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Title

Non-local Amplification of Ca²⁺ Signals by Ca²⁺ Buffer Saturation: A Computational Study

Abstract

Endogenous calcium (Ca²⁺) buffers are abundant in all cell types, and play an important part in cell Ca²⁺ homeostasis. Although the role of many Ca²⁺ buffering molecules is known to go beyond direct regulation of free Ca²⁺ concentration, even “passive” Ca²⁺ buffering can lead to non-trivial dynamical effects on Ca²⁺ dependent processes. In particular, saturation of high-affinity buffers has been proposed as a potential mechanism of short-term facilitation of synaptic response (Neher, 1998), and has been confirmed to contribute to facilitation at calbindin-positive mammalian central synapses (Blatow et al, 2003). In the buffer saturation mechanism, progressive depletion (saturation) of free buffer by Ca²⁺ arriving with each new afferent action potential causes simultaneous increase in local Ca²⁺ transients, leading to short-term facilitation of synaptic response.

Facilitation by buffer saturation can be described as a non-linear summation of free Ca²⁺ elevations produced by the opening of Ca²⁺ channels arriving at the same active zone at different points in time. In this work we use computational modeling to examine the potential impact of buffer saturation on non-local interaction of Ca²⁺ fluxes arriving through spatially separated groups of channels. In this case a Ca²⁺ influx at a single active zone or a group of co-localized active zones would deplete (saturate) Ca²⁺ buffers throughout an axonal segment, leading to an amplification of Ca²⁺ influx arriving at a remote active zone. Note that such non-linear summation of Ca²⁺ fluxes arriving through spatially distant sources is achieved without a concomitant increase in free Ca²⁺, provided that the affinity of the buffer is sufficiently high. Such “non-local” interaction of Ca²⁺ signals necessarily requires highly mobile buffers. Like in the case of local buffer saturation, it also requires buffers of optimal concentration. We examine the dependence of this effect on the geometric parameters and the calcium-binding properties of the Ca²⁺ buffer.