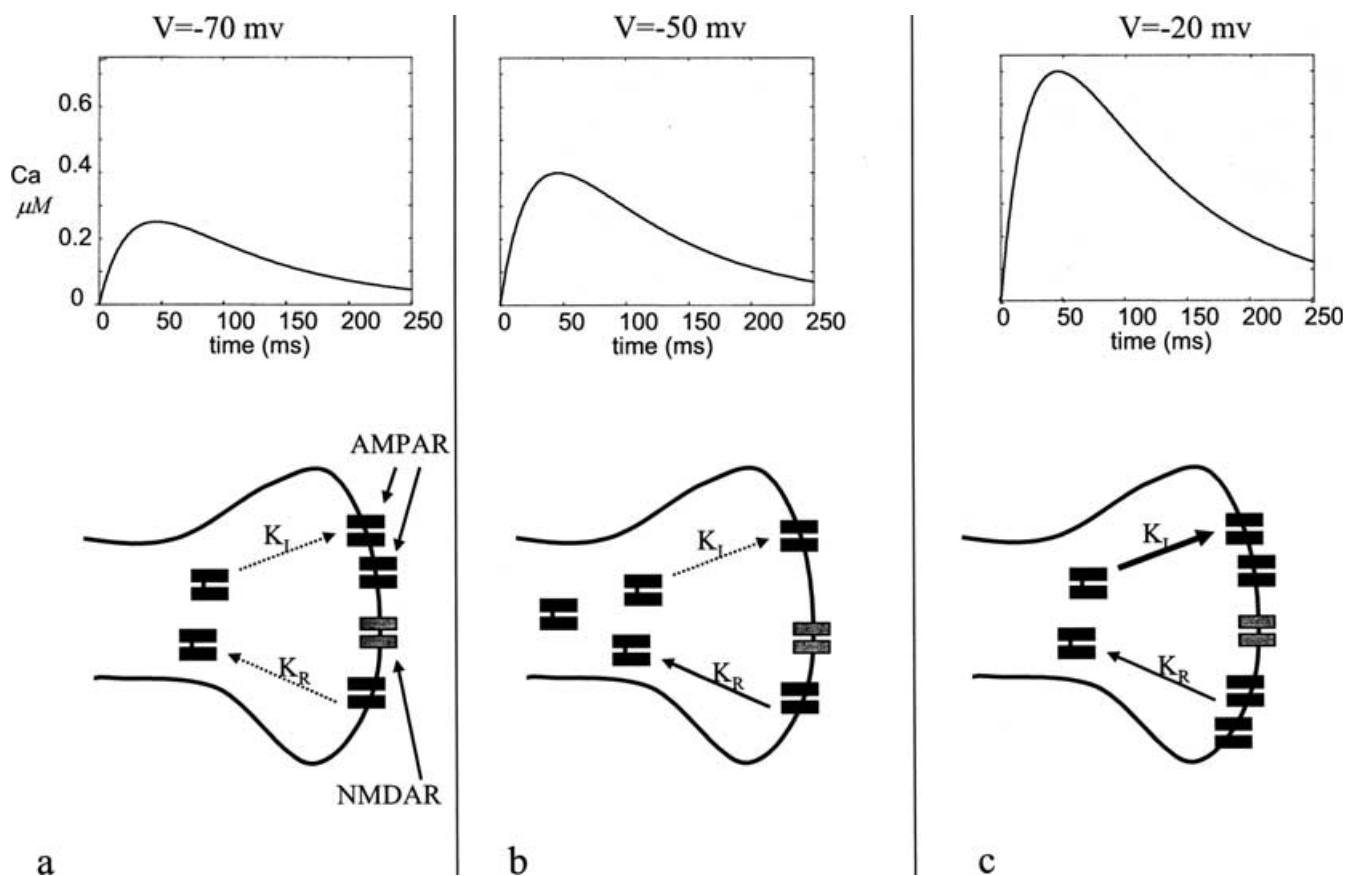

Fig. 1a–c. and Exocytosis of AMPA receptors during a pairing induced plasticity protocol. AMPA receptors are shown in Black, and NMDA receptors in gray. **a** At –70 mv small calcium transients are invoked (top), this does not significantly alter the insertion (K_I) and removal (K_R) coefficients, and conductance remains at basal levels. **b** When a cell is depolarized to –50 mv, higher calcium transients are induced. At this level of calcium, K_R is significantly increased resulting in a removal of AMPA receptors from the membrane, and in reduced conductance at the synapse. **c** At higher depolarization (–20 mv) the K_I becomes significantly larger than K_R resulting in net insertion of AMPA receptors into the membrane and increased conductance

