Automated Reduction of Calcium Release Site Models via State Aggregation

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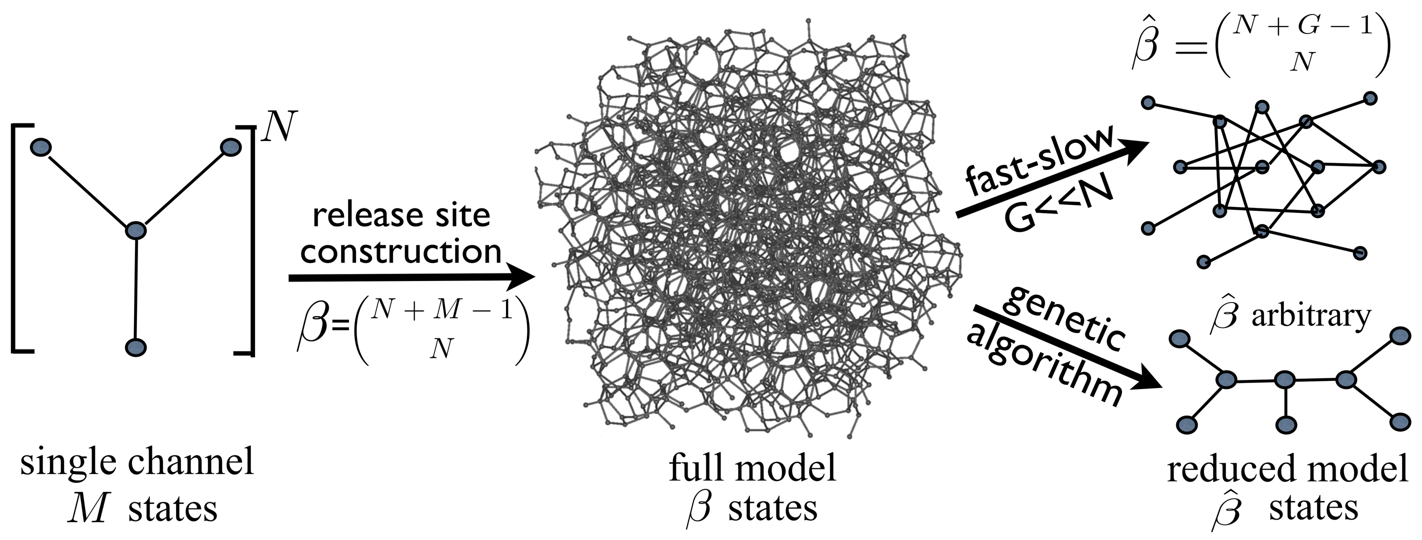
— Introduction —

Realistic Ca^{2+} release unit (CaRU) models consist of one or more L-type Ca^{2+} channels and multiple ryanodine receptors (RyRs). To accelerate multiscale modeling of local control of CICR in cardiac myocytes, **we have implemented and validated several reduction methods applicable to mechanistic CaRU modeling** that feature an automated process of state aggregation and error evaluation.



Keizer-Levine RyR			DeYoung-Keizer IP_3R		
N	β	$\hat{\beta}$	N	β	$\hat{\beta}$
1	4	2	1	120	6
7	120	8	7	8.4×10^{10}	792
100	176,851	101	15	2.7×10^{19}	15,504

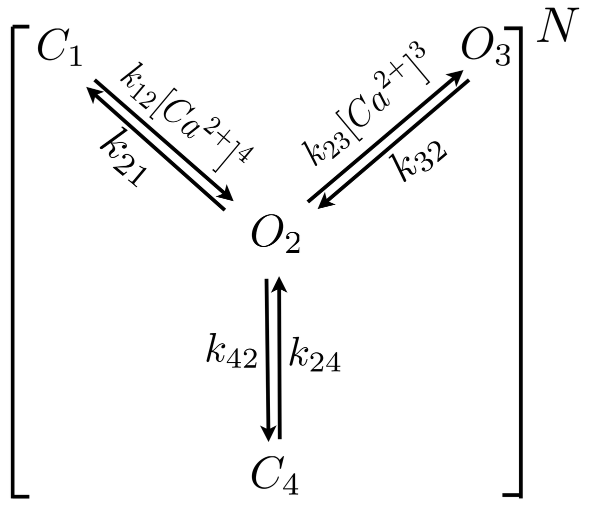
Compositionally defined Ca^{2+} release site models exhibit a combinatorial explosion of release site states. Assuming identical and indistinguishable channels, there are $\beta(N,M)=\mathcal{O}(M^N)$ distinct states.

