Langevin, population density and moment-based modeling of local and global aspects of intercellular calcium signaling

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Abstract

Markov chain models of the coupled gating of intracellular calcium (Ca 2+) channels are often used to study the stochastic dynamic of local Ca2+ release events and whole cell Ca2+ homeostasis. However, the runtime of the Markov chain description of Ca2+ channel gating is exponential in the number of Ca2+ channel states and may thus result in a combinatorial state space explosion when the number of channel states is large. This dissertation presents several novel stochastic modeling approaches that capture important aspects of Ca 2+ signaling while improving computational efficiency. This dissertation presents several novel stochastic modeling approaches that capture important aspects of calcium Ca2+ signaling. First, we present a Ca 2+ release site modeling approach based on a Langevin description of stochastic Ca2+ release. This Langevin model facilitates our investigation of correlations between successive puff/spark amplitudes, durations and inter-spark intervals, and how such puff/spark statistics depend on the number of channels per release site and the kinetics of Ca2+ -mediated inactivation of open channels. Second, we show that when the Ca2+ channel model is minimal, Langevin equations in a whole cell model involving a large number of release sites may be replaced by a single Fokker-Planck equation. This yields an extremely compact and efficient local/global whole cell model that reproduces and helps interpret recent experiments investigating Ca2+ homeostasis in permeabilized ventricular myocytes. Last but not least, we present a population density and moment-based approach to modeling L-type Ca2+ channels. Our approaches account for the effect of heterogeneity of local Ca2+ signals on whole cell Ca currents. Moreover, they facilitate the study of domain Ca-mediated inactivation of L-type Ca channels.