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A kinetic Monte Carlo simulation study of inositol 1,4,5-trisphosphate receptor (IP3R) calcium release channel

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Abstract

Most of the previously theoretical studies about the stochastic nature of the IP3R calcium release channel gating use the chemical master equation (CME) approach. Because of the limitations of this approach we have used a stochastic simulation algorithm (SSA) presented by Gillespie. A single subunit of De Young–Keizer (DYK) model was simulated using Gillespie algorithm. The model has been considered in its complete form with eight states. We investigate the conditions which affect the open state of the model. Calcium concentrations were the subject of fluctuation in the previous works while in this study the population of the states is the subject of stochastic fluctuations. We found out that decreasing open probability is a function of Ca^{2+} concentration in fast time domain, while in slow time domain it is a function of IP3 concentration. Studying the population of each state shows a time dependent reaction pattern in fast and medium time domains (10^{-4} and 10^{-3} s). In this pattern the state of X_{010} has a determinative role in selecting the open state path. Also, intensity and frequency of fluctuations and Ca^{2+} inhibitions have been studied. The results indicate that Gillespie algorithm can be a better choice for studying such systems, without using any approximation or elimination while having acceptable accuracy. In comparison with the chemical master equation, Gillespie algorithm is also provides a wide area for studying biological systems from other points of view.

Keywords: Ion channel; De Young–Keizer model; Stochastisity; Gillespie algorithm; Monte Carlo; Complex reactions

1. Introduction

The importance of calcium in cell biology was first discussed by Sidney Ringer in 1882. He demonstrated that minute amounts of the divalent ion were necessary to maintain heart muscle contractility (Ringer, 1883) and today the specialist are believed that 'Almost everything that we do is controlled by Ca^{2+}: how we move, how our hearts beat and how our brains process information and store memories' (Berridge, 1990). There are many other processes that can be add to this list, such as how eggs are activated upon fertilization, how acinar cells secrete, how wounds heal, how ciliary beat frequency is coordinated, how liver cells coordinate their behavior and how cells die in apoptosis (Falcke, 2004).

In a cellular view, calcium ion is an important second messenger in cells. There are many cellular processes that can be activated by Ca^{2+}. They have evolved to be Ca^{2+}-dependent and/or Ca^{2+}-regulated, such as protein kinases, protein phosphatases, proteases, pumps and channels, cytoskeletal components and enzymes involved in metabolism.

Second messengers also play an important role in controlling the functioning of all cells of the body by acting as carriers of intracellular messages. Cells receive their instructions from the body through hormones and neurotransmitters that bind to receptors on their surface. Many of these messages are relayed by the release of calcium ions from internal stores into the cell cytoplasm, or by opening channels in the membrane of the cell, allowing external calcium to enter the cytoplasm. In the other words calcium controls a wide range of cellular functions such as neurotransmitter and hormone release, muscle contraction, metabolism, cell death, cell division, cell motility and gene expression. Also, Ca^{2+} ions are completely remarkable in the ability of controlling numerous processes within the same cell

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simultaneously (Lodish et al., 2002; Clapham, 1985; Berridge et al., 2000; Bast, 2004).

This ability of calcium to provide a number of signals encoded by the same ion is a result of the way in which calcium levels can be altered in the cell. For instance, Changes in the cytosolic free Ca^{2+} concentration are used by many cells for signaling. Remember that Ca^{2+} is a simple ion which can not transmit information by its binding specificity or simply by its presence. Ca^{2+} ion transmits information as Ca^{2+}waves and oscillations.

Ca^{2+} signaling frequently occur as repetitive, but transient increases in Ca^{2+} concentration (Tsien and Tsien, 1990; Berridge et al., 1998; Falcke, 2003a). Changes in cytosolic [Ca^{2+}] are controlled, in part, by Ca^{2+} channels in the surface membrane and the release of Ca^{2+} from internal stores. Ca^{2+} channels like other ionic channels are membrane protein complexes facilitating the diffusion of calcium ions through the biological membranes. The molecular structure for some of these channels is still not truly determined.

Opening and closing of the Ca^{2+} channels control release of calcium. The organocells such as ER (endoplasmic reticulum) and SR (sarcoplasmic reticulum) (Sun et al., 1998; Thomas et al., 1998; Mak et al., 2000; Mak and Foskett, 1998) employ ion channels in this task.

