MODELING CALCIUM WAVE BASED ON ANOMALOUS SUBDIFFUSION OF CALCIUM SPARKS IN CARDIAC MYOCYTES

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Summary A mathematic model of calcium wave has been developed base on anomalous subdiffusion of calcium sparks in cardiac myocytes. The model successfully reproduces calcium waves using physiological parameters. We presented how Ca^{2+} concentration waves propagated from an initial firing of one CRU in a corner or in the middle.

INTRODUCTION

In the endoplasmic or sarcoplasmic reticulum(SR) of cardiac cells, there stores plenty of Ca^{2+} which is 2-3 orders of magnitude greater than its concentration in the cytosol. During the excitation-contraction(EC) coupling process, triggered by L-type Ca^{2+} channels, Ca^{2+} is released from SR through ryanodine receptors(RyRs) on the z-lines. The event is called "Ca^{2+} spark", where RyR is one kind of Ca^{2+} release units(CRUs) . The process of Ca^{2+}-induced Ca^{2+} release(CICR) makes RyRs fire simultaneously or by turns while Ca^{2+} concentration rises. Then propagating waves of Ca^{2+} concentration occurs, which is called "calcium waves". In physiology, calcium homeostasis is important for the contraction and relaxation of the heart muscle. In pathology, such as heart failure, calcium waves is observed.

The model of Ca^{2+} spark which followed Fick's Law failed to reproduce half maximum(FWHM) of experimentally results for Ca^{2+} sparks. However, the anomalous subdiffusion model of Ca^{2+} spark was certified to fit very well with experimental results. Then, Ca^{2+} wave which is the propagation of Ca^{2+} sparks should obey the anomalous subdiffusion, but currently all the simulation of Ca^{2+} waves is based on Fick's Law[1]. In this work, we presented an anomalous subdiffusion model to show Ca^{2+} waves' formation and development in cardiac myocytes. We reproduced wave velocities of experimental results using a smaller current than ref.[1].

MODELS AND METHODS

Geometry of our model is the 2-dimensional model(establishing line resources along z[1]) which contains plenty of CRUs. The regular intervals of CRUs is $\mathrm{l_x} = 2.0\mu\mathrm{m}$ along x and $\mathrm{l_y} = 0.8\mu\mathrm{m}$ along y. The equations of our model is based on Izu et al.[1,3] and Luyao et al.[4], the difference is that we use the fractional Fick's Law. The anomalous diffusion for Ca^{2+} waves can be expressed as

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_x\frac{\partial^\beta[Ca^{2+}]}{\partial x^\beta} + D_y\frac{\partial^\beta[Ca^{2+}]}{\partial y^\beta} + J_{dye} + J_{buffer} + J_{pump} + J_{leak} + \sigma\sum_{i,j}\delta(x-x_i)\delta(y-y_j)S(x_i,y_j,t;T_{open}) \tag{1}$$

where $[\mathrm{Ca}^{2+}]$ is the free Ca^{2+} concentration; diffusion coefficients for anisotropic diffusion are $D_x = 0.30\mu m^2ms^{-1}$ and $D_y = 0.15\mu m^2ms^{-1}$; $\mathrm{J_{dye}}$ and $\mathrm{J_{buffer}}$ are fluxes due to Ca^{2+} fluorescent indicator dye and endogenous stationary buffers, respectively; $\mathrm{J_{pump}}$ is pumping rate of SR Ca^{2+}-ATPase, $\mathrm{J_{leak}}$ is a SR leak that is to balance $\mathrm{J_{pump}}$;(The expression of $\mathrm{J_{dye}}$, $\mathrm{J_{buffer}}$, $\mathrm{J_{pump}}$, $\mathrm{J_{leak}}$ is the same as ref.[2]). $\sigma = 0.64\mathrm{I_{CRU}}/2\mathrm{F}$ is a molar flux of a clustered RyR channel($\mathrm{I_{CRU}}$ is current through the CRU and F is Faraday's constant); δ is Dirac function. S is a stochastic function which controls the firing of the CRU, and the firing time is $\mathrm{T_{open}}$. In time Δt, the probability that the CRU fires is $P(C(x,y,t),K,n)\cdot\Delta t$, where $P(C(x,y,t),K,n) = P_{max}[Ca^{2+}]^n/(K^n + [Ca^{2+}]^n)$, $P_{max} = 0.3/\mathrm{CRU/ms}$ is maximum probability of $[\mathrm{Ca}^{2+}]$ spark occurrence, $K = 15\mu\mathrm{M}$ is $[\mathrm{Ca}^{2+}]$ sensitivity parameter, $n = 1.6$ is Hill coefficient. $\frac{\partial^\beta}{\partial x^\beta}$ is Riemann-Liouville operators, the definition is as follow

$$\frac{\partial^\beta[Ca^{2+}]}{\partial x^\beta} = \frac{1}{\Gamma(k-\beta)}\frac{\partial^k}{\partial x^k}\int_0^x \frac{[Ca^{2+}]}{(x-\tau)^{1+\beta-k}}d\tau \tag{2}$$

where k is an integer with $\beta < k < \beta + 1$ ($1 < \beta < 3$). When $1 < \beta < 2$, anomalous space superdiffusion occurs; anomalous space subdiffusion occurs when $2 < \beta < 3$. $\beta = 2$ gives the Fick's Law. According to ref.[2], here we only consider the subdiffusion. Our simulation region was a rectangle with the size of $20\mu\mathrm{m} \times 20\mu\mathrm{m}$, mesh size is $0.1\mu\mathrm{m}$ along x and y. Absorbing boundary conditions were used on all edges[4].

