Modeling the Effect of VGCC on Cytosolic Calcium Distribution in Nerve Cells

Devanshi D. Dave, Brajesh Kumar Jha

Department of Mathematics and Computer Science, School of Technology, Pandit Deendayal Petroleum University Raisan, Gandhinagar-382007, Gujarat, India

***Abstract*— Calcium ion, the second messenger, plays pivotal role in many physiological processes like, contraction, signaling, prolification, etc. [2]. Due to calcium ions, nerve cells are able to move from one cytosole to synapse or other cytosole. A mathematical model is developed in the form of advection-diffusion equation to study the effect of different physiological parameters like diffusion coefficient, potential difference, flux at boundary, etc. Laplace transform is employed to find the solution. Graphical results are obtained with the help of MATLAB. In present study it is observed that the effect of advection on cytosolic calcium distribution is significant at high speed flux. VGCC also make the significant effect on cytosolic calcium concentration to increase the concentration.**

***Keywords*— Advection diffusion, VGCC, Laplace transforms, Nerve cell, Similarity transform**

I. INTRODUCTION

Mathematical model plays an important role in understanding various real world problems in science and engineering. In biology, now a days, investigations are made with the help of mathematical models. Neuroscience, one of them, is an emerging area where calcium dynamics are studied through mathematical models. In our nervous system, many kind of nerve cells are found like neuron, astrocytes (glial cells), myocytes, fibrocytes, etc. Neuron and Glial cells are found in central nervous system (CNS) and rests of the cells are found in peripheral nervous system (PNS) [5]. Nerve impulse moves from one cell to another cell and thus information moves from one part to another part of our body. Movement of the neurotransmitter is due to the free calcium ions $[Ca^{2+}]$. As calcium ions enter into the nerve cells, due to the high calcium concentration, the nerve impulse (neurotransmitter) moves towards the synapse with the help of protein. The way how the calcium ions enter into cell is different. Calcium ions are diffused into the cell due to concentration difference. It also moves into the cytosole due to potential difference via various ion channels. Four types of Ca^{2+}-permeable voltage channels are found. They are P, N, L, and Q-type channels [1]. In present study L-type voltage gated calcium channel is considered.

Free calcium ions enter into cytosole through voltage gated cacium channel and work as a second messenger in electrical signaling, which starts various different inter and intracellular events. In neuron, synaptic transmission is started as Ca^{2+} ion enters into the cytosole via voltage gated channels [3,4,6]. In many other cells it regulates enzyme activity, gene expression and other bio-chemical processes [7]. Thus voltage gated calcium channel plays an important role in many cellular processes.

Calcium ions also enter via diffusion process into the cytosole. Diffusion is the process in which free calcium ions move from one place (post synapse) to another place (cytosole), in straight direction due to concentration difference. In literature, many authors have studied the calcium distribution in the form of diffusion equation in presence of voltage gated channel [11,13,16,22]. Mathematical models are solved using various analytical and numerical techniques [9-18,21]. Very few efforts have been made to study the calcium distribution in the form of advection diffusion. Jha et.al have studied the effect of buffer, VGCC, and advection on cytosolic calcium distribution in astrocytes [13]. Panday and Pardasani have studied the role of advection diffusion in calcium regulation in oocytes [15]. In this paper we have studied the combined effect of VGCC and advection diffusion on cytosolic calcium distribution in nerve cells like neuron, astrocytes, etc.

Shuai Z et.al investigated the possible role of VGCC in Ca^{2+} oscillations in astrocytes [22].

A. Mathematical Formulation

The concentration profile of Ca^{2+} is taken into account in the form of advection-diffusion. It is supposed that due to aqueous medium, coupling between various ions and chemical activity, advection-diffusion of Ca^{2+} takes place [12].

