



## **“Automated Reduction of Calcium Release Site Models”**

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### **Abstract**

Markov chain models have played an important role in understanding the relationship between single channel gating of intracellular calcium ( $\text{Ca}^{2+}$ ) channels, specifically 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs), and the stochastic dynamics of  $\text{Ca}^{2+}$  release events, known as  $\text{Ca}^{2+}$  puffs and sparks. Mechanistic  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  signaling in which the stochastic dynamics of localized  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  release site models. A common feature of  $\text{Ca}^{2+}$  channel models is the separation of time scales. 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  $\text{Ca}^{2+}$  activation and slower  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  release site models with small and transient error. For Markov chain  $\text{Ca}^{2+}$  release site models without time-scale separation, the manner in which the full model states should be aggregated for optimal reduction is difficult to determine a priori. In Chapter 3, a genetic algorithm based approach that mimics the inheritance, mutation and selection processes of natural evolution is implemented to reduce these models. Given a full model of interest and target reduced model size, this genetic algorithm searches for set partitions, each corresponding to a potential scheme for state aggregation, that lead to reduced models that well-approximate the full model. A whole cell model with coupled local and global  $\text{Ca}^{2+}$  signaling is simplified by replacing a compositionally defined full  $\text{Ca}^{2+}$  release site model with a reduced model obtained through the genetic algorithm. In Chapter 4, a Langevin formulation of  $\text{Ca}^{2+}$  release sites is introduced as an alternative model reduction technique that is applicable when the number of channels per  $\text{Ca}^{2+}$  release site is too large for the previously discussed reduction methods, but not so large that the stochasticity of  $\text{Ca}^{2+}$  release is negligible. The Langevin formulation for coupled intracellular  $\text{Ca}^{2+}$  channels results in stochastic differential equations that well-approximate the corresponding Markov chain models when release sites possess as few as 20 channels, and the agreement improves as the number of channels per release site increases. Importantly, the computational time required by the Langevin approach does not increase with the size of  $\text{Ca}^{2+}$  release site.