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Brief Introduction of Effect Of Calcium Changes In The Cells of Heart

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Abstract: One of the advance techniques used in medicinal field is mathematical modeling. By this method the real world problems and interpretations of solutions is translated into mathematical problems. For this reason ,mathematical modelers have often played significant roles in the study of calcium dynamics responsible for the expansion and contraction of myocyte cells of heart and interpret the results of cardiac dynamics so that it can help in detecting symptoms and to find the cures of cardiac diseases. This mathematical and computational approach provides a forum to handle issues on electrochemical signaling during ECG analysis. It is the advance methodology through which mankind can be benefited.

Keywords —Mathematical modeling, calcium dynamics, effect of calcium

I. INTRODUCTION

The Heart is a muscular organ found in most vertebrates that is responsible for pumping blood throughout the blood vessels by repeated, rhythmic contractions[3].Heart is made up of cells called cardiomyocytes. Electrical impulses cause the cardiac fibers to contract ,squeezing blood out from the heart muscle. When fibers relax, blood flows into the heart. So, the functioning of heart is achieved through expansion and contraction of cardiac myocytes.

The role of calcium ions [2] is significant in study of cell dynamics especially in myocytes, neuron, astrocytes etc. The cardiac muscles are responsible for pumping of blood via involuntary contractions. The cardiac muscles enclosed by plasma membrane which has high voltage gated ion channels and ATP driven pump systems for exchange of ions such as potassium , calcium and sodium. The plasma membrane acts as a selective barrier for influx and outflux of ions through it. This leads to excitation and contraction coupling and hence contracts and relaxes the cardiac myocytes . Sometimes these channels dominates calcium entry pathway into the myocytes through voltage gated channels. This calcium exchange mechanism is associated with energy dynamics(ATP cycle) [14] [15]. Thus set up a calcium dynamics mechanism in myocytes cell which is responsible for contraction and relaxation and ultimately leading to pumping of blood by heart to all parts of body.

To understand this calcium dynamics and functionality of heart, these mathematical modeling are studied .Thus the development of mathematical models to study calcium dynamics in cardiac myocytes is focused on this advance technique for carrier and quicker approach. The result obtained are purely mathematical and proven correct. Thus is boon for medicine to study various heart issues and neurological issues . This cardiac action potential is studied at cellular level. As cardiac cell has similarity with neurons. Therefore much of the mathematical modeling is drawn from the mathematics of Giant Axon neuron studied first by Hodgkin Huxley Calcium ion mathematical modeling.

Description of the Problem

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

$$Ca^{2+} + B \quad CaB \qquad (1.1)$$

In equation (1.1), B represents free buffer, CaB represents Ca^{2+} bound buffer, and k^+ and k^- are association and dissociation rate constants respectively. If it is further assumed that the reaction of Ca^{2+} with buffer follows mass action kinetics, it can be written as the following system of ODEs for the change in concentration of each species [13].

$$\frac{d[Ca^{2+}]}{dt} = R \qquad (1.2)$$

$$\frac{d[B]}{dt} = R \qquad (1.3)$$

$$\frac{d[CaB])}{dt} = -R \qquad (1.4)$$

Where the common reaction term R, is given by

$$R = -k^+ [Ca^{2+}][B] + k^- [CaB] \qquad (1.5)$$

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

Equations (1.2) to (1.4) are extended to include multiple buffers and the diffusive movement of free Ca^{2+}, Ca^{2+}

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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 [13].

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] + \sum_i R_I + J \qquad (1.6)$$

$$\frac{\partial[B_i]}{\partial t} = D_{B_i}\nabla^2[Ca^{2+}] + R_i \qquad (1.7)$$

$$\frac{\partial[CaB_i]}{\partial t} = D_{CaB_i}\nabla^2[CaB_I] - R_i \qquad (1.8)$$

where the reaction terms, R_i, are given by

$$R_i = - k_i^{+} [Ca^{2+}][B_i] + k_i^{-}[CaB_i] \qquad (1.9)$$

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.

