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Mathematical modeling shows the frequency of Ca^{2+} sparks in cells depends on the ryanodine receptor's arrangement

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Abstract

Calcium dynamics plays key role in many intracellular processes. Studying of calcium sparks, that is events of calcium release via groups of ryanodine receptors, or RyR channels, is of a great importance for live sciences. Recent experimental studies show, that RyRs have a non-uniform arrangement in calcium release units (CRU), however, to our knowledge, there is yet no published Ca^{2+} spark model which takes into account this fact. In the paper we made use of a genetic simulated annealing (GSA) algorithm for the RyR cluster generation and Gillespie algorithm for modeling calcium spark. Computer simulation of the model CRU taking into account a specific homotetrameric structure of the RyR channel shows that experimental nearest neighbor distances (NND) distributions of RyRs in CRU do not provide exact information about calcium spark probability. Having the same NND distribution, the CRUs can have different inverse distance matrices and hence different calcium spark properties. Our model approach opens novel perspectives for studying the calcium release process.

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Keywords: Ryanodine receptor; Calcium sparks; Gillespie algorithm; Global optimization; genetic algorithm; simulated annealing

1. Introduction

Rapid, transient changes in Ca^{2+} concentration directly control muscle contraction, cell locomotion, hormonal secretion, and neural transmission. Events of Ca^{2+} release from a single cluster of Ca^{2+} release channels in calcium release units (CRU) through ryanodine receptors (RyR channels) on sarcoplasmic reticulum (SR) membrane are called Ca^{2+} sparks [1]. They have been intensively studied both theoretically and experimentally for the last 25 years but many questions remain open. Earlier results show that SR membrane contains nearly crystalline 2D arrays of RyRs organized in clusters [2, 3]. However, recent experimental papers on the RyR's arrangement and interaction in vitro [4] and in situ [5] point to an nonuniform and nonstatic spatial distribution of RyRs, that depends on the environmental

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changes such as phosphorylation and change of free Mg^{2+} concentration [5]. The nature and role of these effects is unknown.

The RyR can be readily identified in electron micrographs being a homotetramer, measuring roughly 29x29x12 nm cuboid. According to [5], several types of the RyR neighbourhood in the CRUs were identified:

- **Checkerboard**. It's roughly a corner-sharing physical RyR connection.
- **Side-by-side**. It's roughly an edge-sharing physical RyR connection.
- **Both**. RyR has in this configuration both types of the neighbors.
- **Isolated**. RyR is not physically connected with other channels.

Next question is how the RyRs' spatial distribution in CRU changes calcium spark properties. Recent calcium spark models [6, 7] take into account geometry of CRU. In these works, channels are placed on a two-dimensional square lattice with a defined adjacency matrix for the cluster. It was shown, that the maximum eigenvalue λ_{max} of the adjacency matrix is a reliable predictor of Ca^{2+} spark probability P_{spark}, i.e., the probability that a spontaneous RyR opening triggers a spark in both three-dimensional realistic [6] and simple linear network [7] models. The bigger the λ_{max}, the bigger is the P_{spark}. But these models don't take into account different RyR arrangements to the nearest neighbor distance (NND) and hence don't take into account isolated channels in CRUs.

In this work we model Ca^{2+} spark using simple model based on papers [7, 8] at different CRUs generated with different arrangements considered. We show, that RyRs distribution in CRU makes an effect on calcium spark properties, such as P_{spark}. At the same time, NND distribution doesn't define fully calcium spark properties. We made use of the similar approach as in [7], where adjacency matrix of RyRs was used, but using inverse distance matrix D. It case of nonuniform distributions, maximum eigenvalue λ_{max} of D cannot predict P_{spark} because for the same λ_{max} there is different P_{spark} for different NND distributions.

2. Methods

This section is separated into two parts. The first one is devoted to the calcium spark model, the second one is devoted to the method of generating CRU based on the RyR arrangement distribution.

2.1. Calcium Spark Model

Let N RyR channels in the CRU are placed on a plane. Each channel's state is described by a random variable $X_i(t)$, which is equal to 1 when channel is open and 0 when channel is closed. If the channel i is open, the probability that it closes within an infinitesimal time step dt is given by δdt, where δ is assumed to be constant. If channel i is closed, it transitions into the open state in time dt with a probability $\beta_i dt$, β_i is given by $\beta_i = k_+ C_i^{\mu}$, where k_+ is the opening rate constant, $C_i = \sum_j^N X_j(t) C_{ji}$ is the elevation of Ca^{2+} concentration caused by an open channel at time t, and μ is the Hill coefficient for Ca^{2+} binding.

Recent cryo-electron microscopy study of RyRs [4] shows different types of physical interaction between RyRs and it also depends on Ca^{2+} concentration. Here we incorporate a simple model of the Ca^{2+} diffusion that relates this model to the Ca^{2+}-based communication between RyRs, so we don't take into account conformational interaction of RyRs with neighbors in this work. We use the steady-state diffusion equation for a continuous point source in a semi-infinite volume to obtain the Ca^{2+} concentration sensed by single open channel [9]:

$$C_{ji} = \frac{I_{RyR}}{2\pi z F d_c r_{ji}}, \tag{1}$$

where I_{RyR} is the unitary current of a single channel, $z = 2$ is the valency of Ca^{2+}, F is Faraday's constant, d_c is the effective diffusion coefficient of Ca^{2+} in the release site subspace, and $r = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2}$ is the distance between channels' pores. The probability $p_i(t)$ that channel i is open at time t obeys master equation:

$$\frac{dp_i(t)}{dt} = \beta_i(1 - X_i(t)) - \delta X_i(t). \tag{2}$$