A MODEL TO STUDY CALCIUM DISTRIBUTION IN CARDIAC MYOCYTES

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Abstract

Cardiac Myocytes are also known to state voltage-gated Ca2+ channels analogous in neurons. Calcium ion is a significant negotiator in cardiac Myocytes for excitation-contraction pairing. At the cellular stage, the real meaning of a heartbeat is a rise of calcium concentration. The increased concentration of Calcium causes a temporary disarticulation of contractile filaments, which shows the reduction of cell. Succeeding lessening of Ca leads relaxation of the my filaments and increase in the size of cell. The role of Calcium Distribution in Myocytes is not still well understood. The investigational approaches are very costly and time taken so problems of such mathematical modeling is one more substitute. In this paper it is planned to extend Mathematical Models to study Calcium Distribution in Cardiac Myocytes. Suitable boundary conditions have been framed.

Keywords*: Ca2+ profile, buffer, Advection diffusion reaction.*

I. INTRODUCTION

Nowadays the up-and-coming area is Computational Biology which includes modeling of mathematics involved organs of human beings.Calcium [$Ca2+$] is necessary for almost every method in human organs like heartbeat, contraction of muscles and very important in Cardiac Myocytes. Thus, recognition of the factors that involve the concentration of calcium ions has been a challenge.

1.1Calcium Signaling in Cardiac Myocytes

In inspiring the contraction of heart cells during the heart beat, concentration of calcium ions is very significant. Myocytes are heart cells which are accountable for expansion and contraction of heart, a procedure responsible for the pumping of blood from heart to the other parts of body. Calcium signaling which is taken place by reaction diffusion equation in myocytes for the functioning of heart. Through intracellular signals, the cells react immediately to their surroundings. The modeling of these problems arise new challenges in the field of Mathematics.

As Ca^{2+} ions distribute far from voltage gated plasma membrane Ca^{2+} channels and approach towards the region having increased concentration of ions and trigger proteins connected with neurotransmitter release[1]. Association and releasing of free Calcium and other "Ca^{2+} buffers" conclude the variety of action of Ca^{2+} ions manipulating the time course of their effect and make easy clearance of Ca^{2+} [2]. In this paper, "Ca^{2+} Buffer" means Ca binding species.Ca^{2+} , confined to a small area discharge actions identified as Ca^{2+} "sparks" are observed in Cardiac Myocytes. Ca^{2+} sparks are mediated by RYRS located on the intracellular Ca^{2+} store of muscle cell, the sarcoplasmic reticulum (SR). Concentration coupling, Ca^{2+} sparks activated by Ca^{2+} in flux through sarcolemmal Ca^{2+} channels is the "building blocks" of global Ca^{2+} responses that cause muscles contraction. With the help of mathematical explanation of electrical actions in a cell, cardiac action potentials arise. To a great extent the mathematical work of cardiac cell modeling is like neurons taken from the original work of Hodgkin and Huxley[3], who formulated a mathematical explanation of the giant squid axon (1952).

"Schematic" Action Potential

"Real" Action Potential
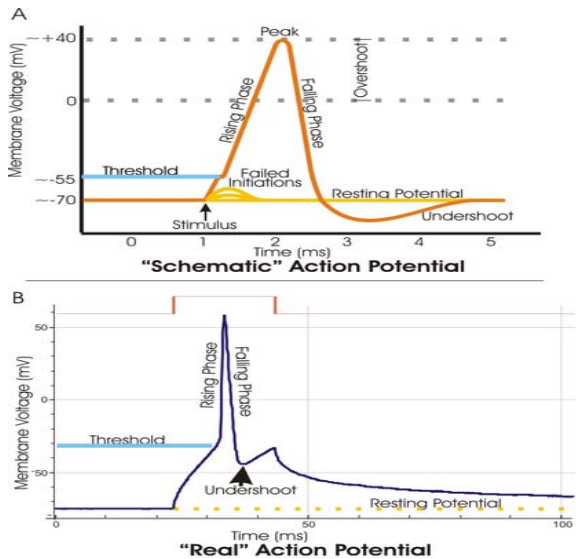
2. Literature analysis