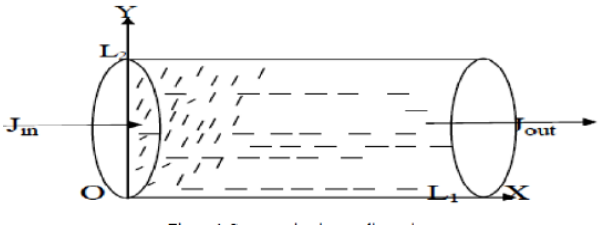

Figure 1: Mass transfers in domain [12]

Advection is the process in which diffusion takes place in the cross flow direction. Smith et.al have shown the nonlinear advection diffusion in presence of rapid buffers in neuron [19]. The theoretical analysis and interpretation of the advection term is based on the conservation law in differential form. [5,22].

$$\frac{\partial u}{\partial t} - \frac{\partial J}{\partial x} = f(x,t,u) \quad \text{--- (1)}$$

Here u is the calcium concentration, $J(x,t)$ is the rate at which u cross the boundary (plasma membrane) at point x from left to right at time t. $f(x,t,u)$ is the net rate of increase of u (through source and sink) per unit volume at location x and time t. Here a uniform macroscopic flow of calcium ion is assumed with speed v along the x-axis, which carries additional u with it. After incorporating diffusive flux and advective flux, the total flux is given as

$$J(x,t) = vu(x,t) - D\frac{\partial u(x,t)}{\partial x} \quad \text{--- (2)}$$

Thus, equation (1) becomes reaction-advection-diffusion equation. i.e.

$$\frac{\partial u}{\partial t} - \frac{\partial (vu(x,t) - D\frac{\partial u(x,t)}{\partial x}}{\partial x} = f(x,t,u) \quad \text{--- (3)}$$

In one dimensional case, the mouth of the channel is assumed at x=0. Calcium ion diffused at x=0 approaches up to x=5 μM.

For the internal behavior of Ca^{2+}, we have taken VGCC as $f(x,t,u)$.

Voltage Gated Calcium Channel (VGCC)

For mathematical formulation of VGCC, the Goldman-Hodgkin-Katz (GHK) current equation is used and given as

$$I_{Ca} = P_{Ca} z_{Ca}^2 \frac{F^2 V_m}{RT} \frac{[Ca^{2+}]_i - [Ca^{2+}]_o \exp(-z_{Ca}\frac{FV_m}{RT})}{1-\exp(-z_{Ca}\frac{FV_m}{RT})} \quad \text{- (4)}$$

where $[Ca^{2+}]_i$ and $[Ca^{2+}]_o$ are the intracellular and extracellular concentrations respectively. P_{Ca} is the permeability of calcium ion. z_{Ca} is the valency of calcium ion, F is Faraday's constant and V_m is membrane potential. R is real gas constant and T is the absolute temperature.

Equation (4) is converted into moles/second by using the following equation.

$$\sigma_{Ca} = \frac{-I_{Ca}}{z_{Ca} F V_{nervecells}} \quad \text{--- (5)}$$

The negative sign in equation (5) is taken by the convention that the inward current is to be negative. Combining equations (3) and (5), we get

$$\frac{\partial u}{\partial t} = D_{Ca}\frac{\partial^2 u}{\partial x^2} + J_{VGCC} - P_{out} u \quad \text{--- (6)}$$

Considering the point source of calcium at x=0, the boundary condition can be given as

$$-D_{Ca}\frac{\partial u}{\partial x} = \sigma_{Ca}, x = 0 \quad \text{--- (7)}$$

Also the background concentration of $[Ca^{2+}]$ is considered 0.1 M. As Ca^{2+} moves away from the mouth of the channel, the another boundary condition is expressed as

$$[Ca^{2+}] = 0.1\mu M \text{ as } x \to 5 \quad \text{--- (8)}$$

In equation (6), we consider

$$u = [Ca^{2+}] - C_o \exp(z_{Ca}\frac{FV_m}{RT}) \quad \text{--- (9)}$$

Therefore, equation (6) is converted as

$$\frac{\partial u}{\partial t} = D_{Ca}\frac{\partial^2 u}{\partial x^2} - v\frac{\partial u}{\partial x} - au \quad \text{--- (10)}$$

where

$$a = P_{out} + \frac{P_{Ca} z_{Ca} F V_m}{RTV_{nervecells}} \cdot \frac{\exp(z_{Ca}\frac{FV_m}{RT})}{1-\exp(z_{Ca}\frac{FV_m}{RT})}$$