plasticity (Yang et al. 1999; Cormier et al. 2001; Cummings et al. 1996). Here we construct a model based on the two following assumptions: (1) AMPAR endocytosis and exocytosis is a mechanism for the induction of LTD and LTP. (2) The primary signal for synaptic plasticity is the postsynaptic calcium level. The model that is based on these assumptions is consistent with many experimental results. This model is depicted schematically in Fig. 1, where we demonstrate its function during low frequency pairing induced plasticity, in which a low frequency presynaptic stimulus is delivered to a cell which is voltage clamped at a fixed postsynaptic voltage.

We consider two populations of AMPAR's in synaptic spines: one population (A_m) is inserted in the membrane, and the other population (A_I) is internal to the postsynaptic compartment. We assume that $A_I + A_m = A_T$, where A_T is constant. The total AMPAR conductance is proportional to the number of AMPARs in the membrane, thus the synaptic strength, $W \propto A_m$. AMPAR's are continually inserted into the membrane and removed from the membrane. The kinetic constants for insertion and removal ($K_I = K_I(Ca)$ and $K_R = K_R(Ca)$) are assumed to depend on intracellular calcium concentration Ca.

This process can be described by the following set of differential equations:

$$\dot{A}_m = -K_R A_m + K_I A_I$$

$$\dot{A}_I = K_R A_m - K_I A_I \; . \tag{1}$$

These equations, by construction, preserve the total number of AMPAR, thus $A_m + A_I = A_T$. Equation 1 is a first order linear differential equation, which can easily be solved:

$$A_m(t) = (A_m(0) - A_m^{fp})e^{-t/\tau(Ca)} + A_m^{fp} \; , \tag{2}$$

where $A_m^{fp} = (A_T K_I)/(K_I + K_R)$ is the fixed point of the equation, $\tau(Ca) = 1/(K_I + K_R)$ is a calcium dependent time constant and $A_m(0)$ is the initial condition of $A_m(t)$. Note that since the kinetic constants are calcium dependent, both the fixed point and the time constant are also calcium dependent.

Equation 1 can be rewritten, using the conserved number of AMPA receptors A_T, to obtain: $\dot{A}_m = -(K_I + K_R)A_m + K_I A_T$. The synaptic strength depends on the conductance, which in turn is proportional to the number of synaptic AMPA receptors, thus $W = \beta A_m$, where β is a proportionality constant. Thus, the synaptic strength obeys the following synaptic plasticity equation:

$$\dot{W}_i(t) = \frac{1}{\tau([Ca]_i)}\left(\Omega([Ca]_i) - W_i\right) \tag{3}$$

where $\Omega(Ca) = \beta K_I A_T/(K_I + K_R) = \beta A_m^{fp}$, $\tau = 1/(K_I + K_R)$, and $[Ca]_i$ is the value of postsynaptic Ca^{2+} concentration at synapse i. We often use the notation Ca instead of $[Ca]_i$ for simplicity. Note that $\Omega([Ca]_i)$ sets the value of the fixed point of W_i and that $\tau([Ca]_i)$ sets the convergence time.

What form of calcium dependence is required of the kinetic constants to produce experimentally plausible LTP/LTD curves? For each calcium level, it is sufficient to measure the variables Ω and τ in order to determine the constants K_R and K_I. We obtain $K_I = c\Omega/\tau$ and $K_R = (1 - c\Omega)/\tau$, where $c = 1/\beta A_T$. For convenience we take $c = 1$. In Fig. 2 we show an example based on a possible functional form of A_m^{fp} and τ.