Gregory D. Smith *et. al.*,[4] have proposed a Simple Numerical Model of Calcium Spark Formation and Detection in Cardiac Myocytes. According to their model, the elementary events of excitation-contraction coupling in heart muscle are Ca2+ sparks,which arise from one or more ryanodine receptors in the sarcoplasmic reticulum (SR). BACKX *et. al.*,[7] constructed a model of propagating Calcium-induced Calcium release mediated by Calcium diffusion. The model was used to evaluate whether propagation of calcium transients and the range of propagation velocities observed experimentally (0.05-15mm s -1) could be predicted. Thomas R. Shannon *et. al*,[6] developed the model includes the following novel features: (i) The addition of a subsarcolemmal compartment to the other 2 commonly formulated cytosolic compartments (junction and bulk) since ion channels in the membrane sense ion concentrations which differ from bulk. (ii) The use of realistic cytosolic Ca buffering parameters (iii) A reversible SR Ca pump (iv) A scheme for Na-Ca exchange transport which is [Na]i-dependent and allosterically regulated by [Ca]i and (v) A practical model of SR Ca release including both inactivation/adaptation and SR Ca load dependence. Luo and Rudy,[7] made a dynamic model of the cardiac ventricular action potential: Simulations of ionic currents and concentration changes. A mathematical model of the cardiac ventricular action potential is presented in which The following processes are formulated: Ca2+ current through the L-type channel , the Na+-Ca2+ exchanger, Ca2+ release and uptake by the sarcoplasmic reticulum (SR), buffering of Ca2+ in the SR and in the myoplasm,

a Ca2+ pump in the sarcolemma, the Na+-K+ pump, and a nonspecific Ca2+-activated membrane current. Depolarizations are induced by spontaneous Ca2+ release from the sarcoplasmic reticulum (SR), which, in turn, activates both the Na+-Ca'+ exchanger and a nonspecific Ca2+-activated current (Ins(Ca)). The relative contributions of INaCa and of Ins (Ca,) to the generation of DADs are different under different degrees of Ca2+ overload..The above discussion gives us the idea about mathematical model or calcium diffusion in cardiac myocytes and neuron cells by which various research workers .This background will be used to perform mathematical investigations on calcium dynamics in cardiac myocytes. Luo and Rudy [8] made another dynamic model of the cardiac ventricular action potential. Shannon *et. al.,* **2004** constructed a mathematical treatment of Integrated Ca dynamics within the ventricular myocyte. The model includes the parameters like (i) The addition of a subsarcolemmal compartment to the other 2 commonly formulated cytosolic compartments (junctional and bulk) since ion channels in the membrane sense ion concentrations which differ from bulk (ii) The use of realistic cytosolic Ca buffering parameters (iii) A reversible SR Ca pump (iv) A scheme for Na-Ca exchange transport which is [Na]i-dependent and allosterically regulated by [Ca]ion and (v) A practical model of SR Ca release including both inactivation/adaptation and SR Ca load dependence.

Objectives:

It is planned to extend mathematical models to realize the mechanism of Calcium dynamics in myocytes. The objectives of this study are as follows:

1. Analyzing the existing model of Calcium dynamics in Cardiac myocytes..

2. Modifying an extent the existing models of Calcium dynamics in Cardiac myocytes for studies in differ rent situations.

3. Developing new models of calcium regulation in Cardiac myocytes which can be useful by bio mathematical scientists of clinical applications.

4. Studying the impact of various parameters like buffers, influxes, out fluxes, leaks and pumps on Calcium dynamics in Cardiac myocytes.

4. Methodology

By assuming a bimolecular association reaction between Ca^{2+} and buffer, we have

$$Ca^{2+} + B \overset{k+}{\underset{}{\Leftrightarrow}} CaB \qquad (1)$$
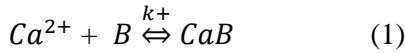
In equation 1, B represents free buffer, CaB represents Ca^{2+} bound buffer, and k^+ and k^- are association and dissociation rate constants, respectively. If we further assume that the reaction of Ca^{2+} with buffer follows mass action kinetics, we can write the following system of ODEs for the change in concentration of each species

$$\frac{d[Ca^{2+}]}{dt} = R + J \qquad (2)$$

$$\frac{d[B]}{dt} = R \qquad (3)$$

$$\frac{d[CaB]}{dt} = -R \qquad (4)$$

Where the common reaction terms R, are given by

$$R = -k^+[Ca^{2+}][B] + k^-[CaB] \qquad (5)$$

and J represents Ca^{2+} influx. Both R and J have units of concentration of per unit time.

Equations (2) to (4) are extended to include multiple buffers and the diffusive movement of free Ca^{2+}, Ca^{2+} bound buffer and Ca^{2+} free buffer. Assuming, Fick's diffusion in a homogeneous, isotropic medium, the system of reaction diffusion equations is written as [9].

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] + \sum_i R_i + J \qquad (6)$$

$$\frac{\partial[B_i]}{\partial t} = D_{B_i}\nabla^2[B_i] + R_i \qquad (7)$$

$$\frac{\partial[CaB_i]}{\partial t} = D_{CaB_i}\nabla^2[CaB_i] - R_i \qquad (8)$$

Where the reaction terms, R_i, are given by
$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-[CaB_i]$$

Where, i is an index over Ca^{2+} buffers, D_{Ca}, D_{B_i}, D_{CaB_i} are diffusion coefficients of free Ca^{2+}, bound calcium and free buffer respectively.

