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Ca^{2+} buffering as a mechanism of short-term synaptic plasticity

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Spatio-temporal compartmentalization allows Ca^{2+} signals to simultaneously regulate multiple vital cell processes and relies in part on Ca^{2+} buffers that absorb at least 98% of Ca^{2+} ions entering the cytoplasm. Computational modeling has played a central role in the understanding of localized Ca^{2+} signals in neurons and other cell types. Although many models consider only simple, one-to-one Ca^{2+} buffering stoichiometry, practically all buffers have multiple Ca^{2+} binding sites which often display cooperative binding (e.g., calretinin [1-3], calmodulin [4,5]). Given the simplest case of two binding sites, cooperativity manifests itself in an order of magnitude difference in the binding and/or unbinding rates of the two consecutive Ca^{2+} binding steps in the following buffer reaction:

$$B \underset{k_1^-}{\overset{2\,[Ca]\,k_1^+}{\rightleftharpoons}} CaB \underset{2\,k_2^-}{\overset{[Ca]\,k_2^+}{\rightleftharpoons}} Ca_2B$$

Here we extend recent modeling studies of cooperative buffering [1-5], and find that it can lead to spatio-temporal Ca^{2+} signals that cannot be achieved by any combination of non-cooperative buffers, in particular during a sequence of action potentials or synaptic inputs. Namely, Figure 1B shows that cooperative Ca^{2+} buffering can potentially serve as a mechanism of short-term synaptic depression, in contrast to the case of non-cooperative buffers (Figure 1A), which are believed to underlie short-term synaptic facilitation in certain types of mammalian synapses [6,7].

We explore this phenomenon in detail, demonstrating the dependence of such buffer-induced short-term synaptic plasticity on all relevant buffering parameters. These results may lead to better understanding of *post*-synaptic Ca^{2+} dynamics as well, yielding a deeper insight into synaptic transmission and its dynamic regulation, and may also have relevance for Ca^{2+}-dependent processes in other cells such as endocrine cells, myocytes and immune system cells.

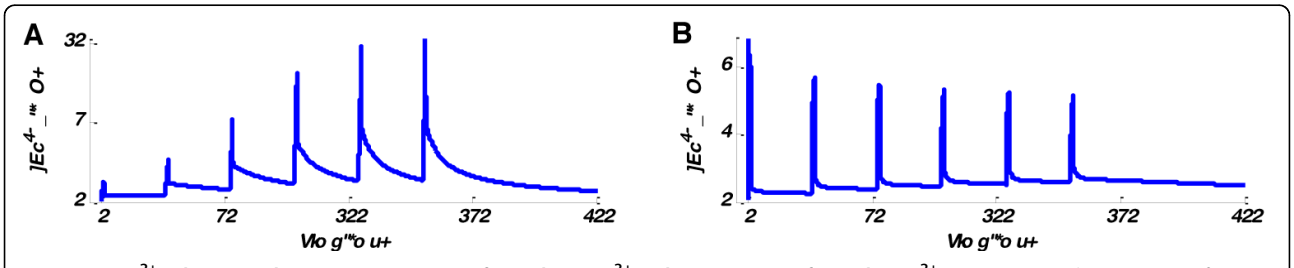

Figure 1 [Ca^{2+}] elevation during a 40 Hz train of 1ms-long Ca^{2+} pulses at 100nm from the Ca^{2+} source. A: In the presence of a *non-cooperative* buffer, Ca^{2+} transients facilitate due to gradual depletion (saturation) of free buffer [6,7]. **B:** In the presence of a *cooperative* buffer, Ca^{2+} transients depress as a result of increasing exposure of the high-affinity Ca^{2+} binding site. Both simulations done in 1D geometry (0.5 μm axonal segment), computed using CalC version 7.2 (http://www.calciumcalculator.org)

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