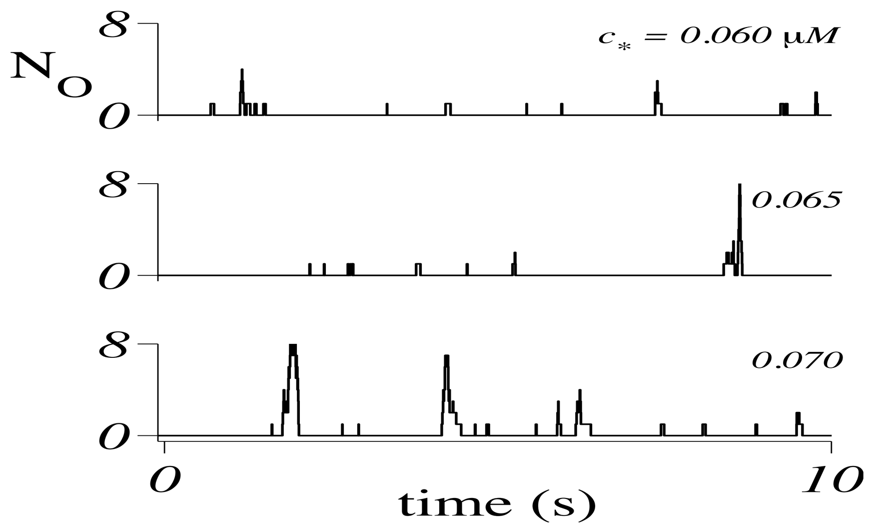
— Compositional Ca^{2+} Release Site Modeling —

Eight Keizer-Levine RyRs [2] (left) are coupled via a domain Ca^{2+} given by

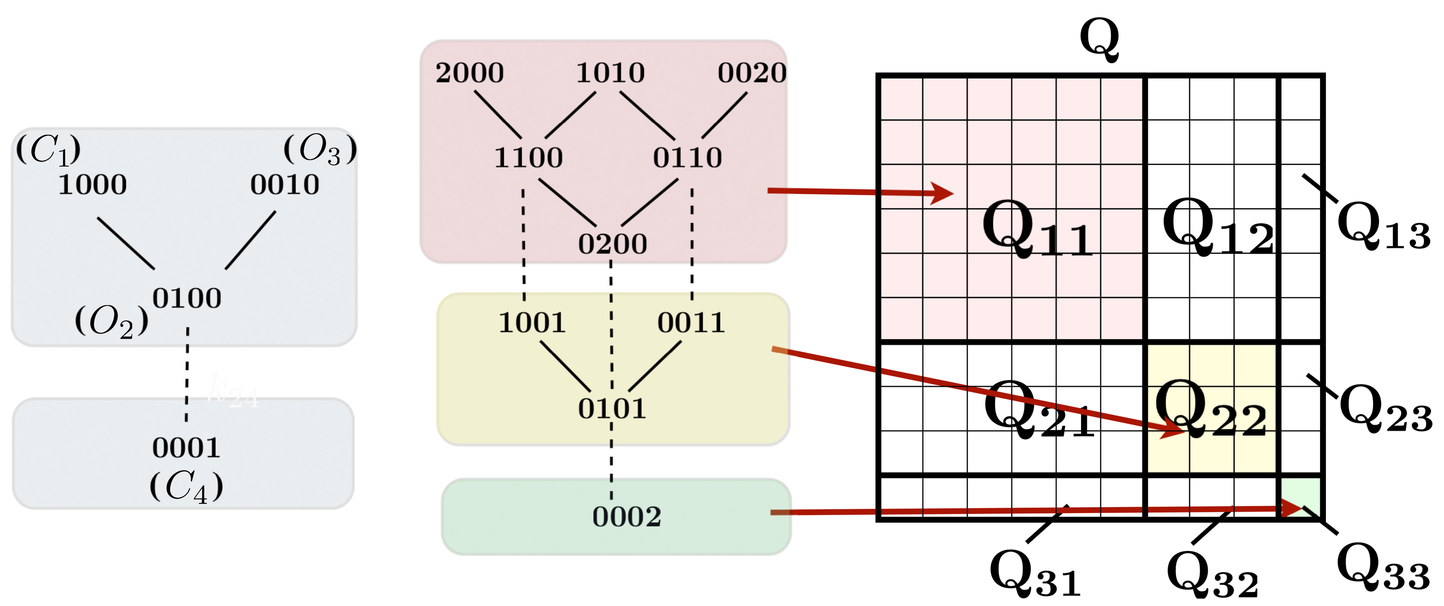
$$[\mathrm{Ca}^{2+}](t)=c_\infty+c_* N_O(t).$$

The stochastic dynamics of the number of open channels, $N_O(t)$, is reminiscent of sparks when the coupling strength c_* is sufficiently large (right).