We have used experimental results in order to construct the functional form of Ω and τ in Fig. 2. The plot for Ω was inspired by the results of Cormier et. al. 2001 (Cormier et al. 2001). Further, with the assumption $c = 1$, Ω represents the fraction of total AMPAR in the
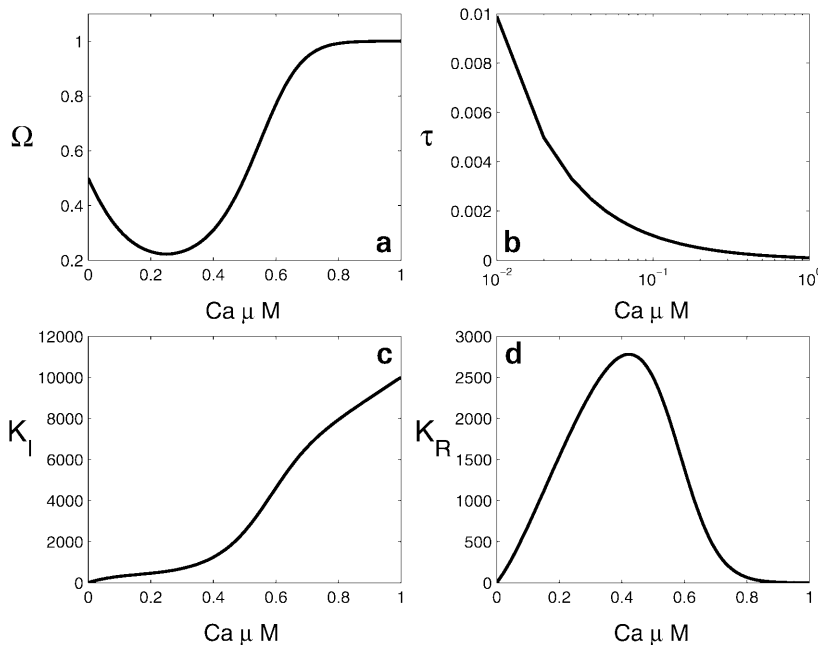

Fig. 2a–d. AMPAR insertion model, an example: **a** The Ω function, here we assume a saturating U shape, inspired by Cormier et. al. (2001). **b** A monotonically decreasing τ function. **c** The resulting K_I **d** The resulting K_R. The kinetic constants are calculated from the displayed Ω and τ

synapse, which is embedded in the membrane. In constructing the plot for τ, we have again utilized experimental results. We set τ for very low calcium levels to be ≈ 150 min, which is inspired by the time constant for the decay of early LTP and LTD when protein syntheses inhibitors are used (Otani et al. 1989; Manahan-Vaughan et al. 2000). The value of τ for $Ca = 1\mu M$ was set to ≈ 1.5 min because LTP induction mechanisms are fast, taking not more than a few minutes to complete.

Results show that K_I is monotonically increasing with calcium (Fig. 2c), whereas K_R (Fig. 2d) has approximately a bell shape. However, it must be noted that these plots are not unique and have been created for purposes of illustration. In particular, qualitatively similar forms for Ω and τ can be obtained for monotonically increasing K_I and K_R.

3 Simplified dynamics of a biophysical phosphorylation cycle

The AMPAR is a heteromer, composed of multiple subtypes of subunit proteins (GluR1-GluR4). GluR1 can be phosphorylated on Ser 831 by CaMKII and protein kinase C, whereas protein kinase A phosphorylates Ser 845. The induction of LTP specifically increase phosphorylation of Ser 831 (S831) (Barria et al. 1997). Both the increase in synaptic strength and GluR1 phosphorylation are blocked when a CaMKII inhibitor is present during the LTP induction protocol (Lee et al. 2000; Barria et al. 1997). Phosphorylation of S831 increases, by approximately two-fold, the single channel conductance of homomeric GluR1 AMPA receptors, as

seen in heterologous expression systems (Derkach et al. 1999). LTD is accompanied by a decrease in the phosphorylation of Ser 845 (S845), which appears to be phosphorylated at normal resting potential (Lee et al. 1998; Lee et al. 2000). Physiologically induced LTD is blocked by either PP1 or PP2b inhibitors (Mulkey et al. 1993; Lee et al. 2000) and reduced by PKA inhibitors (Otmakhova et al. 2000). It has also been shown that phosphorylation of the AMPAR at the PKA site (S845) increases the mean channel open probability, which increases the macroscopic conductance by slightly less than a factor of two (Greengard et al. 1991; Banke et al. 2000).

We have used these experimental results to construct a detailed biophysical model of bi-directional synaptic plasticity (Castellani et al. 2001). Here, we examine its temporal dynamics and show how it can be approximated by a simpler model, formally equivalent to our AMPAR insertion model derivation. Similar to the phenomenological model in the previous section, for a fixed calcium level, the synaptic conductance reaches a fixed point depending on Ca. Thus, as above, the fixed point of W, denoted by W_{fp} is determined by Ω, such that: $W_{fp} = W_{fp}(Ca) = \Omega(Ca)$. This fixed point, as well as the dynamics, depend on the various phosphatases and kinases, including CamKII. However, by describing them directly as a function of Ca we present a simpler expression.