II. NOTEWORTHY CONTRIBUTION OF THE STUDY

1.The most important work is of Hodgkin and Huxley [4], who developed the first quantitative model of the propagation of an electrical signal along a squid giant axon. Current can be carried through the membrane either by charging the membrane capacity or by movement of ions through the resistances in parallel with the capacity. The ionic current is divided into components carried by sodium and potassium ions (INa and Ik) and a small 'leakage current' (Il) made up by chloride and other ions. Each component of the ionic current is determined by a driving force which may conveniently be measured as an electrical potential difference and a permeability coefficient which has the dimensions of a conductance. Thus the sodium current (INa) is equal to the sodium conductance (gNa) multiplied by the difference between the membrane potential (E) and the equilibrium potential for the sodium ion (ENa).

2. Backx, P. H., De Tombe, P. P., Van Deen, J. H., Mulder, B. J., & Ter Keurs, H. E. [1] gave a model of propagating calcium-induced calcium release mediated by calcium diffusion. The effect of sudden local fluctuations of the free sarcoplasmic [Ca2+]I in cardiac cells on calcium release and calcium uptake by the sarcoplasmic reticulum (SR) was calculated with the aid of a simplified model of SR calcium handling. The model was used to evaluate whether propagation of calcium transients and the range of propagation velocities observed experimentally (0.05-15 mm s(-1)) could be predicted. Calcium fluctuations propagate by virtue of focal calcium release from the SR, diffusion through the cytosol (which is modulated by binding to troponin and calmodulin and sequestration by the SR), and subsequently induce calcium release from adjacent release sites of the SR. The minimal and maximal velocities derived from the simulation were 0.09 and 15 mm s(-1) respectively. The method of solution involved writing the diffusion equation as a difference equation in the spatial coordinates. Thus, coupled ordinary differential equations in time with banded coefficients were generated. The coupled equations were solved using Gear's sixth order predictor-corrector algorithm for stiff equations with reflective boundaries. The most important determinants of the velocity of propagation of the calcium waves were the diastolic [Ca++]i, the rate of rise of the release, and the amount of calcium released from the SR. The results are consistent with the assumptions that calcium loading causes an increase in intracellular calcium and calcium in the SR, and an increase in the amount and rate of calcium released. These two effects combine to increase the propagation velocity at higher levels of calcium loading.

3.Wagner, J., & Keizer, J. [15] derived and investigated models of Ca2+ diffusion in the presence of rapid buffers and also discussed the effect of mobile fluorescent indicators on Ca2+ diffusion. Based on realistic mechanisms of Ca2+ buffering that include both stationary and mobile buffers, they derived and investigate models of Ca2+ diffusion in the presence of rapid buffers. They obtained a single transport equation for Ca2+ that contains the effects caused by both stationary and mobile buffers For stationary buffers alone, they obtained an expression for the effective diffusion constant of Ca2+ that depends on local Ca2+ concentrations. Mobile buffers, such as fura-2, BAPTA, or small endogenous proteins, give rise to a transport equation that is no longer strictly diffusive. Calculations are presented to show that these effects can modify greatly the manner and rate at which Ca2+ diffuses in cells, and they compared these results with recent measurements by Allbritton et al. (1992). As a prelude to work on Ca2+ waves, they used a simplified version of the model of the activation and inhibition of the IP3 receptor Ca2+ channel in the ER membrane to illustrate the way in which Ca2+ buffering can affect both the amplitude and existence of Ca2+ oscillations.

4. Luo, C. H., & Rudy, Y. [6] 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 depolarization are induced by spontaneous Ca2+ release from the sarcoplasmic reticulum (SR), which, in turn, activates both the Na+-Ca2+ 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.

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5. Luo, C. H., & Rudy, Y. [7] made another dynamic model of the cardiac ventricular action potential. II. After depolarizations, triggered activity, and potentiation wherein delayed after Shannon et. al.,2004 constructed a mathematical treatment of integrated Ca dynamics within the ventricular myocyte. The model includes the following novel features: 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.

6. Smith, G. D., Keizer, J. E., Stern, M. D., Lederer, W. J., & Cheng, H. [13] explored the necessary conditions for the validity of the rapid buffering approximation for an isolated Ca2+ channel. Later, Smith G.D, applied analytical and numerical methods to find solutions to steady state problems of calcium diffusion in single neuronal cell.Punctate releases of Ca2+, called Ca2+ sparks, originate at the regular array of t-tubules in cardiac myocytes and skeletal muscle. During Ca2+ overload sparks serve as sites for the initiation and propagation of Ca2+ waves in myocytes. Computer simulations of spark-mediated waves are performed with model release sites that reproduce the adaptive Ca2+ release observed for the ryanodine receptor. The speed of these waves is proportional to the diffusion constant of Ca2+, D, as is true for reaction-diffusion equations in a continuous excitable medium. A simplified “fire-diffuse-fire” model that mimics the properties of Ca2+-induced Ca2+ release (CICR) from isolated sites is used to explain this saltatory mode of wave propagation. Saltatory and continuous wave propagation can be differentiated by the temperature and Ca2+ buffer dependence of wave speed.

