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Research Paper

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One Dimensional Numerical Study of Advection Diffusion of Calcium in a Hepatocyte Cell

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***Abstract*—** In a human body, in almost all types of cells, the calcium plays a vital role in chemical signalling required for communication and maintenance of structure and functions of a cell. Almost all chemicals and proteins are produced in liver therefore, it is also known as body's chemical factory. The calcium regulates all vital functions of a hepatocyte cell. The calcium concentration is tightly regulated by various processes like diffusion and advection in cytosol, binding with buffers etc. In this paper an unsteady state numerical approach is prefer to investigate the effect of advection and diffusion of calcium in a hepatocyte cell. The initial and boundary conditions are formulated according to physiology of a hepatocyte cell. The finite volume approach is used for simulation on MATLAB to obtain numerical results. The results are used to analyze the effect of advection, diffusion and buffer concentration on calcium profiles in a hepatocyte cell.

Keywords—*Calcium, Advection, Diffusion, Hepatocyte cell, Finite Volume Method*

I. INTRODUCTION

Liver is a chief functional unit of human digestive system. The liver plays vital role in synthesis and secretion of proteins and bile, in the process of glycogenolysis, contraction of bile canaliculi, regulation of cell cycle and apoptosis etc. [1, 2]. The liver comprises of building blocks of hepatocyte cell. Almost all the functions of liver are controlled by free calcium ions in hepatocyte cell [1]. Therefore, metabolism of calcium is an important factor in calcium regulation in the liver. The endoplasmic reticulum (ER) is main storage compartment for intracellular calcium. The huge difference in calcium concentration between ER and cytosol causes calcium release either from $InSP_3$ channel located on the membrane of ER or leakage through the membrane of ER [2]. The released calcium undergoes various transportation phenomenons like, diffusion, advection and buffering. The transport of calcium due to concentration gradient causes diffusion of calcium from the calcium store to remainder of cell, while the various forces like, pressure, gravity, viscosity acting upon and within it causes the advection of calcium. The various buffers present in cytosol of cell bind with free calcium to reduce concentration of free calcium [3].

In the past, research workers performed the numerical study of the calcium dynamics in different cells like neuron cell [4, 5], astrocyte [6,7], myocyte [8,9], fibroblast [10,11], hepatocyte [12], acinar cell [13,14,15], oocyte [16,17,18,19] etc. But very few researchers studied the effect of advection diffusion on calcium dynamics in various cells. In this paper an attempt has been made to study advection diffusion of calcium in presence of EGTA buffer in a hepatocyte cell. The problem of one dimensional reaction diffusion equation describing calcium dynamics is solved by implementing finite volume method in a hepatocyte cell.

The paper is organized in the following manner. Section I contains the introduction of calcium release and transportation of calcium in cytosol of hepatocyte cell. Section II contains the related work of calcium dynamics in hepatocyte cell. Section III contains the mathematical model describing advection diffusion of calcium in presence of EGTA buffer. Section IV describes results obtained by simulations and discussion. Section V contains conclusion of research paper with future directions.

II. RELATED WORK

A. P Thomas et al. [20] have noticed that, the increase in intracellular calcium concentration arises from a sub cellular region, nearer to plasma membrane. G. Dupont et al. [1] noticed the effect of diffusion coefficient for calcium and buffering capacity on calcium concentration in a hepatocyte cell. L. D. Gasper [21] did experimental work to study

intercellular calcium dynamics in the liver. The numerical study of advection diffusion of calcium in astrocyte [22] and myocyte [23] is reported in the literature. G. D. Smith [24] studied the effect of buffer on calcium concentration in the cell. But, very few attempts are found in literature to study advection diffusion of calcium in a hepatocyte cell.

III. MATHEMATICAL FORMULATION

According to the principal of superposition total calcium flux in a hepatocyte cell is addition of fluxes due to diffusion and advection. Thus,

Total calcium flux= Fluxes due to diffusion
+ Fluxes due to advection.