The models we have developed here are of induction, not maintenance, of synaptic plasticity. The complex biophysical model (Castellani et al. 2001), on which this section is based, includes the modeling of CamKII phosphorylation, which has been suggested as a basis for
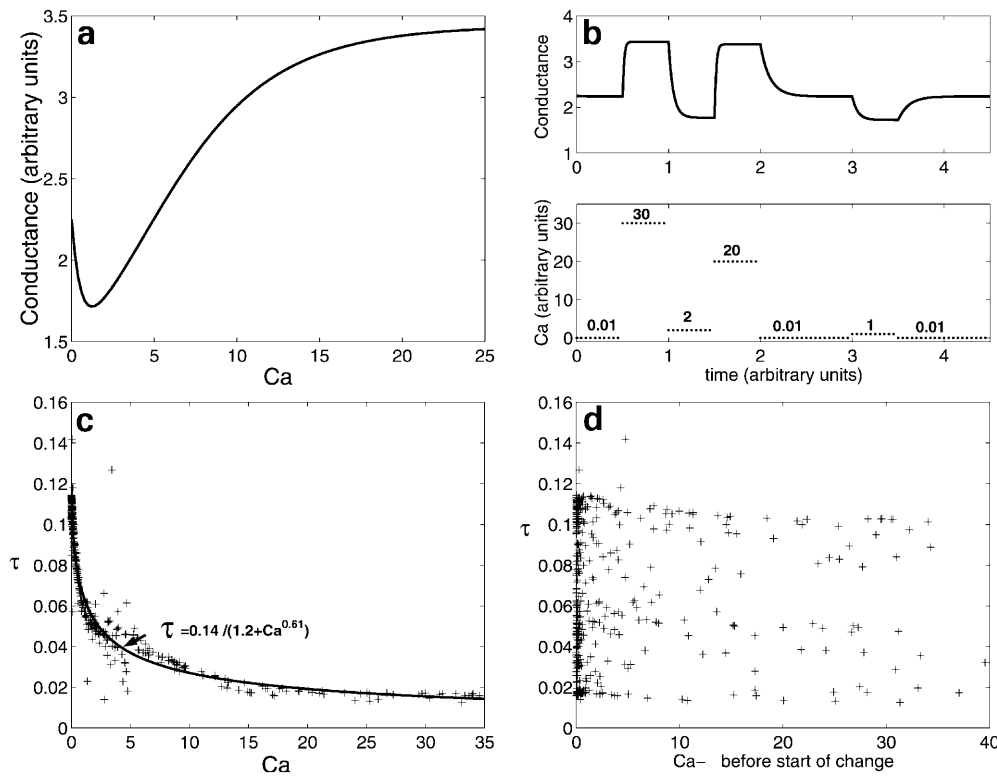

Fig. 3a–d. Dynamics of a phosphorylation cycle model of synaptic plasticity. **a** The fixed points of the conductance as a function of intercellular Ca level. **b** An example of the dynamics of the phosphorylation model. Calcium levels are changed discretely as indicated. The dynamics of approaching the fixed points are approximately exponential. **c** An estimate of the dependence of the plasticity time constant τ on the calcium level. The data are represented by + and the line is the fit. **d** Calcium level before the start of the dynamics was uncorrelated with the time constant

In plot c: $\tau = 0.14 / (1.2 + Ca^{0.61})$

maintenance (Lisman and Goldring 1988). However, in this model, although CamKII phosphorylation can outlast the rise in *Ca* levels, it is not essential for induction obtained by a prolonged rise in calcium levels.

It is difficult to solve the dynamics of such models analytically. However, they are easily solved numerically. In Fig. 3 we show the resulting fixed points and dynamics of this complex biophysical model for a specific set of parameters. This is one example from the set of models described in Castellani et. al. 2001, which has four selective enzymes and uses Michaelis-Menten dynamics. The kinetic constants in this example are chosen to produce results that are qualitatively similar to experimental results.