7. Naraghi, M., & Neher, E. and . Neher, E. [9] [10] gave detailed analysis on the linearized buffered Ca2+ diffusion in micro domains and its implication for calculation of [Ca2+] at the mouth of a calcium channel. Immobile and mobile calcium buffers shape the calcium signal close to a channel by reducing and localizing the transient calcium increase to physiological compartments. In this paper, they focussed on the impact of mobile buffers in shaping steady-state calcium gradients in the vicinity of an open channel, i.e. within its “calcium microdomain.” .They presented a linear approximation of the combined reaction–diffusion problem, which can be solved explicitly and accounts for an arbitrary number of calcium buffers, either endogenous or added exogenously. It is valid for small saturation levels of the present buffers and shows that within a few hundred nanometers from the channel, standing calcium gradients develop in hundreds of microseconds after channel opening. It has been shown that every buffer can be assigned a uniquely defined length-constant as a measure of its capability to buffer calcium close to the channel. The length-constant clarifies intuitively the significance of buffer binding and unbinding kinetics for understanding local calcium signals. Hence, they examine the parameters shaping these steady-state gradients. The model can be used to check the expected influence of single channel calcium micro domains on physiological processes such as excitation–secretion coupling or excitation–contraction coupling and to explore the differential effect of kinetic buffer parameters on the shape of these micro domains.

8. Smith, G. D., Keizer, J. E., Stern, M. D., Lederer, W. J., & Cheng, H. [12] 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). Here a simple numerical model is constructed to explore Ca2+ spark formation, detection, and interpretation in cardiac myocytes. This model includes Ca2+ release, cytosolic diffusion, resequestration by SR Ca2+-ATPases, and the association and dissociation of Ca2+ with endogenous Ca2+ binding sites and a diffusible indicator dye (fluo-3). Their proposed equations are-

$$J_{leak} + J_{ryr} = Dc\nabla 2[Ca2+] + J_{dye} + J_{buffers} + J_{pump} +$$
$$= DF\nabla 2[CaF] - J_{dye}$$
$$= -Jn$$

9. Michailova, A., DelPrincipe, F., Egger, M., & Niggli, E..[8] proposed a model to study spatiotemporal features of Ca2+ buffering and diffusion in atrai cardiac myocytes with inhibited Sarcoplasmic Reticulum” to examine Ca(2+) signaling in cardiac atrial myocytes.A mathematical model of Ca(2+) diffusion was developed which represents several subcellular compartments, including a subsarcolemmal space with restricted diffusion, a myofilament space, and the cytosol. The model was used to quantitatively simulate experimental Ca(2+) signals in terms of amplitude, time course, and spatial features.

10. Shannon, T. R., Wang, F., Puglisi, J., Weber, C., & Bers, D. M. [11] proposed a mathematical treatment of integrated Ca dynamics within the ventricular myocytes. The effect of sudden local fluctuations of the free sarcoplasmic [Ca++]i in cardiac cells on calcium release and calcium uptake by the sarcoplasmic reticulum (SR) was calculated with the aid of a simplified model of SR calcium .The model was used to evaluate whether propagation of calcium transients and the range of propagation velocities observed experimentally (0.05-15

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11.Jha, A., & Adlakha, N.[5] gave a model to study the calcium dynamics due to the exogenous buffers, in dendritic spines with the help of a sectional model. Dendritic spine plays an important role in calcium regulation in a neuron cell. It serves as a storage site for synaptic strength and receives input from a single synapse of axon. In order to understand the calcium dynamics in a neuron cell, it is crucial to understand the calcium dynamics in dendritic spines.The compartments of dendritic spines are discretized using triangular elements. Appropriate boundary conditions have been framed. Finite element method has been employed to obtain the solution in the region for a two-dimensional unsteady state case.

III. Concluding Remarks

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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