The initial and boundary conditions are given as

$$\lim_{x\to 0} u = 0.1 - C_0 \exp\left(z_{Ca}\frac{FV_m}{RT}\right) \quad \text{--- (11)}$$

$$\lim_{x\to 0}\left(D_{Ca}\frac{d[C]}{dx}\right) = \sigma_{Ca} \quad \text{--- (12)}$$

$$\lim_{x\to\infty}[C] = 0 \quad \text{--- (13)}$$

We have fixed the calcium concentration of post synaptic cleft around 22-23 μM. Therefore the condition becomes

$$[C]|_{t=0} = 0 \quad \text{--- (14)}$$

Now we employ the similarity transformation in equation (10). By considering the coordinate transforms given by [8]

$$\eta = x - (x_0 + ut), \ \tau = t \quad \text{--- (15)}$$

Where η is moving reference frame spatial coordinate. For the sake of convenience, origin is assumed at the mouth of the channel (x=0) is cytosole i.e. x=0 is the injector point of tracer where the Ca^{2+} flux enter into cytosole. v is the mean velocity of flow of Ca^{2+} and ut is the distance travelled by the Ca^{2+} flux. Using the coordinate transfer equation (14) and (15), equation (10) is converted using chain rule as

$$\frac{\partial u}{\partial \tau}\frac{\partial \tau}{\partial t}+\frac{\partial u}{\partial \eta}\frac{\partial \eta}{\partial t}+v\left(\frac{\partial u}{\partial \tau}\frac{\partial \tau}{\partial x}+\frac{\partial u}{\partial \eta}\frac{\partial \eta}{\partial x}\right)$$
$$=D_{Ca}\left(\frac{\partial}{\partial \tau}\frac{\partial \tau}{\partial x}+\frac{\partial}{\partial \eta}\frac{\partial \eta}{\partial x}\right)\left(\frac{\partial u}{\partial \tau}\frac{\partial \tau}{\partial x}+\frac{\partial u}{\partial \eta}\frac{\partial \eta}{\partial x}\right)-au \quad \text{--- (16)}$$

which is reduced to

$$\frac{\partial u}{\partial \tau}=D_{Ca}\frac{\partial^2 u}{\partial \eta^2}-au \quad \text{--- (17)}$$

which is one dimensional partial differential equation with diffusion term. Applying the transformation on initial and boundary conditions on (12), (13) and (14),

$$\lim_{x\to 0}\left(D_{Ca}\frac{du}{d\eta}\right)=\sigma_{Ca} \quad \text{--- (18)}$$

$$\lim_{x\to 0}u=u_{\infty} \quad \text{--- (19)}$$

And

$$u_{\tau=0}=u_{\infty} \quad ,0\le\eta\le\infty \quad \text{--- (20)}$$

The point source solution of equation (17) is obtained using Laplace transform. Applying the Laplace transform on (17) and using the initial condition (20), we obtain

$$\frac{d^2\bar{u}}{d\eta^2}-\frac{s+a}{D_{Ca}}\bar{u} \quad \text{--- (21)}$$

Applying the Laplace transform along boundary conditions, we get

$$\frac{du}{d\eta}(0,s)=\frac{\sigma}{D_{Ca}s} \quad \text{--- (22)}$$

And

$$\lim_{x\to 0}u_{(\eta,s)}=0 \quad \text{--- (23)}$$

The solution of equation (21) is given as,

$$u_{(\eta,s)}=c_1e^{\sqrt{\frac{s+a}{D_{Ca}}}\eta}+c_2e^{-\sqrt{\frac{s+a}{D_{Ca}}}\eta} \quad \text{--- (24)}$$

The c_1 and c_2 is obtained using the boundary conditions (22) and (23) and are given as below

$$c_1=0 \quad \text{and} \quad c_2=\frac{\sigma}{\sqrt{D_{Ca}}\sqrt{s+a}} \quad \text{--- (25)}$$

Now from equation (25), solution of equation (24) is given as

$$\bar{u}_{(\eta,s)}=\frac{\sigma}{\sqrt{D_{Ca}}\sqrt{s+a}}e^{-\sqrt{\frac{s+a}{D_{Ca}}}\eta} \quad \text{--- (26)}$$