RESULTS AND DISCUSSION

Figure 1 shows propagating Ca^{2+} waves on a discrete rectangle lattice for different initial conditions. (a) is initiating from a 10ms opening of the CRU on the point (20,8).(The subdiffusion order $\beta = 2.25$ here). The images are the Ca^{2+}

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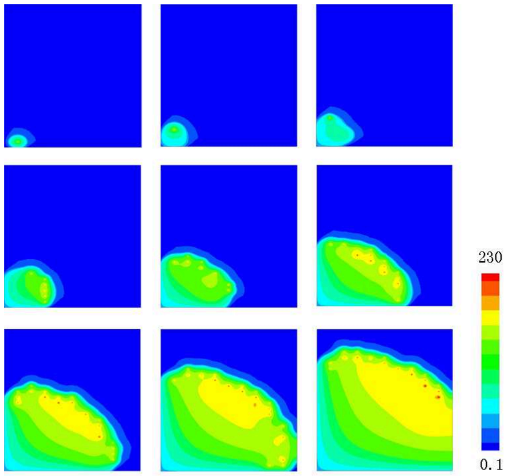

Figure 1. *
(a)

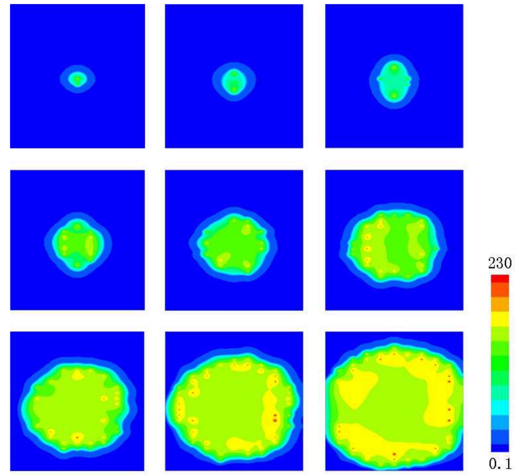

Figure 2. *
(b)

Figure 3. Snapshots of $\mathrm{Ca^{2+}}$ waves for different initial conditions. (a) In a corner of the geometry, 10ms opening of the CRU on (20,8), snapshots was taken at 10, 30, 50, 70, 90, 110, 130, 150 and 170 ms (left to right, top to bottom). (b) In the middle of the geometry, 10ms opening of the CRU on (100,96), snapshots was taken at 10, 20, 30, 40, 50, 60, 70, 80 and 90 ms (left to right, top to bottom).

concentration distribution at 10, 30, 50, 70, 90, 110, 130, 150 and 170 ms (left to right, top to bottom). From image to image, we can see CRUs fire stochastically by turns while $\mathrm{Ca^{2+}}$ concentration wave propagates to the points. At the beginning, CRUs fire one by one, the amplitude(maximum of $\mathrm{Ca^{2+}}$ concentration in a region) is not very high; but when time passes, some of CRUs fire simultaneously in a short time, $\mathrm{Ca^{2+}}$ sparks influence each other, and the amplitudes of $\mathrm{Ca^{2+}}$ sparks become bigger and bigger. (b) is initiating from a 10ms opening of the CRU on the point (100,96). The images are the $\mathrm{Ca^{2+}}$ concentration distribution at 10, 20, 30, 40, 50, 60, 70, 80 and 90 ms. We can see, when 90ms passes, the wave from the middle has propagated to the boundary.

The parameters except for current through the CRU($\mathrm{I_{CRU}}$) are the same with ref.[1,4]. In their model, they must take $\mathrm{I_{CRU}} = 20\mathrm{pA}$, then $\mathrm{Ca^{2+}}$ waves can propagate from a initial concentration of $\mathrm{Ca^{2+}}$ in a $4\mu\mathrm{m} \times 4\mu\mathrm{m}$ square. However, in our model, our initial source is a 10ms opening of one CRU, and when we take $\mathrm{I_{CRU}} = 12\mathrm{pA}$, wave velocity($\mathrm{v_x} = 105\mu\mathrm{m/s}$ initialing from the corner) can be compared with the experimental result($\approx 100\mu\mathrm{m/s}$). The physical reason is, diffusion is slower for subdiffusion than that for Fick's diffusion, then a high value of $\mathrm{Ca^{2+}}$ concentration may stay in a larger region (in $\mathrm{Ca^{2+}}$ spark, half maximum is $2.0\mu\mathrm{m}$ for subdiffusion and $1.0\mu\mathrm{m}$ for Fick's diffusion), the firing of CRUs becomes easier, then $\mathrm{Ca^{2+}}$ waves can propagate more easily for subdiffusion than Fick's diffusion.

CONCLUSIONS

An anomalous diffusion model was presented to study calcium waves from stochastic calcium sparks in cardiac cells. Based on anomalous diffusion of $\mathrm{Ca^{2+}}$ sparks, we expanded the anomalous diffusion model to $\mathrm{Ca^{2+}}$ waves, studied the situation that several $\mathrm{Ca^{2+}}$ sparks fire by turns or simultaneously. We presented how the $\mathrm{Ca^{2+}}$ concentration wave propagated from an initial fire of one CRU in a corner and in the middle. We used a smaller $\mathrm{I_{CRU}}$ to reproduce $\mathrm{Ca^{2+}}$ waves of experimentally results in subdiffusion than in Fick's diffusion. $\mathrm{Ca^{2+}}$ waves can propagate more easily in the subdiffusion model.

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