Markov Chain Models of Instantaneously Coupled Intracellular Calcium Channels

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Abstract

Localized calcium elevations known as calcium puffs or sparks are cellular signals arising from cooperative activity of clusters of inositol 1,4,5-trisphosphate receptors (IP_3Rs) or ryanodine receptors (RyRs) located at calcium release sites on the endoplasmic or sarcoplasmic reticulum membrane. When Markov chain models of these intracellular calcium-regulated calcium channels are coupled via a mathematical representation of the calcium microdomain, simulated calcium release sites may exhibit the phenomenon of "stochastic calcium excitability'" where the IP_3Rs or RyRs open and close in a concerted fashion. Although the biophysical theory relating the kinetics of single channels to the collective phenomena of puffs and sparks is only beginning to be developed, Markov chain models of coupled intracellular channels give insight into the dynamics of calcium puffs and sparks.

Interestingly, under some conditions simulated puffs and sparks can be observed even when the single channel model used does not include slow calcium inactivation or any long-lived closed state. In this case termination of the localized calcium elevation occurs when all of the intracellular channels at a release site simultaneously close through a process called stochastic attrition.This dissertation investigates the statistical properties of stochastic attrition viewed as an absorption time on a terminating Markov chain that represents a calcium release site composed of two-state channels that are activated by calcium. Assuming that the local calcium concentration experienced by a channel depends only on the number of open channels at the calcium release site, the probability distribution function for the time until stochastic attrition occurs is derived and an analytical formula for the expectation of this random variable is presented. Also explored is how the contribution of stochastic attrition to the termination of calcium puffs and sparks depends on the number of channels at a release site, the source amplitude of the channels, the background calcium concentration, channel kinetics, and the cooperativity of calcium binding.

This dissertation also studies whether single channel models with calcium inactivation are less sensitive to the details of release site ultrastructure than models that lack a slow calcium-inactivation process. Release site dynamics obtained from simulated calcium release sites composed of instantaneously coupled calcium-regulated calcium channels whose random spatial locations were chosen from a uniform distribution on a disc of specified radius are compared to simulations with channels arranged on hexagonal lattices. Analysis of puff/spark statistics confirm that puffs and sparks are less sensitive to the spatial organization of release sites when the single channel model includes a slow inactivation process. The validity of several different mean-field reductions that do not explicitly account for the details of release site ultrastructure is also investigated.

Calcium release site models are stochastic automata networks that involve many functional transitions, that is, the transition probabilities of each channel depend on the local calcium concentration and thus the state of the other channels. A Kronecker structured representation for calcium release site models is presented and benchmark stationary distribution calculations using both exact and approximate iterative numerical solution techniques that leverage this structure are performed. When it is possible to obtain an exact solution, response measures such as the number of channels in a particular state converge more quickly using the iterative numerical methods than occupation measures calculated via Monte Carlo simulation. When an exact solution is not feasible, iterative approximate methods based on the power method may be used, with performance similar to Monte Carlo estimates.