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How does single channel behavior cause cellular Ca2+ spiking?

The behavior of signaling pathways is determined by the molecular properties of their components, feedbacks and self-organization among the participating molecules. But usually systems are too complex to understand in detail how cellular behavior relates to molecular behavior. Intracellular Ca2+ signaling offers an opportunity to understand that relation in detail, since it is comprised from relatively few different types of molecules. A well-studied system involves Ca2+ liberation through inositol trisphosphate receptor (IP3R) channels wherein the cellular dynamics emerge through a hierarchy of events. Opening of single Ca2+ channels can induce local Ca2+ release events evoked by channel clusters (called puffs), the combined action of which results in repetitive global cellular Ca2+ spikes. Although cellular behavior and single channel properties have been characterized in detail before, this study investigates statistical properties of the cluster dynamics by analyzing high-resolution data from TIRF microscopy in two mammalian cell lines. We find that interpuff intervals (IPIs) are significantly shorter than cellular interspike intervals (ISIs), that puff-activity is stochastic with a recovery time much shorter than the cellular refractory period, and that IPIs show no sign of periodicity. These results strongly suggest that Ca2+ spikes do not arise from oscillatory cluster dynamics, but that cellular repetitive spiking and its typical time scales arise from collective dynamics of the whole cluster array.