Now we apply inverse Laplace transform on (26) [20], we obtain

$$u=\frac{\sigma}{\sqrt{\pi D_{Ca}\tau}}\left[\exp\left(\frac{-\eta^2}{4D_{Ca}\tau}-a\tau\right)\right] \quad \text{--- (27)}$$

Using transform (15) in equation (27), we get

$$u=\frac{\sigma}{\sqrt{\pi D_{Ca}t}}\left[\exp\left(\frac{-(x-vt)^2-4aD_{Ca}t^2}{4D_{Ca}t}\right)\right] \quad \text{--- (28)}$$

B. *Results and Discussion*

The numerical values of parameter to obtain the results for calcium profile are given in Table-1 unless stated along with figures. The source amplitude is converted into µM/s and it is divided by diffusion coefficient for applying boundary condition and computing the results.

Table I.
Values of physiological parameters. [11]

Symbol	Parameter	Values
D_{Ca}	Diffusion Coefficient	200–300 µ m^2 /s
σ	Source Amplitude	1 pA
[Ca2+]∞	Background[Ca2+] Concentration	0.1 µM
$v_{nervecells}$	Volume of Cytosol	5.233×10^{13}l
F	Faraday's Constant	96, 485 C/mol
R	Ideal Gas Constant	8.31 J/(mol.K)
T	Temperature	300 K
Pout	Rate of Calcium Efflux from the Cytosol	0.5 s^{-1}
Z_{Ca}	Valance of [Ca2+] ion	2

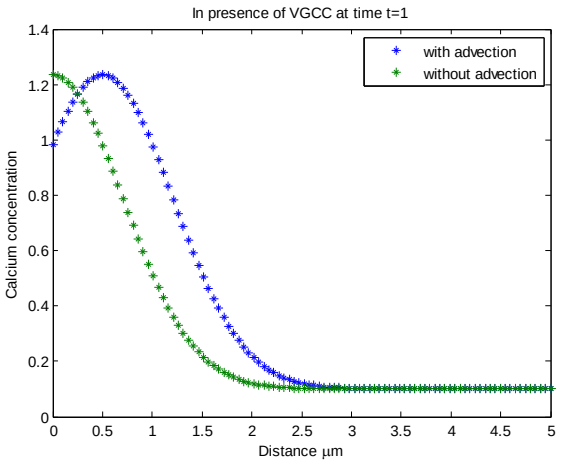

Fig. 2 (a)

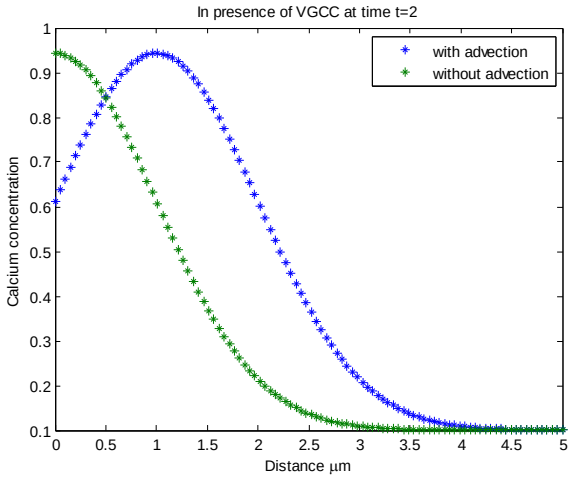

Fig. 2 (b)

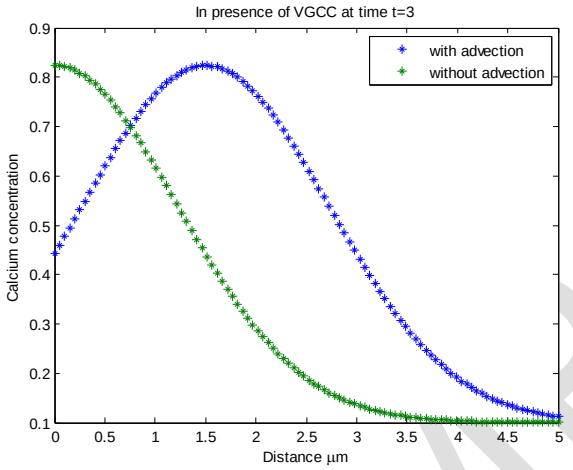

Fig. 2 (c)

