Markov Chain Models of Calcium Puffs and Sparks

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Abstract

Localized cytosolic Ca^{2+} elevations known as puffs and sparks are important regulators of cellular function that arise due to the cooperative activity of Ca^{2+}-regulated inositol 1,4,5-trisphosphate receptors (IP_3Rs) or ryanodine receptors (RyRs) co-localized at Ca^{2+} release sites on the surface of the endoplasmic reticulum or sarcoplasmic reticulum. Theoretical studies have demonstrated that the cooperative gating of a cluster of Ca^{2+}-regulated Ca^{2+} channels modeled as a continuous-time discrete-state Markov chain may result in dynamics reminiscent of Ca^{2+} puffs and sparks. In such simulations, individual Ca^{2+}-release channels are coupled via a mathematical representation of the local [Ca^{2+}] and exhibit "stochastic Ca^{2+} excitability" where channels open and close in a concerted fashion. This dissertation uses Markov chain models of Ca^{2+} release sites to advance our understanding of the biophysics connecting the microscopic parameters of IP_3R and RyR gating to the collective phenomenon of puffs and sparks.

The dynamics of puffs and sparks exhibited by release site models that include both Ca^{2+} coupling and nearest-neighbor allosteric coupling are studied. Allosteric interactions are included in a manner that promotes the synchronous gating of channels by stabilizing neighboring closed-closed and/or open-open channel pairs. When the strength of Ca^{2+}-mediated channel coupling is systematically varied, simulations that include allosteric interactions often exhibit more robust Ca^{2+} puffs and sparks. Interestingly, the changes in puff/spark duration, inter-event interval, and frequency observed upon the random removal of allosteric couplings that stabilize closed-closed channel pairs are qualitatively different than the changes observed when open-open channel pairs, or both open-open and closed-closed channel pairs are stabilized. The validity of a computationally efficient mean-field reduction applicable to the dynamics of a cluster of Ca^{2+}-release Ca^{2+} channels coupled via the local [Ca^{2+}] and allosteric interactions is also investigated.

Markov chain models of Ca^{2+} release sites composed of channels that are both activated and inactivated by Ca^{2+} are used to clarify the role of Ca^{2+} inactivation in the generation and termination of puffs and sparks. It is found that when the average fraction of inactivated channels is significant, puffs and sparks are often less sensitive to variations in the number of channels at release sites and the strength of Ca^{2+} coupling. While excessively fast Ca^{2+} inactivation can preclude puffs and sparks, moderately fast Ca^{2+} inactivation often leads to time-irreversible puff/sparks whose termination is facilitated by the recruitment of inactivated channels throughout the duration of the puff/spark event. On the other hand, Ca^{2+} inactivation may be an important negative feedback mechanism even when its time constant is much greater than the duration of puffs and sparks. In fact, slow Ca^{2+} inactivation can lead to release sites with a substantial fraction of inactivated channels that exhibit nearly time-reversible puffs and sparks that terminate without additional recruitment of inactivated channels.