**Analysis of calcium dynamics leading to spike time dependent plasticity**

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Summary

Activity of NMDA receptors is essential for the induction of many forms of synaptic plasticity. This includes rate based LTP (Bliss and Lomo, 1973) and LTD (Dudek and Bear, 1992), as well as the more recently described spike time dependent plasticity (STDP) (Markram et al., 1997; Bi and Poo, 1998; Feldman, 2000). NMDA receptors are a voltage sensitive, calcium permeable channel, there are strong indications that calcium influx through NMDAR is a primary signal for the induction of bi-directional plasticity (Cummings et al., 1996). There is a clear correlation between the level of calcium influx and the sign and magnitude of synaptic plasticity (Cormier et al., 2001). Furthermore, calcium influx alone, is sufficient for inducing bi-directional synaptic plasticity (Yang et al., 1999).

We have recently introduced a unified model of synaptic plasticity, this model can account for various induction protocols (Shouval et al., 2001). This includes (1) rate based induction, in which the rate of presynaptic stimulation determines the sign and magnitude of synaptic plasticity (Dudek and Bear, 1993; Kirkwood et al., 1993), (2) paring based, in which a postsynaptic cell is voltage clamped to a fixed level during low frequency presynaptic stimulation, the voltage level determines the sign and magnitude of synaptic plasticity, (3) spike timing dependent plasticity, in which the precise time difference between a pre and a postsynaptic spike determines the sign and magnitude of synaptic plasticity. In this model calcium determines the dynamics of synaptic plasticity according to the calcium control hypothesis, which is mathematically embodied by the following equation:

$$\dot{W}_j = \eta([Ca]_j)\left(\Omega([Ca]_j) - W_j\right) \qquad (1)$$

where $W_k$ is the synaptic weight in synapse k, $\Omega$ determines the sign and magnitude of synaptic plasticity and $\eta$ determines the rate of convergence. Our model assumes calcium influx through NMDA receptors, using their standard mathematical description. An additional essential assumption is that the back propagating action potential has a long tail component (Magee and Johnston, 1997; Larkum et al., 2001).

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Given these assumptions the calcium concentration due to influx through NMDAR is a key variable of the model. Therefore, we set out to calculate analytically the calcium dynamics due to influx through NMDAR, for the different induction protocols. The key parameter, in low frequency, spike timing dependent plasticity is Δt the time lag between the presynaptic and the postsynaptic spikes. Our aim here is to calculate how the calcium transient depend on Δt.

We assume that the calcium dynamics are governed by a simple ODE of the form:

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

where [Ca(t)] is the calcium concentration at the spine at time t and $\tau_{Ca}$ is the decay time constant of calcium in the spine, and $I_{NMDA}$ is the calcium current through NMDAR. Further, we assume that the NMDA current have an exponential time course, with a time constant $\tau_N$, and that the back propagating action potential is composed of either one exponent with a time constant $\tau_B$ of or two exponents with time constants $\tau_B^f$, and $\tau_B^s$.

Under these assumptions, in addition to using an approximation of the voltage dependence of the NMDA receptor, we have analytically calculated the ensemble average of the calcium transients. The magnitude of the calcium transients, as well as their temporal structure, depend on the system parameters, such as the time constants and Δt. We find that calcium transients are composed of a sum of two components, one component depends only on the presynaptic spike, the second component is associative and it depends on the time difference between the pre and postsynaptic spike. The peak concentration of the associative components depends on Δt. If Δt>0 it has the form: $[Ca]^+_{\max} \propto \exp(-\Delta t/\tau_N)$, and for Δt>0 it has the form $[Ca]^+_{\max} \propto \exp(-|\Delta t|/\tau_B)$. Thus, we can deduce that the NMDA receptor dynamics determine the width of the LTP window in spike time dependent plasticity, whereas the LTD window is determined by the dynamics of the back propagating action potential.

To calculate the variance of calcium dynamics, due to the stochastic properties of NMDAR, we assume a simplified Markov model of the NMDAR. Given this model we can analytically calculate the variance of calcium concentration at each point in time given a pair of pre and postsynaptic action potentials.

This solution provides us with a functional form of how calcium dynamics and their fluctuations depend on key parameters and variables, such as Δt, and postsynaptic action potentials as well as the different time constants in the problem.

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