—State Space Partitioned Using a Fast/Slow Criterion—



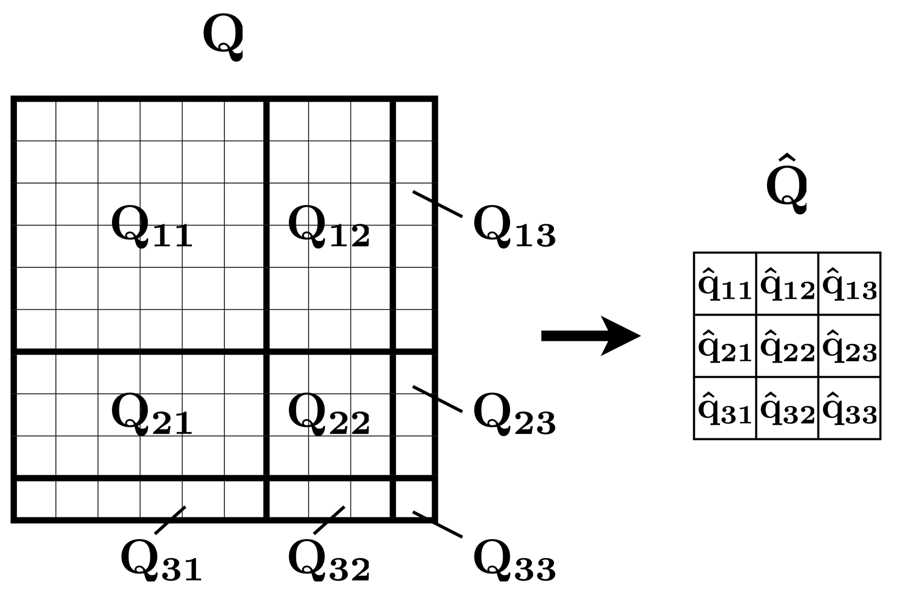
The transition rates between the de-inactivated states (C_1, O_2, and O_3; connected by solid line) are much faster than the transition rates to and from the inactivated state C_2 [2]. The 4-state RyR can be reduced to two states by lumping de-inactivated states;

$$(\text{de-inactivated})\ C_1\cup O_2\cup O_3 \underset{\hat{q}_{21}}{\overset{\hat{q}_{12}}{\rightleftharpoons}} C_4\ (\text{inactivated}).$$

Similarly, release sites composed of many coupled channels can be partitioned by lumping fast communicating states. (Illustrated above using two Keizer-Levine RyRs)

— Model Contraction via Fast/Slow Approximation—

Fast/slow reduction requires computation of the entries of the smaller Q-matrix corresponding to the reduced model. For example, the 10×10 Q-matrix for two coupled Keizer-Levine RyRs is partitioned into a 3×3 block-matrix $\boldsymbol{Q}=(\boldsymbol{Q}_{ij})$ consistent with fast/slow state space partitioning. Assuming quasi-static equilibrium between rapidly communicating states, the conditional probability distributions within each group $\hat{\boldsymbol{\pi}}_i$ are approximated by:



$$\hat{\boldsymbol{\pi}}_i \boldsymbol{Q}^+_{ii}=\boldsymbol{0} \text{ subject to } \hat{\boldsymbol{\pi}}_i\boldsymbol{e}_i=1$$

where $\boldsymbol{Q}^+_{ii}=\boldsymbol{Q}_{ii}+\mathrm{diag}\left(\sum_{j\neq i}\boldsymbol{Q}_{ij}\boldsymbol{e}_j\right)$. The transition rates between lumped states are:

$$\hat{\boldsymbol{Q}}=(\hat{q}_{ij}) \quad \text{where} \quad \begin{cases} \hat{q}_{ij} = \hat{\boldsymbol{\pi}}_i\boldsymbol{Q}_{ij}\boldsymbol{e}_j & i\neq j \\ \hat{q}_{ij} = -\sum_{j\neq i}\hat{q}_{ij} & i=j. \end{cases}$$

