Probability Density Methods for Modeling Local and Global Aspects of Intracellular Calcium Signaling

George S. B. Williams

College of William & Mary, Department of Applied Science, 2008
Field: Computational Biology, Degree: PhD

Advisor: Gregory Smith, Associate Professor of Applied Science

Abstract

Considerable insight into intracellular calcium (Ca) responses has been obtained through the development of whole cell models that are based on molecular mechanisms, e.g., the kinetics of intracellular Ca channels and the feedback of Ca upon these channels. However, a limitation of most deterministic whole cell models to date is the assumption that channels are globally coupled by a single [Ca], when in fact channels experience localized "domain" Ca concentrations. More realistic stochastic Monte Carlo simulations are capable of representing individual domain Ca concentrations but suffer from increased computational demand. This dissertation introduces a novel probability approach which captures important aspects of local Ca signaling while improving computational efficiency.

In many cell types calcium release is mediated by diffusely distributed 1,4,5-trisphosphate receptors (IP_3Rs). In Chapter 2 a Monte Carlo whole cell model is presented where each IP_3R has a local cytosolic and luminal domain [Ca]. The Monte Carlo model is used to validate a probability density approach where local cytosolic and luminal domains Ca concentrations are represented as bivariate probability densities jointly distributed with IP_3R state. Using this probability density approach, analysis shows that the time scale of Ca domain formation and collapse (both cytosolic and luminal) influences global Ca oscillations. Additionally, two reduced models of Ca signaling are derived that are valid when there is a separation of time scales between the stochastic gating of IP_3Rs and the dynamics of domain Ca. These reduced whole cell models account for the influence of local Ca signaling on global Ca dynamics and are therefore more realistic than other conventional deterministic whole cell models.

In cardiac myocytes, Ca influx through voltage gated channels causes the release of intracellular Ca, a process known as Ca -induced Ca release (CICR). In Chapter 3 a probability density approach to CICR is derived from advection-reaction equations relating the time-dependent probability density of subsarcolemmal subspace and junctional sarcoplasmic reticulum [Ca] conditioned on "Ca release unit" state. When these equations are coupled to ordinary differential equations for the bulk myoplasmic and sarcoplasmic reticulum [Ca], a realistic but minimal whole cell model is produced. Modeling Ca release unit activity using this probability density approach avoids the computationally demanding task of resolving spatial aspects of global Ca signaling, while accurately representing heterogeneous local Ca signals in a population of diadic subspaces and junctional sarcoplasmic reticulum domains. The probability density approach is validated and benchmarked for computational efficiency by comparison to traditional Monte Carlo simulations. However, a probability density calculation can be significantly faster than the corresponding Monte Carlo simulation, especially when cellular parameters are such that univariate rather than multivariate probability densities may be employed.

Expanding upon the computational advantages of the probability density approach, a moment closure technique is introduced in Chapter 4 which facilitates whole cell modeling of cardiac myocytes when the dynamics of subspace [Ca] are much faster than those of junctional SR [Ca]. The method begins with the derivation of a system of ODEs describing the time-evolution of the moments of the univariate probability density functions for junctional SR [Ca] jointly distributed with CaRU state. This open system of ODEs is then closed using an algebraic relationship that expresses the third moment of junctional SR [Ca] in terms of the first and second moments. Benchmark simulations indicate that the moment closure approach is nearly 10,000-times more computationally efficient than corresponding Monte Carlo simulations while leading to nearly identical results.