In Fig. 3a we display the fixed points of the conductance for different calcium levels. This result is qualitatively similar to the results by Cormier et. al. (2001). However, it should be kept in mind that the x and y axis, here, have arbitrary units. In Fig 3b we see an example in which we switch the calcium level between different random values. The calcium level is kept at each value long enough for the weights to nearly converge to the fixed point. By inspecting the figure we see that the dynamics of approaching the fixed points are approximately exponential, however the time constant, τ, is different at each calcium level. The values of τ and Ω at each calcium level depend implicitly on the levels of kinases, phosphatases and their temporal dynamics. To assess the dependence of τ on calcium levels we repeated the type of simulation displayed in Fig. 3b several times as follows. First, we randomly set an initial calcium level (*Ca*1) and let the state converge to a fixed point. We then abruptly changed the calcium level to another randomly chosen value (*Ca*2) and let the dynamics approach the new fixed point. We fit the changing level of conductance, after we switched over to $Ca = Ca2$, to an exponential with time constant τ. In Figs. 3c and 3d we display τ as a function of *Ca*2 and *Ca*1 respectively. The value of τ is clearly correlated with *Ca*2 but not with *Ca*1. To estimate the dependence of τ on *Ca*2 we fit the data points to a function of the form $\tau = p_1/(p_2 + Ca^{p_3})$. We obtained a good fit with $p_1 = 0.14, p_2 = 1.2$ and $p_3 = 0.61$. No physiological relevance should be ascribed to these numbers as we do not have many of the kinetic constants necessary for obtaining a quantitatively precise model.

Based on these results, we assume that synaptic weights approach their fixed point exponentially, thus

$$W(t) = W_0 + (W_{fp}(Ca) - W_0)(1 - e^{-t/\tau(Ca)}) \; , \tag{4}$$

where $W(t)$ is the synaptic weight at time t, W_0 is the initial synaptic weight and $\tau(Ca)$ is the dynamic time constant which may depend on the level of calcium.

Under the assumption of fixed calcium levels, these dynamics are a solution to the following differential equation:

$$\dot{W}_i = \frac{1}{\tau([Ca]_i)} \left(\Omega([Ca]_i) - W_i \right) \; . \tag{5}$$

This approximate equation for the dynamics of conductance in the phosphorylation cycle model is formally equivalent to the dynamics of the phenomenological model for AMPA receptor insertion (Equation 3). Therefore, Equation 3, which we call the calcium control hypothesis, is a good candidate for the fundamental equation governing synaptic plasticity.

4 Accounting for the various induction protocols

We have used the calcium control hypothesis (Equation 3) as one of three basic postulates in another paper (Shouval et al. 2002). The two additional assumptions we have made are: (1) that the primary source of calcium influx is through the NMDA receptors, and (2) that the back propagating action potential, which contributes to synaptic plasticity, has a long tail component (Magee and Johnston 1997; Larkum et al. 2001). Given these three assumptions we have shown that our model accounts for various experimentally induced forms of synaptic plasticity for a single set of parameters. It can account for pairing induced synaptic plasticity in which the postsynaptic cell is clamped at a fixed potential and low-frequency presynaptic stimulation is delivered (Stevens and Wang 1994; Crair and Malenka 1995; Feldman et al. 1998; Feldman 2000). It can also account for presynaptic frequency-dependent synaptic plasticity in which low-frequency stimuli produce LTD (Dudek and Bear 1992) and high frequency stimuli produce LTP (Bliss and Lømo 1973).

The third induction protocol that we can account for is spike-timimg dependent plasticity (Markram et al. 1997; Bi and Poo 1998; Feldman 2000), in which the precise time difference between pre- and postsynaptic spikes determines the sign and magnitude of synaptic plasticity. To account for LTD, which occurs when the postsynaptic spike precedes the presynaptic spike by 5–20 ms, we had to make an assumption about the tail component of the back propagating action potential. This model can also account for LTP that occurs when the postsynaptic spike follows the presynaptic EPSP. However, the model also predicts a novel form of LTD that is induced when the presynaptic stimulus precedes the postsynaptic spike by a larger time lag than the one producing LTP. This robust prediction, which could form an experimental test for this model, has already been observed experimentally in one study (Nishiyama et al. 2000).

It is unclear at this point if the second LTD window, which is a consequence of our model, is indeed observed in various experimental conditions. This determination would require additional experiments. The existence of this additional LTD region is a factor that can distinguish between this calcium based model and other models based directly on the coincidence between pre- and post-synaptic effects (Senn et al. 2001).

These results, described in detail in another paper (Shouval et al. 2002), show that the calcium control hypothesis, which can be derived from lower level biophysical mechanisms, can also account for various experimental results at the cellular level.

5 Deriving a rate based multi-synapse learning rule

Equations 3 and 5 express synaptic plasticity as a function of postsynaptic calcium at the synapse. Calcium is a local variable which will differ significantly from synapse to synapse, but is dependent on the global level of depolarization in the whole cell. In this section we assume that presynaptic spikes are generated from a non-stationary Poisson distribution and that their rate varies slowly enough so that we can use the calcium levels at steady state. Using these assumptions we derive the average postsynaptic calcium levels and use these levels for driving synaptic plasticity. Since the plasticity equations are non-linear, this is a valid approach only when the level of fluctuations is small compared to the mean. In this paper we did not analyze the fluctuations. However, we expect the relative fluctuations to be smaller at higher presynaptic frequency.