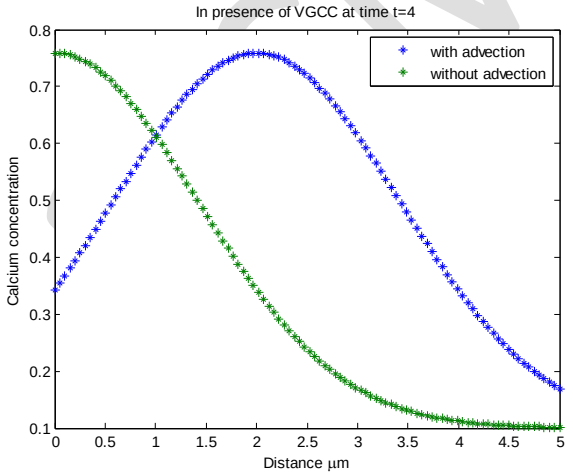

Fig. 2 (d)

Fig. 2: Calcium distribution along x-direction in presence and absence of advection at different time steps in presence of VGCC

In figure 2(a, b, c, d), the variation in calcium profile is shown to see the effect of advection term in presence of VGCC at different time steps. In all the figures, (2a, 2b, 2c, 2d) it is observed that the calcium concentration is lesser in presence of advection than the absence of advection. But it increases along x-axis at x=0.5 µM (fig 2a), x=0.6 µM (fig 2b), x=0.8 µM (fig 2c) and x=1 µM (fig 2d) as it moves far away from the source. It maintains the background concentration level thereafter at x=2.6 µM, 3.7 µM, 4.9 µM in figure 2a, 2b, 2c respectively. As time increases upto t=4 ms, calcium ion moves far away from the calcium profile that are found in absence of advection. Thus it is observed that the calcium concentration maintain the higher level throughout the region. The role of advection is found significant and matched with the results found by Jha et.al. We have found more deviation due to the speed of flux, 100 µM/s,

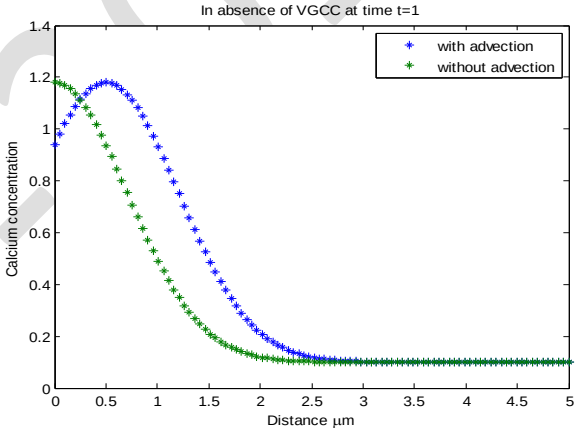

Fig. 3 (a)

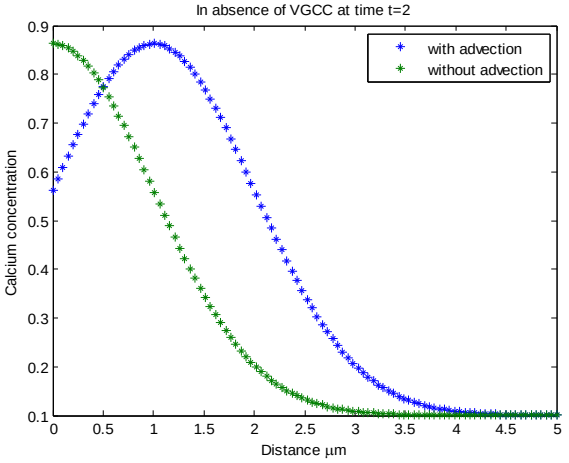

Fig. 3 (b)