By Fick's law calcium ions move at a rate proportional to the concentration gradient from calcium channel to remaining part of cell. With this assumption the diffusive flux (F_D) is given by [25],

$$F_D = -D_C \frac{\partial C}{\partial x} \quad (1)$$

Here, D_C represents diffusion coefficient of calcium. C is calcium concentration in cytosol. The negative sign attached in (1) represents the direction of calcium diffusion, from area of high concentration to area of low concentration.

The flux due to advection is directly proportional to concentration itself, therefore advective flux (F_A) is given by,

$$F_A = vC \quad (2)$$

Thus by adding diffusive and advective fluxes, total calcium flux (F_C) is given by,

$$F_C = vC - D_C \frac{\partial C}{\partial x} \quad (3)$$

By conservation law, reaction diffusion equation is given as,

$$\frac{\partial C}{\partial t} = D_C \frac{\partial^2 C}{\partial x^2} - v \frac{\partial C}{\partial x} \quad (4)$$

For one dimensional unsteady state case, the buffered advection diffusion equation is given by [4],

$$\frac{\partial C}{\partial t} = D_C \frac{\partial^2 C}{\partial x^2} - v \frac{\partial C}{\partial x} - k^+ [B]_\infty (C - C_\infty) \quad (5)$$

Where, buffer concentration at equilibrium is given as [4],

$$[B]_\infty = \frac{K[B]_T}{K + C}$$

Here, $[B]_T$ is total EGTA buffer concentration and K is its dissociation constant.

The initial and boundary conditions can be set as follows,

Initial Condition: The basal level of calcium concentration is 0.1 μM initially before opening of $InSP_3$ channel [1]. Therefore,

$$(C)_{t=0} = 0.1\mu M \quad (6)$$

Boundary Conditions: The $InSP_3$ channels are densely concentrated in the vicinity of apical surface of hepatocyte cell [20]. Thus, calcium source (σ_C) is considered to be present very close to apical surface kept at the node 1.

$$\lim_{x \to 0} -D_C \frac{dC}{dx} = \sigma_C \quad (7)$$

The calcium concentration away from $InSP_3$ channel close to basal surface of a hepatocyte cell is considered to have equilibrium concentration 0.1 μM. The hepatocyte cell is approximately 15μm in length [1]. Therefore second boundary condition is set as follows,

$$\lim_{x \to 15} C = C_\infty = 0.1\mu M \quad (8)$$

The standard numerical values of parameters are given as the following [26].

- $D_c = 180 - 200\ \mu m^2/s$
- $[B]_T = 50 - 100\,\mu M$
- $K = 0.2\mu M$ for EGTA buffer
- $k^+ = 1.5\ \mu M^{-1} s^{-1}$

Solution by finite volume method:

To employ finite volume method [27], in the first step the hepatocyte cell in one dimension is discretized into sub intervals (control volumes) as shown in figure (1). The midpoints of subintervals are considered as nodes. The equidistant 30 nodal points are considered to discretize space between A and B, which are separated by equal distance δ_x.

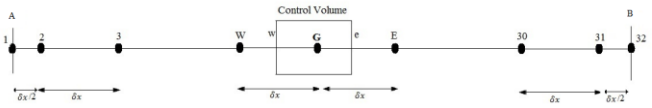

Figure 1. Discretization of hepatocyte in one dimension.

In the second step of finite volume method equation (5) is integrated over control volume w. r. t time and space as follows,

$$\frac{1}{D_C} \int_t^{t+\Delta t} \int_{x_w}^{x_e} \frac{\partial C}{\partial t} dx dt = \int_t^{t+\Delta t} \int_{x_w}^{x_e} \left(\frac{\partial^2 C}{\partial x^2} - b \frac{\partial C}{\partial x} - aC + aC_\infty \right) dx dt \quad (9)$$

Where,

$$a = \frac{k^+ [B]_\infty}{D_C} \text{ and } b = \frac{v}{D_C}$$

Simplifying time and space integration gives,

$$\frac{1}{D_C \Delta t\, \delta x}[C_G - C_G^0] = \alpha \left[\frac{C_E - C_G}{\delta x} - \frac{C_G - C_W}{\delta x} \right] + (1-\alpha) \left[\frac{C_E^0 - C_G^0}{\delta x} - \frac{C_G^0 - C_W^0}{\delta x} \right]$$

$$-b \left(\alpha \left[\frac{C_E + C_G}{2} - \frac{C_G + C_W}{2} \right] + (1-\alpha) \left[\frac{C_E^0 + C_G^0}{2} - \frac{C_G^0 + C_W^0}{2} \right] \right)$$

$$-a\, \delta x [\alpha C_G + (1-\alpha) C_G^0] + a C_\infty \delta x$$

(10)