— Error Measure and Model Evaluation —

To validate the automated fast/slow reduction procedure, we compare the transition probability matrix of the reduced model ($\hat{\boldsymbol{P}}=e^{t\hat{\boldsymbol{Q}}}$) to the transition probability matrix of the full model ($\boldsymbol{P}=e^{t\boldsymbol{Q}}$). Because $\boldsymbol{P}$ and $\hat{\boldsymbol{P}}$ are significantly different in size (b and $\hat{b}$ states, respectively), $\boldsymbol{P}$ is contracted using a $b\times\hat{b}$ collector matrix $\boldsymbol{V}$ and a $\hat{b}\times b$ distributor matrix $\boldsymbol{U}$ where

$$\boldsymbol{V}=\begin{bmatrix} \boldsymbol{e}_1 & 0 & \cdots & 0 \\ 0 & \boldsymbol{e}_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \boldsymbol{e}_{\hat{b}} \end{bmatrix} \quad \text{and} \quad \boldsymbol{U}=\begin{bmatrix} \bar{\boldsymbol{\pi}}_1 & 0 & \cdots & 0 \\ 0 & \bar{\boldsymbol{\pi}}_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \bar{\boldsymbol{\pi}}_{\hat{b}} \end{bmatrix}.$$

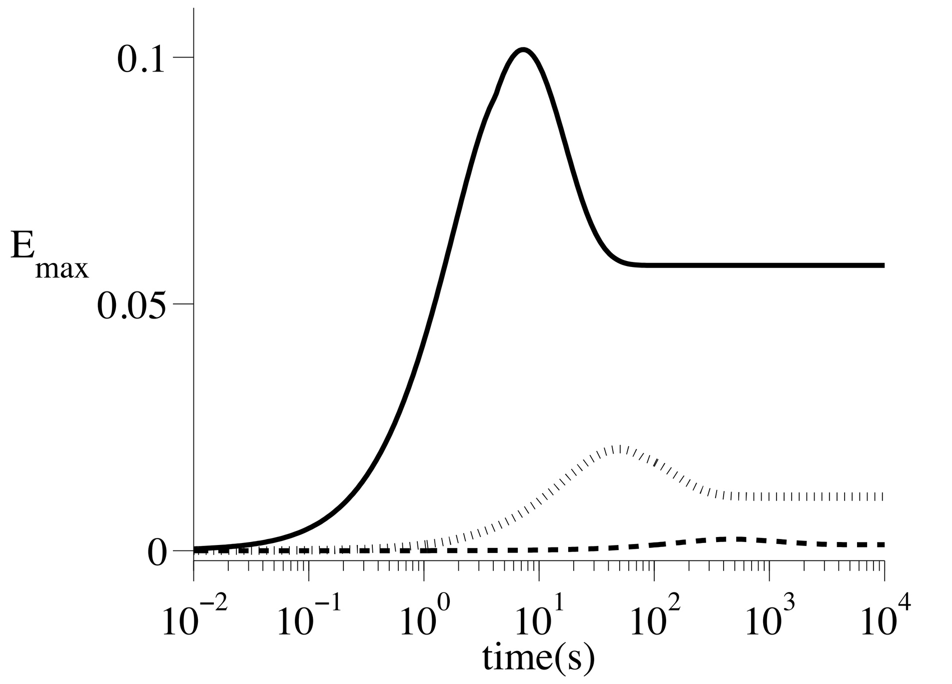
Note that $\boldsymbol{\pi}=\left[\boldsymbol{\pi}_1,\boldsymbol{\pi}_2,\cdots,\boldsymbol{\pi}_{\hat{b}}\right]$ is the conformally partitioned exact stationary distribution of the full model satisfying $\boldsymbol{\pi}\boldsymbol{Q}=\boldsymbol{0}$ subject to $\boldsymbol{\pi}\boldsymbol{e}=1$ and

$$\bar{\boldsymbol{\pi}}_i=\frac{\boldsymbol{\pi}_i}{\boldsymbol{\pi}_i\boldsymbol{e}_i}.$$

To quantify the validity of the reduction we define the error matrix:

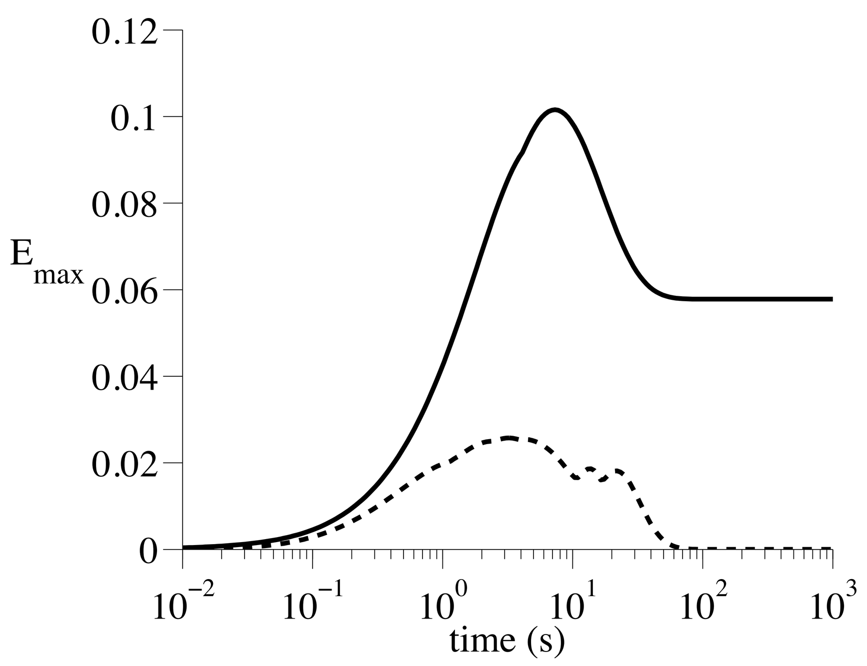
$$\hat{\boldsymbol{E}}(t)=\left|\hat{\boldsymbol{P}}(t)-\boldsymbol{U}\boldsymbol{P}(t)\boldsymbol{V}\right|$$

and plot the largest element, $E_{max}(t)=\max_{ij}\hat{\boldsymbol{E}}_{ij}(t)$, as a function of time.



Solid curve (left) shows the error of the fast/slow reduction for a release site composed of 8 Keizer-Levine RyRs (330 → 9 states). The automated fast/slow reduction procedure is validated by the fact that $E_{max}(t)$ decreases as the rates of Ca^{2+} inactivation and de-inactivation are decreased by a factor of 10 and 100 (dotted and dashed lines).

— Reduction Using Exact Conditional Distribution —

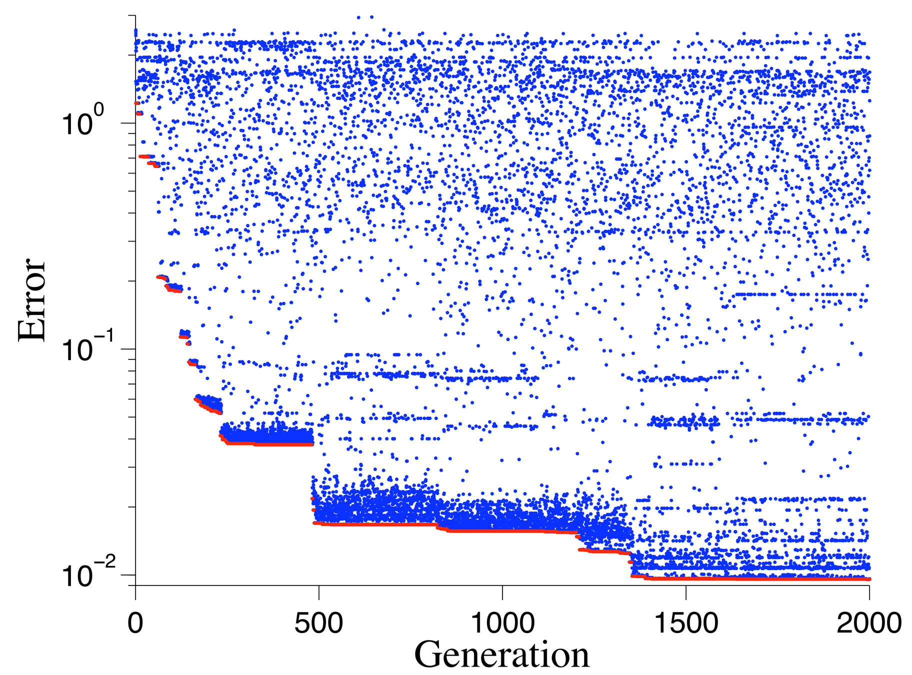


When the time scales in the Ca^{2+} release site model are not well separated, the fast/slow reduction error increases because the estimates of the conditional probability distribution within blocks ($\hat{\boldsymbol{\pi}}_i$) become less accurate. However, when the rate constants $\hat{q}_{ij}$ of the reduced model are calculated using the exact conditional probability distribution $\bar{\boldsymbol{\pi}}_i$,

