Automated Reductions of Markov Chain Models of Calcium Release Site Models

Yan (Amy) Hao

College of William & Mary, Department of Applied Science, 2012
Field: Mathematical Biology, Degree: Ph.D.

Advisor: Greg Smith, Professor of Applied Science

Abstract

Markov chain models have played an important role in understanding the relationship between single channel gating of intracellular calcium (Ca2+) channels, specifically 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs), and the stochastic dynamics of Ca2+release events, known as Ca2+ puffs and sparks. Mechanistic Ca2+release site models are defined by the composition of single channel models whose transition probabilities depend on the local calcium concentration and thus the state of the other channels. Unfortunately, the large state space of such compositional models impedes simulation and computational analysis of the whole cell Ca2+ signaling in which the stochastic dynamics of localized Ca2+ release events play an important role. This dissertation introduces, implements and validates the application of several automated model reduction techniques that significantly reduce the computational cost of mechanistic compositionally defined Ca2+ release site models. A common feature of Ca2+ channel models is the separation of timescales. For example, the well-known bell-shaped equilibrium open probability of IP3Rs can be reproduced by Markov Chain models that include transitions mediated by fast Ca2+ activation and slower Ca2+inactivation. Chapter 2 introduces an automated model reduction technique that is based on fast/slow analysis that leverages these time scale differences. Rate constants in the single channel model are categorized as either fast or slow, groups of release site states that are connected by fast transitions are identified and lumped, and transition rates between reduced states are chosen consistent with the conditional probability distributions among states within each group. The fast/slow reduction approach is validated by the fact that puff/spark statistics can be efficiently computed from reduced Ca2+release site models with small and transient error.