Rearranging (10) we get,

$$a_G C_G = a_E[\alpha C_E + (1-\alpha)C_E^0] + a_W[\alpha C_W + (1-\alpha)C_W^0] - \frac{b}{2}a_E[\alpha C_E + (1-\alpha)C_E^0] + \frac{b}{2}[\alpha C_W + (1-\alpha)C_W^0] + a_G^0 C_G^0 + S_u \quad (11)$$

Where,

$$a_G = \left[\frac{1}{D_C\,\Delta t\,\delta x} + \frac{\alpha}{\delta x} + \frac{\alpha}{\delta x} + \alpha a \delta x\right]$$

$$a_G^0 = \left[\frac{1}{D_C\,\Delta t\,\delta x} - \frac{(1-\alpha)}{\delta x} - \frac{(1-\alpha)}{\delta x} - (1-\alpha)a\delta x\right]$$

$$a_E = \left(\frac{1}{\delta x} - \frac{b}{2}\right), \quad a_W = \left(\frac{1}{\delta x} + \frac{b}{2}\right), \quad S_u = aC_\infty \delta x$$

We put, $\alpha = \frac{1}{2}$ in (11) in order to employ Crank Nicolson method. For all internal nodes it gives,

$$a_G C_G = \frac{a_E}{2}[C_E + C_E^0] + \frac{a_W}{2}[C_W + C_W^0] - \frac{b}{4}[C_E + C_E^0] + \frac{b}{4}[C_W + C_W^0] + a_G^0 C_G^0 + S_u \quad (12)$$

Where,

$$a_G = \left[\frac{1}{D_C\,\Delta t\,\delta x} + \frac{1}{2\delta x} + \frac{1}{2\delta x} + \frac{1}{2}a\delta x\right]$$

$$a_G^0 = \left[\frac{1}{D_C\,\Delta t\,\delta x} - \frac{1}{2\delta x} - \frac{1}{2\delta x} - \frac{1}{2}a\delta x\right]$$

$$a_E = \left(\frac{1}{\delta x} - \frac{b}{2}\right), \quad a_W = \left(\frac{1}{\delta x} + \frac{b}{2}\right), \quad S_u = aC_\infty \delta x$$

To incorporate first boundary condition (7) at node 2, put $C_W = C_W^0 = \sigma_C$ and $a_W = 0$ it gives,

$$a_G C_G = \frac{a_E}{2}[C_E + C_E^0] + a_G^0 C_G^0 + S_u \quad (13)$$

Where,

$$a_G = \left[\frac{1}{D_C\,\Delta t\,\delta x} + \frac{1}{2\delta x} + \left(\frac{1}{\delta x} + \frac{1}{2}a\delta x\right)\right]$$

$$a_G^0 = \left[\frac{1}{D_C\,\Delta t\,\delta x} - \frac{1}{2\delta x} - \left(\frac{1}{\delta x} + \frac{1}{2}a\delta x\right)\right]$$

$$a_E = \left(\frac{1}{\delta x} - \frac{b}{2}\right), \quad S_u = \left(\frac{1}{\delta x} + \frac{b}{2}\right)\sigma_C + aC_\infty \delta x$$

Similarly second boundary condition (8) at node 31 can be incorporated by putting $C_E = C_E^0 = C_\infty$, and $a_E = 0$, it gives equation in the following form,

$$a_G C_G = \frac{a_W}{2}[C_W + C_W^0] + a_G^0 C_G^0 + S_u \quad (14)$$

Where,

$$a_G = \left[\frac{1}{D_C\,\Delta t\,\delta x} + \frac{1}{2\delta x} + \left(\frac{1}{\delta x} + \frac{1}{2}a\delta x\right)\right]$$

$$a_G^0 = \left[\frac{1}{D_C\,\Delta t\,\delta x} - \frac{1}{2\delta x} - \left(\frac{1}{\delta x} + \frac{1}{2}a\delta x\right)\right]$$

$$a_W = \left(\frac{1}{\delta x} + \frac{b}{2}\right), \quad S_u = \left(\frac{1}{\delta x} + \frac{b}{2}\right)C_\infty + aC_\infty \delta x$$

