Supporting Text

Ca^{2+} Threshold Model with Feedback from VDCCs. The model has a number of interacting components, including the NMDA-mediated Ca^{2+} flux and associated accumulation of Ca^{2+}, the back-propagating action potential (bAP), the pathways that convert the peak of the Ca^{2+} flux into competing long-term potentiation (LTP) and long-term depression (LTD) signals and feedback from voltage-dependent Ca^{2+} channels (VDCCs) that temporarily suppresses LTP.

The NMDA-receptor-mediated Ca^{2+} flux is modeled by using the classical description

$$I_{NMDA} = -G_{NMDA} \cdot m \cdot (V(t) - V_{Ca}) \cdot B(V). \qquad \textbf{[1]}$$

In Eq. **1**, G_{NMDA} = 1 is a constant corresponding to the maximal conductance of the receptor, $V(t)$ is the postsynaptic membrane potential, and V_{Ca} (150 mV) is the reversal potential for calcium ions. Finally, $B(V)$ is a function describing the magnesium block of the receptor.

The glutamate activation m is a time-varying signal that varies from 0 to 1. In response to each postsynaptic AP, $m(t)$ rises and falls biexponentially:

$$m(t) = \left[e^{-(t-t_{sp})/\tau_{NMDA\_f}} - e^{-(t-t_{sp})/\tau_{NMDA\_r}}\right] u(t - t_{sp}), \qquad \textbf{[2]}$$

where t_{sp} is the time of occurrence of the presynaptic spike, τ_{NMDA_f} is the decay time constant of the conductance (14 ms), and τ_{NMDA_r} is the rising time constant (1 ms). The Heaviside step function $u(t-t_{sp})$ ensures that $m(t)$ is engaged only after the presynaptic AP.

$V(t)$ is the membrane potential of the postsynaptic cell at the synapse site during the bAP, which contributes to the driving force of the NMDA-mediated flux. The depolarization associated with the bAP is assumed to follow a dual exponential waveform:

$$V(t) = V_{rest} + \frac{A}{K_1}\left[e^{-(t-t_{bAP})/\left(AP_{width}\tau_{bAP\_fall}\right)} - e^{-(t-t_{bAP})/\tau_{bAP\_rise}}\right]\cdot u(t-t_{bAP})\,. \qquad \textbf{[3]}$$

In Eq. **[3]**, K_1 is the peak amplitude of the subtracted exponentials, related to the two time constants: rising, τ_{bAP_rise} = 0.2 ms, and falling, τ_{bAP_fall} = 1.0 ms. The resting potential, V_{rest}, is chosen to be –60 mV, and the amplitude, A, to be 80 mV. The model AP, therefore, consists of a depolarization from [minus]60 to +20 mV. The factor AP_{width} is used to scale the decay-time constant. We used AP_{width} = 1.0 for control conditions and AP_{width} = 1.5 to model the spike-broadening effects of internal TEA.

The "magnesium block" function $B(V)$ is defined as:

$$B(V) = \frac{3.57}{\left[Mg^{2+}\right]}\cdot\frac{1}{1+e^{-0.062\left(V-V_B^{*}\right)}}\,, \qquad \textbf{[4]}$$

where $[Mg^{2+}]$ is the constant external concentration of magnesium ions. V_B^{*} = –9 mV, and the value of $B(V)$ increase rapidly near this potential to allow considerable receptor current and Ca^{2+} influx.

Ca^{2+} entering through NMDA receptors is assumed to accumulate in a region near the receptor (microdomain) and to passively diffuse away from this region. These processes are modeled using a first-order differential equation:

$$\frac{d}{dt}\left[Ca^{2+}\right] = I_{NMDA}\cdot\gamma - \frac{\left[Ca^{2+}\right]}{\tau_{Ca^{2+}}}. \qquad \textbf{[5]}$$

In equation [5], I_{NMDA} is the NMDA-receptor current calculated from Eq **[1]**. γ = 0.78 is a normalization factor controlling how fast $[Ca^{2+}]$ rises for a given Ca^{2+} influx. This factor depends on the size of microdomain. Calcium concentrations are assumed to decay to 0 with a time constant of τ_{Ca}^{2+} = 5 ms.

The calcium signal that drives LTP pathway is passed to a quadratic nonlinearity:

$$f(x(t)) = ax^2(t) + bx(t), \quad \textbf{[6]}$$

where a = 0.0065, b = 0.902, and

$$x(t) = \left[Ca^{2+}\right](t) \cdot \left(1 - S(t)\right). \quad \textbf{[7]}$$

This nonlinear gain for LTP is qualitatively compatible with the autocatalytic nature of calcium-calmodulin kinase II, known to be crucial for mediating LTP. In Eq. **[7]**, $\left[Ca^{2+}\right](t)$ is the numerical solution of Eq. [5]. The voltage-dependent calcium channel (VDCC)-mediated suppression signal $S(t)$ is assumed to have a biexponential waveform, triggered after a specific delay after the onset of the bAP:

$$S(t) = \frac{AP_{Width} S_{\max}}{K_2}\left[e^{-(t-t_{bAP}-Sdelay)/\tau_{fall}} - e^{-(t-t_{bAP}-Sdelay)/\tau_{rise}}\right] \cdot u\left(t - \left(t_{bAP} + Sdelay\right)\right). \quad \textbf{[8]}$$

In Eq. **[8]**, the normalization factor K_2 is equal to the maximum value of the subtracted exponentials. $S_{\max}$ is the maximum value of the suppression signal. This suppression signal S rises with time constant τ_{rise}, and falls with time constant $\tau_{fall,}$ and is triggered after the onset of the bAP by an absolute delay, *Sdelay*. In the model, we used the values $S_{\max}$ = 0.65, τ_{rise} = 2ms, τ_{fall} = 20 ms, and *Sdelay* = 0.5 ms. The amount of suppression is scaled by AP_{width}, described for Eq. **[3]**.

The direction of the plasticity is then simply determined by the mathematical difference between the peak [Ca^{2+}] of LTP and LTD pathways:

$$LTP - LTD = \max\left(f(x(t))\right) - \max\left(\left[Ca^{2+}\right](t)\right). \quad \textbf{[9]}$$