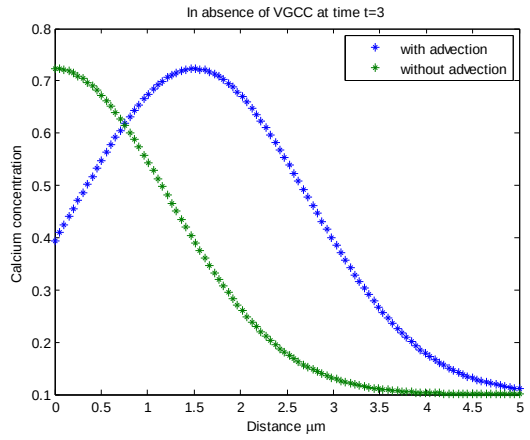

Fig. 3 (c)

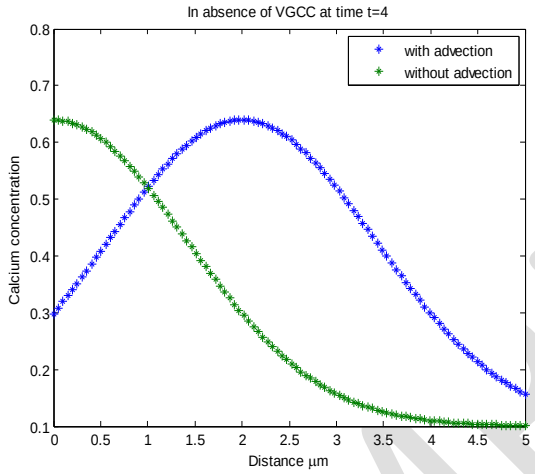

Fig. 3 (d)

Fig. 3: Calcium distribution along x-direction in absence and presence of advection at different time steps in absence of VGCC

In figure 3(a, b, c, d), the variation in calcium profile is shown to see the effect of advection term in absence of VGCC at different time steps. In all the figures (3a, 3b, 3c, 3d) it is observed that the calcium concentration is lesser in presence of advection than the absence of advection. But it increases along x-axis at x=0.5 µM (fig 3a), x=0.6 µM (fig 3b), x=0.8 µM (fig 3c) and x=1 µM (fig 3d) as it moves far away from the source. It maintains the background concentration level thereafter at x=2.6 µM, 3.7 µM, 4.9 µM in figure 3a, 3b, 3c respectively. As time increases upto t=4 ms, calcium ion moves far away from the calcium profile that found in absence of advection. Thus it is observed that the calcium concentration maintain the higher level throughout the region. The role of advection is found significant in presence of VGCC. The speed of Ca^{2+} flux at mouth of channel is taken 100 µM/s. It is observed that the effect of VGCC from Fig. 2 and Fig. 3 is surpassed by advection diffusion. To check the significant effect of VGCC on cytosolic calcium distribution in nerve cell, the speed of Ca^{2+} flux is assumed 10 µM/s.

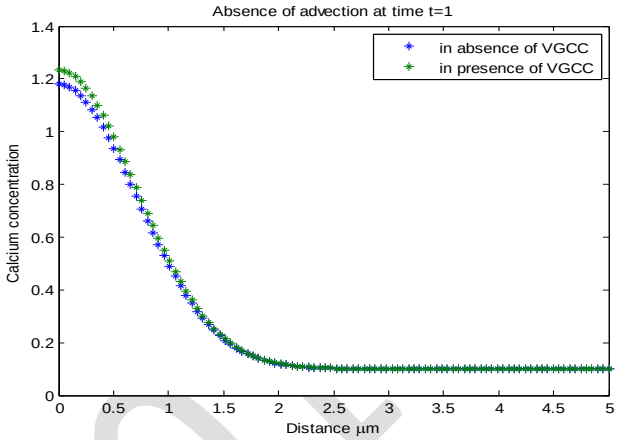

Fig. 4 (a)

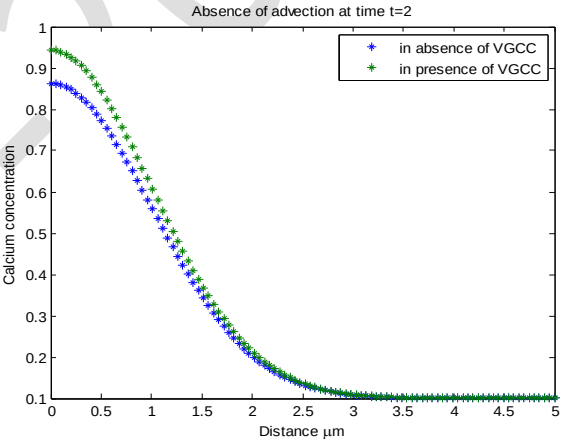

Fig. 4 (b)