The equations (12) to (14) can be put in matrix as follows;

$$[A]_{32\times 32}[C]_{32\times 1} = [B]_{32\times 1} \quad (15)$$

By Gauss elimination method (15) can be solve to obtain required solution vector $[C]_{32\times 1}$. The obtained results are discussed in the following section.

IV. RESULTS AND DISCUSSION

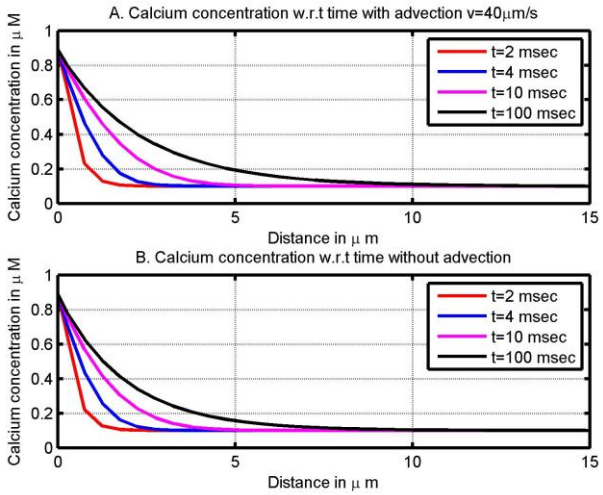

Figure 2. The spatial concentration profile of calcium with different advection velocities, A. v = 40 $\mu m/s$ and B. v = 0 $\mu m/s$ in a hepatocyte cell

In Figure 2A, the spatial variation of calcium concentration at time t=2, 4, 10, 100 msec is plotted at advection velocity 40 $\mu m/s$ and 50 μM EGTA buffer concentration. It can be noticed that, the calcium concentration is peaked at x=0, where the source of calcium is situated. The calcium released from calcium channel diffuses in cytosol of a hepatocyte cell. Initially at time t = 2 msec, calcium concentration is noticed to be minimum at each node of cell.

As time increases gradually from t = 2 msec to t = 100 msec, nodal calcium concentration increases gradually. After t = 100 msec the calcium concentration remains almost constant at each nodal point in hepatocyte cell. The calcium concentration profile with diffusion and without advection is plotted in figure 2B. It can be noticed that, calcium concentration decreases slightly without advection mechanism. This is due to the fact that, advection mechanism counters the diffusion of free calcium ions, which results in accumulation of calcium ions at each node in hepatocyte cell. Thus, advection mechanism increases nodal calcium concentration.

In Figure 3A, calcium concentration profile w. r. t. time with advection velocity 40 $\mu m/s$ and 50μM EGTA buffer concentration is plotted at nodes 2, 3, 5, 10, 15. It can be seen that, initially calcium concentration is 0.1 μM at each node in a hepatocyte cell. As time increases, the calcium concentration increases sharply within short period of time. Afterwards it increases gradually and becomes constant forever w. r. t. time. The calcium concentration is noticed to be decreasing from node 2 to node 15 at each time step. The figure 3B, shows the calcium concentration profile without advection mechanism in a hepatocyte cell. The effect of advection is not noticed at node 2. But, when we move away from node 2 towards node 3 and onwards the calcium concentration noticed decreasing. Thus advection mechanism plays a role of increasing nodal calcium concentration in a hepatocyte cell.

