Induction and binary expression of LTP/LTD in a minimal model of the CaMKII kinase-phosphatase system

Michael Graupner$^{1,2}$, and Nicolas Brunel$^1$

$^1$ Laboratoire de Neurophysique et Physiologie, CNRS UMR 8119, Université René Descartes - Paris V, 45, rue des Saints Pères, 75270 Paris Cedex 06, France
$^2$ Max-Planck-Institut für Physik komplexer Systeme, Nöthnitzer Straße 38, 01187 Dresden, Germany

The calcium/calmodulin-dependent protein kinase II (CaMKII) plays a key role in the induction of long-term post-synaptic modifications following calcium entry. Experiments suggest that these long-term synaptic changes are all-or none switch-like events between discrete states [1]. The biochemical network involving CaMKII and its regulating protein signaling cascade has been hypothesized to durably maintain the evoked synaptic state in form of a bistable switch [2,3]. However, it is still unclear whether different experimental LTP/LTD protocols lead to corresponding transitions between the two states in realistic models of such a network. Furthermore, the biochemical mechanisms giving rise to the non-linearities exhibited during LTP/LTD induction remain elusive.

Starting from a detailed biochemical model, a reduced model of the CaMKII autophosphorylation and the protein signaling cascade governing CaMKII dephosphorylation is presented. Dephosphorylation is mediated by protein phosphatase 1 whose activity is indirectly regulated by a calcium-dependent balance of kinase (protein kinase A) and phosphatase (calcineurin) activity.

As previously shown [2], two stable states of the CaMKII phosphorylation level exist at resting intracellular calcium concentration and high calcium transients can switch the system from the weakly- (DOWN) to the highly-phosphorylated (UP) state of the CaMKII (similar to a LTP event). We show here that increased CaMKII dephosphorylation activity at intermediate Ca$^{2+}$ concentrations can lead to switching from the UP to the DOWN state (similar to a LTD event). This can be achieved if protein phosphatase activity promoting CaMKII dephosphorylation activates at lower Ca$^{2+}$ levels than kinase activity. Finally, it is shown that the CaMKII system can qualitatively reproduce results of plasticity outcomes in response to spike-timing dependent plasticity (STDP) protocols, presynaptic stimulation protocols and pairing protocols. We also address the question to which extent such a biochemical realization of bistable synaptic plasticity can account for the non-linearities exhibited during LTP/LTD induction by pre- and postsynaptic spikes. Our investigations show that a reduced model of the CaMKII protein network can account for both induction - through LTP/LTD-like transitions - and storage - due to its bistability - of synaptic changes.

Acknowledgments
Supported by the French Ministry of Research, ACI Neurosciences intégratives et computationnelles and the ANR (Agence Nationale de la Recherche).

References