Since Ca^{2+} has a molecular weight that is small in comparison to most Ca^{2+} binding species, the diffusion constant of each mobile buffer is not affected by the binding of Ca^{2+} that is $D_{B_i} = D_{CaB_i} = D_i$. Substituting this in equation (7) & (8) and on summation it gives

$$\frac{\partial[B_i]_T}{\partial t} = \frac{\partial[CaB_i]}{\partial t} + \frac{\partial[B_i]}{\partial t} = D_i\nabla^2[CaB_i] + D_i\nabla^2[B_i] = D_i\nabla^2[B_i]_T \qquad (10)$$

And

$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-([B_i]_T - [B_i]) \qquad (11)$$

Where
$$[B_i]_T = [CaB_i] + [B_i]$$

Thus, $[B_i]_T$, profiles are initially uniform and there are no sources or sinks for Ca^{2+} buffer, $[B_i]_T$ remains uniform for all times. Thus, the following equations are written for the diffusion of Ca^{2+},

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] + \sum_i R_i + J \qquad (12)$$

$$\frac{\partial[B_i]}{\partial t} = D_{B_i}\nabla^2[B_i] + R_i \qquad (13)$$

Where
$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-([B_i]_T - [B_i]) \qquad (14)$$

Here both R_i & J have units of concentration per unit time.

Considering simplification of equations (2) to (4) that come about when buffer parameters are in select regimes: the so called "excess buffer" approximation.

In the excess buffer approximation (EBA), equations (2) to (4) are simplified by assuming that the concentration of free Ca^{2+} buffer $[B_i]$, is high enough such that its loss is negligible. The EBA gets its name because this assumption of the unsaturability of Ca^{2+} buffer is likely to be valid when Ca^{2+} buffer is in excess.

4.1 Initial and Boundary conditions & Geometry of Simulations

To complete a reaction – diffusion formulation for the buffered diffusion of Ca^{2+}, a particular geometry of simulation must be specified and equation (2) – (4) must supplement with boundary conditions and initial concentration profiles. If Ca^{2+} is released from intracellular Ca^{2+} stores deep within a large cell (so that the plasma membrane is far away and doesn't influence the time course of the event), and the intracellular milieu is homogenous and isotropic, then we have spherical symmetry. In this case the evolving profiles of Ca^{2+} and buffer (through a function of time and distance from the source) will not be a function of the polar (f) or azimuthally (q) angle. In the case of such spherical or radial symmetry the Laplacian Ca^{2+} reduces to

$$\nabla^2 = \frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2\frac{\partial}{\partial r}\right] = \frac{\partial^2}{\partial r^2} + \frac{2}{r}\frac{\partial}{\partial r}$$

The reasonable initial condition for this simulation is uniform background Ca^{2+} profile of $[Ca^{2+}]_\infty = 0.1 \ \mu M$. we require

buffer far from the source to remain in equilibrium with Ca^{2+} at all times.

$$\lim_{r \to \infty} [Ca^{2+}] = [Ca^{2+}]_{\infty} \qquad (15)$$

And

$$\lim_{r \to \infty} [B_i] = [Bi]_{\infty} \qquad (16)$$

Near the source, the boundary conditions

$$\lim_{r \to \infty} \left(4\pi D_c r^2 \frac{\partial [Ca^{2+}]}{\partial r} \right) = \sigma \qquad (17)$$

and

$$\lim_{r \to \infty} \left(4\pi D_c r^2 \frac{\partial [B_i]}{\partial r} \right) = 0 \qquad (18)$$

We define an influx of free Ca^{2+} at the rate σ by faraday's law,

$$\sigma = \frac{I_{ca}}{ZF}$$

5. Possibilities of the study

The modeling of the calcium dynamics in myocytes gives new challenges for mathematics. The future study will initially direct to produce information regarding drawbacks, restrictions and gaps in the presented models and studies of calcium dynamics in cardiac myocytes. Subsequently the proposed study may lead to modifications an extension of existing models of calcium dynamics in cardiac myocytes. Also, it will lead to development of new models of calcium dynamics in cardiac myocytes. Addressing the existing issues and challenges of such studies. Apart from this, it will lead to development of new mathematical approaches for solution involving advanced mathematical and numerical techniques like integral transforms, special functions, finite element, finite difference methods. The proposed study will generate information about interrelationship among various parameters and their impact on calcium dynamics in cardiac myocytes. The information generated will be better insights of mechanisms involved in calcium dynamics in cardiac myocytes which will be quite useful to biomedical scientists for developing protocols for diagnosis and treatment of heart diseases. In all the proposed study will contribute new knowledge not only to mathematical sciences but also to computational neurosciences.

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