We assume that the relevant point of calcium entry into the postsynaptic compartment are the NMDA receptors. Influx of ions through NMDARs is dependent on voltage and on glutamate binding to the receptor, and therefore signals a coincidence of presynaptic and postsynaptic activity. In addition, there is recent experimental evidence suggesting that the major source of calcium influx into spines is through NMDARs. Calcium influx into the cell, through a single NMDAR, approximately follows the equation

$$[I_{Ca}]_i = G \cdot x_i B(V)(V - V_r) = G \cdot x_i Y \qquad (6)$$

where $[I_{Ca}]_i$ is the calcium flowing into synapse i, x_i represents the presynaptic state in synapse i, where $x_i = 1$ if there is glutamate binding and is zero if there is no binding, G is the gain of the NMDA receptors, $B(V)(V - V_r) = Y$ describes the dependence of NMDA currents on the postsynaptic potential V, and V_r is the reversal potential of the Ca ions[1]. The voltage dependence of calcium influx through the NMDAR, which is captured by the variables $B(V)$ and Y (Fig. 4), is based on the results of Jahr and Stevens (1990). We use $B(V) = 1/\left(1 + \exp(-0.062V)(\frac{Mg}{3.57})\right)$, where $Mg = 1mM$ is the extracellular magnesium concentration.

Influx into a single spine depends on the fraction of NMDAR in the open state. Each presynaptic release event, as well as the opening and closing of each NMDAR, are stochastic processes. The variable $P_i^N(t)$ denotes the probability of an NMDAR in an open state at synapse i. We describe the dynamics of P_i^N:

$$\frac{dP_i^N(t)}{dt} = \frac{-1}{\tau_N} P_i^N(t) + P_0 \sum_{\{t_i < t\}} \delta_{t,t_i}(1 - P_i^N(t_i)) \qquad (7)$$

where P_0 is the increase in open probability for each presynaptic action potential, t_i are times of presynaptic spike arrivals in synapse i, δ_{t,t_i} is a Kroneker delta which is equal to one if $t - t_i = 0$ and zero otherwise and τ_n is the NMDAR time constant. This is a highly simplified

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[1] We use this simple expression although it is not exact for calcium channels (Johnston and Wu 1995).
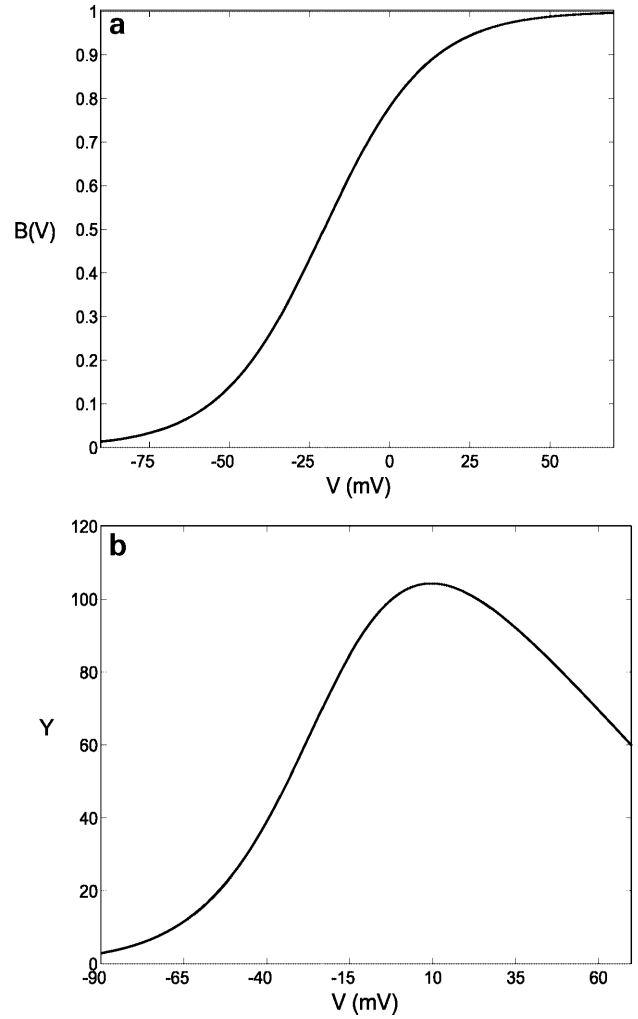

