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Random but Reliable: Properties of Spike Sequences of IP_3-induced Ca^{2+} signaling

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Abstract Ca^{2+} is a universal second messenger in eucaryotic cells transmitting information through sequences of concentration spikes. A prominent mechanism to generate these spikes involves Ca^{2+} release from the endoplasmic reticulum (ER) Ca^{2+} store via IP_3-sensitive channels. Puffs are elemental events of IP_3-induced Ca^{2+} release through single clusters of channels. Intracellular Ca^{2+} dynamics are a stochastic system, but a complete stochastic theory has not been developed yet. As a new concept, we formulate the theory in terms of interpuff interval and puff duration distributions, since unlike the properties of individual channels, they can be measured in vivo. Our theory reproduces the typical spectrum of Ca^{2+} signals like puffs, spiking and bursting in analytically treatable test cases as well as in more realistic simulations. We find conditions for spiking and calculate interspike interval (ISI) distributions. Signal form, average ISI and ISI distributions depend sensitively on the details of cluster properties and their spatial arrangement. In difference to that, the relation between the average and the standard deviation of ISI does not depend on cluster properties and cluster arrangement, and is robust with respect to cell variability. It is controlled by the global feedback processes in the Ca^{2+} signaling pathway (e.g. via IP_3-3-kinase or ER depletion). That relation is essential for pathway function, since it ensures frequency encoding despite the randomness of ISI and determines the maximal spike train information content. Hence, we find a division of tasks between global feedbacks and local cluster properties which guarantees robustness of function while maintaining sensitivity of control of the average ISI.

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