

Role of calmodulin in controlling vesicular release probability

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Increases in concentration of free Ca^{2+} ions ($[\text{Ca}^{2+}]$) in presynaptic boutons of hippocampal cells trigger vesicular release of neurotransmitters. Changes in $[\text{Ca}^{2+}]$ are primarily due to Ca^{2+} influx through voltage-gated Ca^{2+} channels located at the plasma membrane and activated during an action potential. Different endogenous buffers such as Calbindin- $\text{D}_{28\text{k}}$ (CB), Calmodulin (CaM), Adenosine Triphosphate (ATP), are present in the cytosolic volume of the presynaptic bouton and by interacting with free Ca^{2+} ions they can affect the dynamics of vesicular release and therefore the short-term synaptic plasticity. One mechanism for synaptic facilitation through Ca^{2+} buffer saturation has been introduced earlier, and CB has been shown to contribute to short-term facilitation through this mechanism in different types of central synapses (Blatow et al 2003). Recently we have demonstrated that CaM can have a more significant role in shaping vesicular release probability than other buffers and we proposed a novel mechanism for synaptic facilitation through buffer dislocation (under review). CaM molecules are known to be in both mobile and immobile states inside the cytosol, although the precise distribution of CaM in these two states remains unknown. In our recent work we considered that immobile CaM is attached to the plasma membrane and it can dissociate from it when Ca^{2+} levels increase. We also assumed that this process of dislocation is instantaneous and irreversible.

In this project we will develop a two-compartmental model of Ca^{2+} dynamics, buffering and Ca^{2+} -triggered synaptic vesicle fusion for analysing synaptic facilitation through the mechanism of dislocation when this dislocation can occur at different rates depending on a number of binding Ca^{2+} ions and also when it is reversible. In particular, we will investigate the role of CaM in short-term synaptic plasticity in the presence of CB. Ca^{2+} interaction with CaM will be modelled using the two-step binding model of cooperative binding to each N- and C-lobe of CaM (Faas et al 2011). Each CB molecule will contain four independent Ca^{2+} binding sites (two fast and two slow) (Muller et al 2005). Vesicular release probabilities will be calculated using a six-state allosteric model of Ca^{2+} activation of vesicle fusion in the calyx of Held (Lou et al 2005). This will be a mostly computational project which focuses on the formulation, implementation and numerical analysis of the model. If time permits a generalisation to a three-dimensional spatial model of the presynaptic bouton will be considered.

Some relevant publications:

1. T C Sudhof (2013) Neurotransmitter release: The last millisecond in the life of a synaptic vesicle, *Neuron*, Vol 80.
2. M Blatow et al (2003) Ca^{2+} buffer saturation underlies paired pulse facilitation in calbindin- $\text{D}_{28\text{k}}$ -containing terminals *Neuron*, Vol 38.
3. G C Faas et al (2011) Calmodulin as a direct detector of Ca^{2+} signals *Nature Neuroscience*, Vol. 14.
4. A Muller et al (2005) Endogenous Ca^{2+} buffer concentration and Ca^{2+} microdomains in hippocampal neurons *J Neuroscience*, Vol. 25.
5. X Lou et al (2005) Allosteric modulation of the presynaptic Ca^{2+} sensor for vesicle fusion *Nature*, Vol. 435.