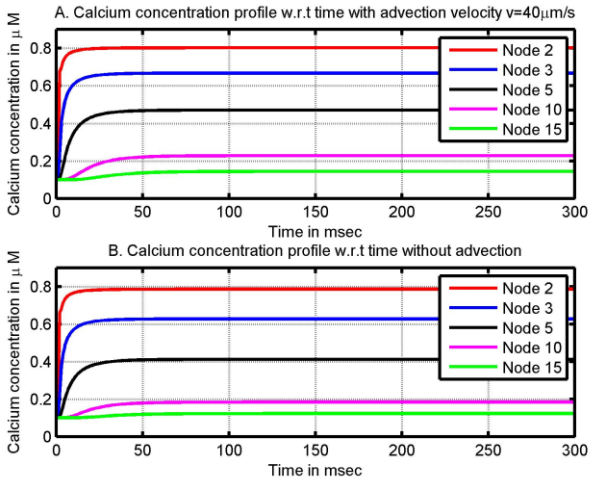

Figure 3. The calcium concentration profile w. r. t. time with different advection velocities A. v = 40 $\mu m/s$ and B. v = 0 $\mu m/s$ in a hepatocyte cell

In Figure 4A, the spatial variation of calcium concentration at time t=2, 4, 10, 100 msec is plotted at advection velocity 10 $\mu m/s$ and 100 μM EGTA buffer concentration. To study effect of buffer concentration on spatial calcium concentration profile, in figure 4B, spatial calcium concentration profile has been plotted in presence of 50 μM EGTA buffer concentration. It can be noticed that, the decrease in calcium concentration results into increase in nodal calcium concentration at each time step. This is due to fact that, buffers bind with free calcium ions and reduce the free calcium concentration in a hepatocyte cell.

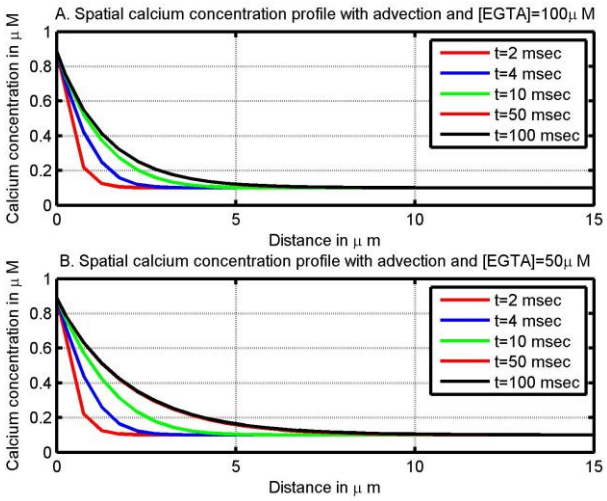

Figure 4. The spatial concentration profile of calcium with different EGTA buffer concentrations, A. [EGTA]=100 μM and B. [EGTA]=50 μM in a hepatocyte cell

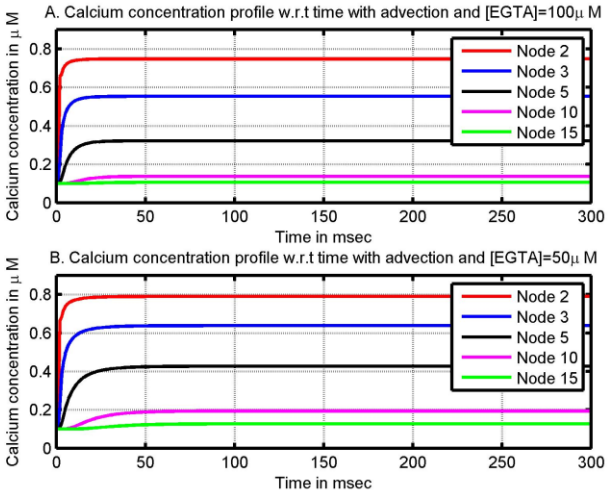

Figure 5. The calcium concentration profile w. r. t. time with different EGTA buffer concentrations, A. [EGTA]=100 μM and B. [EGTA]=50 μM in a hepatocyte cell

In Figure 5A, calcium concentration profile w. r. t. time with advection velocity 10 $\mu m/s$ and 100μM EGTA buffer concentration is plotted at nodes 2, 3, 5, 10, 15. The calcium concentration profile w. r. t. time in presence of 50μM EGTA buffer is plotted in figure 5B. It can be noticed that, the calcium concentration increases at each node and at each time step with decrease in buffer concentration. Thus, calcium concentration varies inversely proportional to buffer concentration in hepatocyte cell.