$$\hat{q}_{ij}=\bar{\boldsymbol{\pi}}_i\boldsymbol{Q}_{ij}\boldsymbol{e}_j \text{ for } i\neq j,$$

both the transient and limiting ($t\to\infty$) reduction errors improve (dashed line). Note that the storage required to calculate the exact conditional distributions is far in excess of that needed to estimate them via fast/slow approximation. To overcome this problem, we employ iterative aggregation/disaggregation (IAD) methods [1] to calculate the stationary distribution of full Ca^{2+} release site models. **Numerical experiments benchmarking automated reductions of release sites composed of up to 80 RyRs consistently yielded small residuals.**

— Model Reduction with No Time Scale Separation —

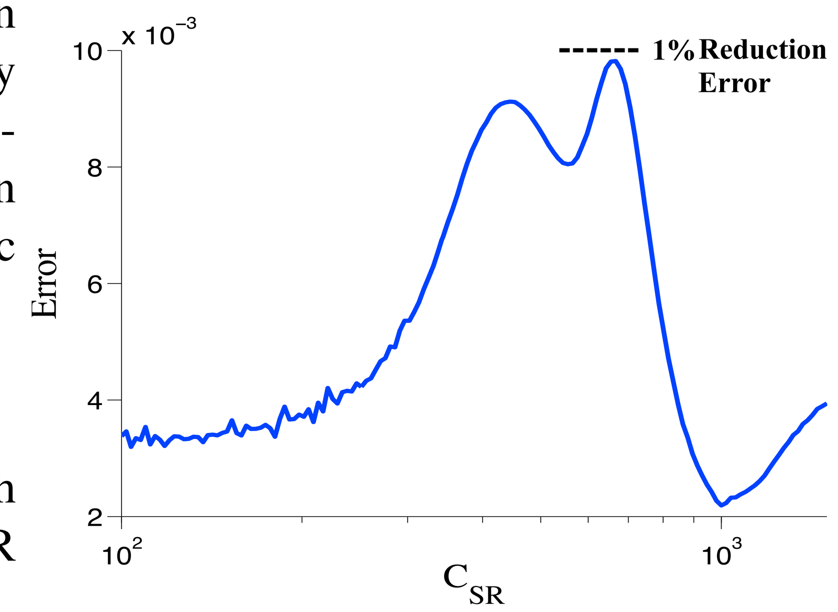


When time scale separation is absent from the full model, a **genetic algorithm is applied to search all possible partitions for those that result in low-error reduced models whose size is arbitrarily decided by the user.** If a $\hat{\beta}$-state reduced model is required, the program will search partitions that divide the full model into $\hat{\beta}$ groups for those that yield low-error reductions (red). A small 'population' of partitions is randomly selected and the 'fitness' of each partition is evaluated (blue). The next generation of partitions is constructed as mutants of current generation partitions randomly sampled in a manner that favors high fitness (i.e., small reduction error).

The genetic algorithm-based reduction method can be extended to compositionally defined Ca^{2+} release sites with more realistic coupling. For example, when depletion of SR Ca^{2+} is represented and the diadic subspace $[Ca^{2+}]$ is given by

$$[\mathrm{Ca}^{2+}](t)=c_\infty+f\left(N_O,c_{SR}\right),$$

the method yields reduced models with their errors <1% for a wide range of SR $[Ca^{2+}]$ (C_{SR}, right).



— References —

[1] W. Stewart, *Introduction to the numerical solution of Markov chains*, Princeton Univ. Press (1994).

[2] J. Keizer and L. Levine. Ryanodine receptor adaptation and Ca^{2+}-induced Ca^{2+} release-dependent Ca^{2+} oscillations, *Biophys J* 71(6):3477 (1996).

[3] Y. Hao, P. Kemper and G. D. Smith. Reduction of calcium release site models via fast/slow analysis and iterative aggregation/disaggregation, *Chaos* 19:037107 (2009).

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