Measurements have shown that ER and SR release Ca^{2+} into the cytosol during Ca^{2+}oscillations (Alberts et al., 1994). The ion channel that is most abundant on the membrane of the SR is the Ryanodine receptor (RyR) release channel. It is Ca^{2+} that controls the opening of the release channel. The probability for an open channel grows with increasing cytosolic Ca^{2+} concentration. This autocatalytic behavior is pivotal for intracellular Ca^{2+} dynamics (Berridge et al., 2000). The channel type in the endoplasmic reticulum membrane is the inositol-1,4,5-trisphosphate (IP3) receptor (IP3R). It is the prevailing receptor on the membrane of the ER that controls Ca^{2+} liberation from the ER to the cytosol.

The open probability of the IP3R depends on the calcium concentration on the cytosolic side of the channel and the IP3-concentration (Tsien and Tsien, 1990; Taylor, 1998; Patel et al., 1999; Putney and Bird, 1993). It increases nonlinearly with the IP3-concentration and the Ca^{2+} concentration. Hence, Ca^{2+} released by one channel increases the open probability of neighboring channels. That provides a self amplifying release mechanism.

The IP3R channel consists of four subunits (Mikoshiba, 1993; Michikawa et al., 1994). Both homotetrameric and heterotetrameric channel complexes have been found (Monkawa et al., 1995; Joseph et al., 2000; Galvan et al., 1999; Onoue et al., 2000; Bezprozvanny et al., 1991; Watras et al., 1991; Jiang et al., 2002). The receptors are proteins about 2700 amino acids long (Falcke, 2004). Since now three different types have been found (Falcke, 2004; Taylor, 1998; Patel et al., 1999; Taylor and Swatton, 2003; Falcke and Malchow, 2003; Taylor and Laude, 2002). They differ in the characteristics of the regulation by IP3 and Ca^{2+} (Taylor and Swatton, 2003; Falcke and Malchow, 2003). All of them share basically the same response with respect to the Ca^{2+} concentration. Inositol 1,4,5-trisphosphate receptor channels open and close randomly. The open probability depends on the state of the receptor. The state of the receptor is mainly determined by binding of Ca^{2+} and IP3. The open probability is the highest when a minimum number of activating Ca^{2+} ions and IP3 molecules are bound and very small otherwise. In the other words, a subunit in IP3R channel needs to bind IP3 and Ca^{2+} (Taylor, 1998; Bezprozvanny et al., 1991; Marchant and Taylor, 1998; Finch et al., 1991; Parker et al., 1996; Hajnoczky and Thomas, 1997), so the open probability of the channel is dependent to IP3 and Ca^{2+}.

This dependence of open probability on cytosolic Ca^{2+} creates the possibility of communication between the channels, since Ca^{2+} released from one channel modulates the open probability of the other ones. Ca^{2+} controls the IP3R in a biphasic manner since high calcium concentrations inhibit the channel. The channel is closed in the inhibited state irrespective of binding of IP3 and activating Ca^{2+}. Inhibition is the main process causing a decrease of open probability at high Ca^{2+} concentration.

The stochastic gating of the calcium channels have been studied in different ways.

The previous works included Monte Carlo simulations with using the master equation approach (Mazzag et al., 2005) or some derivations of the models with the stochasticity approach (Falcke, 2003a).

In the present work, the single subunit dynamics was studied as a stochastic realization of the De Young–Keizer model. The model has been introduced as a deterministic model by its authors at first and was later on used as a stochastic scheme by Falcke (2003a) and Falcke et al. (2000).

The model maybe considered as a set of complicated reactions, too. We used a Monte Carlo based exact simulation algorithm (Gillespie algorithm) for simulating the set of reactions in this model, without any simplifications of the model. The basis of the model and the description of the algorithm are described in the next section.

2. Description of model

2.1. IP3R channel models: the De Young–Keizer model

Most of the theoretical research has focused on deterministic models of intracellular Ca^{2+} waves (Atri et al., 1993; Dupont, 1998; Dupont and Goldbeter, 1994; Falcke et al., 1999; Sneyd et al., 1998, 1995; Wagner and Keizer, 1994; Wagner et al., 1998). Only recently, the stochastic nature of gating channels has been considered (Falcke et al., 2000; Falcke, 2003b; Keizer and Smith, 1998; Shuai and Jung, 2002). There are different types of IP3R channel models, such as general models, models of Ca^{2+} pool content and mathematical IP3R channel models (Falcke, 2004). In the last category, many models of IP3Rs have been published to date (Atri et al., 1993; De Young and Keizer, 1992; Bezprozvanny and Ehrlich, 1994; Tang et al., 1995; Kaftan et al., 1997; Swillens et al., 1998) most of which are designed to reproduce various aspects of the single channel kinetics of the type 1 IP3R. Models of the IP3R-2 and -3 can be found on (LeBeau et al., 1999) and (Sneyd and Dufour, 2002).

The model studied was De Young–Keiser model. Using of this model needs a closer look on the IP3 receptor. As men-