Fig. 4a,b. The dependence of NMDAR calcium conductance on voltage, based on Jahr and Stevens, 1990. **a** B- the probability of having an NMDAR unblocked from magnesium as a function of postsynaptic voltage. **b** The postsynaptic variable Y as a function of voltage

equation for the kinetics of NMDAR, however it will suffice for the current analysis. We further assume presynaptic non-stationary Poisson statistics with a time varying rate $r_i = r_i(t)$. This results in the following equation for the averaged open probability $\bar{P}_i^N$:

$$\frac{d\bar{P}_i^N(t)}{dt} = \frac{-1}{\tau_s} \bar{P}_i^N(t) + P_0 r_i \quad , \qquad (8)$$

where $\tau_s = \tau_N/(1 + \tau_N P_0 r_i)$ is the time scale for convergence to the fixed point. We can carry out this averaging due to the Poisson input statistics because the probability of obtaining a spike in the interval $[t, t + \Delta t]$ is conditionally independent of $P_i^N(t)$.

At steady state, $\bar{P}_i^N = P_0 r_i \tau_s$, we denote the steady state presynaptic variable $S_i = \bar{P}_i^N(t)$. Thus:

$$S_i = \frac{P_0 \tau_N r_i}{1 + P_0 \tau_N r_i} \qquad (9)$$

Therefore, the steady state value of the calcium influx is: $[\bar{I}_{Ca}(t)]_i = S_i(t)N \cdot G \cdot Y(t)$, where N is the number of

NMDARs and G is the maximal chord conductance of each NMDAR.

The variable $[Ca^{2+}]_i$ represents the calcium concentration at synapse i. A simple equation that can describe the calcium kinetics in the spine is:

$$\frac{d[Ca]_i}{dt} = \frac{-1}{\tau_{Ca}}[Ca]_i + [I_{Ca}]_i \ . \tag{10}$$

Employing the steady state assumption we obtain:

$$[Ca(t)]_i^s = \tau_{Ca}G \cdot S_i(t)Y(t) \tag{11}$$

where the superscript s denotes the steady state value.

We now intend to use the expression in Equation 11 to calculate synaptic plasticity at steady state using Eqs. 3 and 5. In order to form an explicit expression, we must assume an explicit expression for Ω and η. It is relatively easy to form such an expression if we use a low order polynomial form for Ω and η that is qualitatively similar to experimental observations. We assume here a quadratic form for Ω where $(\Omega([Ca]_i) = [Ca]_i ([Ca]_i - \theta_0) + \Omega_0)$, and a linear choice for $\eta(Ca) = \eta_0 \cdot Ca$. We then obtain:

$$\dot{W}_i = \eta_0 \tau_{Ca} G S_i Y (\tau_{Ca} G S_i Y (\tau_{Ca} G S_i Y - \theta_0) + \Omega_0 - W_i) \ . \tag{12}$$

Thus

$$\dot{W}_i' = \eta_0 \tau_{Ca} G S_i Y (\tau_{Ca} G S_i Y (\tau_{Ca} G S_i Y - \theta_0) - W_i') \ , \tag{13}$$

where we have defined $W_i' = W_i - \Omega_0$. The variable W' is a measure of the deviation of the synaptic weight W from its baseline value Ω_0 and can be positive or negative.

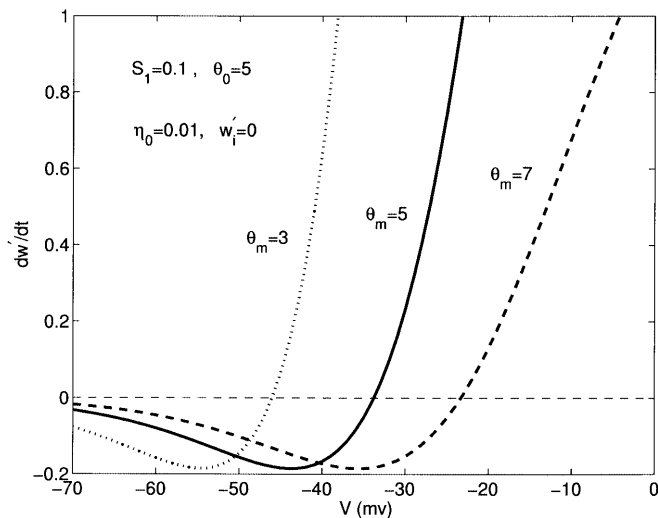In analogy with BCM, we now define a modification threshold $\theta_M = \theta_0/(G\tau_{Ca})$ and obtain:

Fig. 5. The plasticity curve as a function of postsynaptic depolarization for three different levels of θ_m. $\theta_m = 3$ (dots), $\theta_m = 5$ (solid) $\theta_m = 7$ (dash)

$$\dot{W}_i' = \eta_0 \left(\frac{\theta_0}{\theta_M}\right)^3 \left((S_iY)^2(S_iY - \theta_M)\right) - W_i' \frac{\theta_0\eta_0}{\theta_M} S_iY \tag{14}$$

In Fig. 5 we show how $\dot{W}_i$ depends on the postsynaptic depolarization V, where we have used the function $Y(V)$ to convert this from the variable Y to the variable V. We have fixed the other parameters $S_i = 0.1$, $\eta_0 = 0.01$, $\theta_0 = 5$, and assumed that $W_i = 0$. We show this for three different values of $\theta_m = 3, 5, 8$. As in BCM, changing the value of θ_m alters the crossover threshold between LTP and LTD. However, if we change the value of the presynaptic variable S_i, the form of the plasticity curve, as well as the crossover between LTD and LTP, would change as well.

These results seem similar to the BCM theory. However, they differ in several respects. We would like to point out one significant difference, and that is, in Equation 15, the presynaptic variable S_i and the postsynaptic variable Y are always paired. It is not yet clear if this can be converted to separable form as in the BCM theory, in which we have a presynaptic variable times a function of the postsynaptic variable.

Since θ_m is a function of the chord conductance of the NMDAR, as defined above, this result demonstrates that a possible mechanism for the sliding modification threshold is plasticity of the NMDAR conductance.

Like in the BCM theory, θ_M itself can be a slowly varying dynamic variable that can help stabilize learning. This can be done by making θ_M a function of the history of postsynaptic. For example we can set $\theta_M \propto <Y^\mu>_{\tau_M}$, where Y^μ is Y to the power μ, and $<>_{\tau_M}$ denotes a temporal average with a time constant τ_M. This can be accomplished by the differential equation:

$$\dot{\theta}_M = \frac{-\dot{G}}{G^2}\frac{\theta_0}{\tau_{Ca}} = \frac{1}{\tau_M}(Y^\mu - \theta_M) \ . \tag{15}$$

We can express this metaplasticity in terms of the NMDAR conductance, thus:

$$\dot{G} = \frac{G}{\tau_M}\left(1 - \frac{\tau_{Ca}G}{\theta_0}Y^\mu\right) \tag{16}$$

Since we know that at high frequencies and high Y, the LTP term dominates, it is reasonable to assume that this metaplasticity is necessary for stabilization of learning. However, we have not yet examined if these equations lead to stable selective receptive fields as in the BCM theory (Bienenstock et al. 1982; Intrator and Cooper 1992; Castellani et al. 1998) and other BCM-like models (Blais et al. 1998). We are currently examining the implications of the complete spike time dependent and averaged versions of these plasticity equations.

6 Discussion

This word attempts to bridge the vast gap between the molecular basis of synaptic plasticity and abstract

plasticity equations. These results, in combination with some of our previous results (Castellani et al. 2001; Shouval et al. 2002), produce converging evidence for the calcium control hypothesis, which includes a dependence of synaptic plasticity on the level of intracellular calcium as well as on the temporal pattern of calcium transients.

We have used a calcium dependent equation of synaptic plasticity, together with a well known model for the voltage dependence of calcium influx through NMDAR, to extract a multi-synapse plasticity equation. This equation depends on a global postsynaptic variable that is a function of postsynaptic depolarization and on many local presynaptic variables that represent glutamate binding to the glutamate receptors. It is possible to compare this rate based version of the learning rule to previously proposed rate based rules.

Like many other plasticity equations, additional assumptions are necessary to obtain stability. We show how plasticity of NMDAR can produce metaplasticity that, like the sliding modification threshold of BCM, may stabilize synaptic plasticity.

To derive the multi-synapse rule we made significant simplifying assumptions. Most notably, we have ignored the impact of the detailed times of pre- and postsynaptic action potentials by assuming that we can use an average postsynaptic depolarization variable. In another paper (Shouval et al. 2002), we show the consequences of precise spike times on synaptic plasticity.

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