

Krasimira Tsaneva-Atanasova (University of Exeter)

Mathematical modelling of Ca^{2+} influx and calmodulin activation in dendritic spines: implications for synaptic plasticity

Abstract

The rise of intracellular calcium concentration $[\text{Ca}^{2+}]$ is believed to play a critical role in triggering synaptic plasticity. This is supported by experimental evidence demonstrating that both, synaptic long-term potentiation (LTP) and depression (LTD), are blocked by pharmacological buffering of Ca^{2+} . The importance of intracellular Ca^{2+} is reflected in the fact that the dynamics of $[\text{Ca}^{2+}]$, acting as intermediate signals for induction of plasticity, are a common feature of most biophysical models of STDP.

Calcium-based biophysical models of STDP include a description of the changes in $[\text{Ca}^{2+}]$ due to pre- and post-synaptic spiking. Ca^{2+} sources may depend on the particular synapse to be modelled, but most frequently include: influx via NMDA receptors (NMDARs); influx via Ca^{2+} -permeable AMPA receptors (AMPA); influx via voltage-gated Ca^{2+} channels, or Ca^{2+} release from intracellular stores. Entry of extracellular Ca^{2+} via postsynaptic membrane ion channels can be dependent on both the postsynaptic membrane-potential and the action of neurotransmitters in the synaptic cleft, therefore biophysical models of STDP often contain descriptions of electrophysiological cell membrane phenomena and AMPAR/NMDAR ligand-gating in response to neuron pair-spiking.

It is an open question how the multiple spatial and temporal scales involved in intracellular Ca^{2+} handling within the STDP models affect the plasticity outcomes predicted by these models. Hebbian or associative plasticity is triggered by postsynaptic Ca^{2+} influx which activates calmodulin and CaMKII. The influx of Ca^{2+} through voltage-dependent NMDA receptors and Ca^{2+} channels is regulated by Ca^{2+} -activated K^{+} channels (SK-channels) providing negative feedback regulation of postsynaptic $[\text{Ca}^{2+}]$. Using 3-dimensional modelling of Ca^{2+} and calmodulin dynamics within dendritic spines we show that the non-linear relationship between Ca^{2+} influx and calmodulin activation endows SK-channels with the ability to gate calmodulin activation and therefore the induction of Hebbian synaptic plasticity. Since SK-channels are inhibited by several neuro-modulator receptors including acetylcholine and noradrenaline, the gating of synaptic plasticity by SK-channels could represent a common mechanism by which neuro-modulators control the induction of synaptic plasticity.