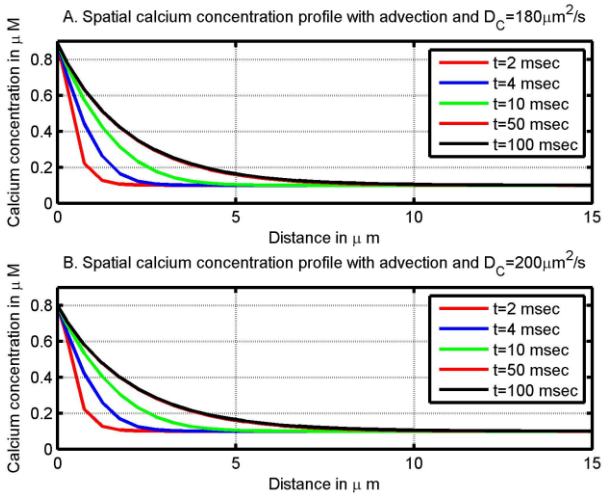

Figure 6. The spatial concentration profile with different diffusion coefficient, A. $D_c = 180\mu m^2/s$ and B. $D_c = 200\mu m^2/s$ in a hepatocyte cell

In Figure 6A, the spatial variation of calcium concentration at time t=2, 4, 10, 100 msec is plotted at advection velocity $10^{\mu m/s}$ and diffusion coefficient $180^{\mu m^2/s}$. The diffusion is a phenomenon in which diffusing substance is transported from domain of higher concentration to domain of lower concentration. The effect of increase in diffusion coefficient to 200 $\mu m^2/s$ is noticed in figure 6B. The calcium concentration decreases slightly at each node.

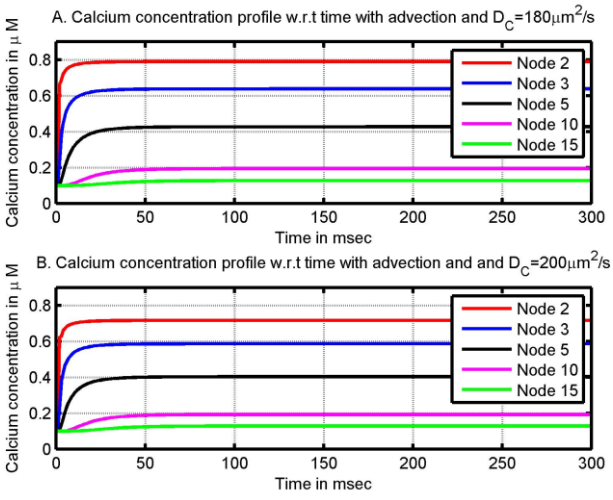

Figure 7. The calcium concentration profile w. r. t. time with different diffusion coefficient, A. $D_c = 180\mu m^2/s$ and B. $D_c = 200\mu m^2/s$ in a hepatocyte cell

In Figure 7A, calcium concentration profile w. r. t. time with advection velocity 10 $\mu m/s$ and diffusion coefficient $180^{\mu m^2/s}$ is plotted at nodes 2, 3, 5, 10, 15. An increase in diffusion coefficient to 200 $\mu m^2/s$, decreases calcium concentration at each node. The maximum effect is noticed at node 2, which is in the vicinity of calcium channel. The diffusion coefficient shows less effect away from calcium channel calcium.

V. CONCLUSION AND FUTURE SCOPE

The finite volume method is employed effectively to study, unsteady state calcium concentration distribution in a hepatocyte cell. The advection velocity, diffusion coefficient of calcium in the cytosol, concentration of buffer in cytosol etc. has different effects on calcium concentration profile in different parts of a hepatocyte cell. It is concluded that, the calcium concentration in a cytosol of a hepatocyte cell directly varies with advection velocity and inversely varies with buffer concentration and diffusion coefficient of calcium in cytosol. Thus, for regulation of calcium concentration level inside the cell to perform specific function the cell exhibits the beautiful coordination among its parameters and processes for the proper functioning of the cell. The development of such models can be useful for generating information about calcium signals in a hepatocyte cell and their implications on function of cell, which should be useful for clinical applications.

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