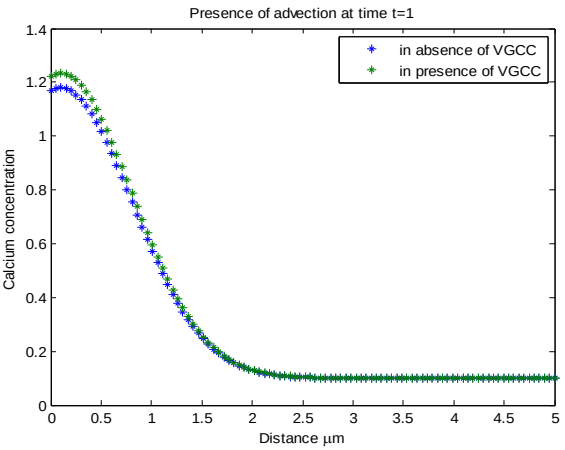

Fig. 4 (c)

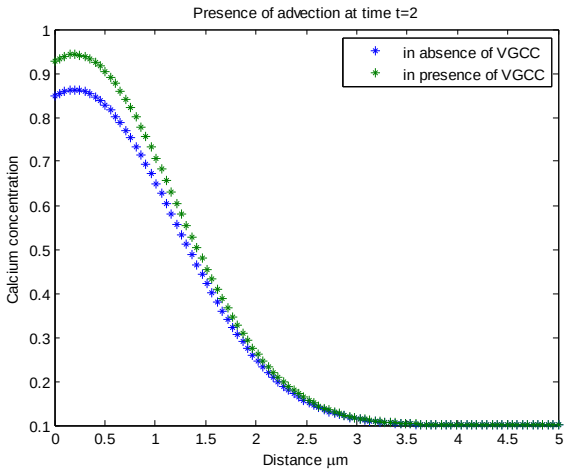

Fig. 4 (d)

Fig. 4: Calcium distribution along x-direction in absence and presence of advection at different time steps

In Fig. 4(a, b, c, d), the effect of VGCC on cytosolic calcium distribution is shown along x-axis. It is observed that the calcium concentration is maximum at the source ,x=0, and it decreases sharply upto x=1.5 μM and after that decreases slowly upto x=2.5 μM. Finally it attends the background concentration (0.1 μM). In presence of VGCC, initially the calcium concentration level is not increasing significantly but as time increases the significant effect of VGCC is visible. In Fig. 4(c and d), behavior of Ca^{2+} profile is same as fig 4 (a and b) and the effect of VGCC on Ca^{2+} profile is significant. It happens due to low speed of Ca^{2+} flux at source. Comparing Fig. 3 and Fig. 4, it is observed that the effect of VGCC is significant at low speed flux only.

II. CONCLUSIONS

A mathematical model is developed in form of advection diffusion equation. To find the analytical solution of equation (10), Laplace transforms and similarity transforms are employed. The behavior of Ca^{2+} profile is matched with the previous results [14] throughout the region. The effect of VGCC and advection on cytosolic Ca^{2+} concentration in nerve cells is shown. It is observed that the effect of VGCC is significant in absence of advection term or at low speed flux at source. The effect of advection on Ca^{2+} profile is significant throughout the region of low and high speed flux as time increases. The Ca^{2+} level in cytosole is higher as time increases, in presence of advection than that of only diffusion. Physiologically more transmitter will be released from the cytosol in presence of advection. On the other side, if Ca^{2+} level remains high for long time, than this will have toxic effect on the nerve cells. The effect of buffers, ER, mitochondria, IP3 receptor, etc needs to be included to observe the effect of advection and to obtain more transformed result.

REFERENCES

[1] Bertram R., Greenstein J.L., Hinch R., Pate E., Reisent J, Sanderson M.J., Shannon T.R., Wilson R.L,, James J, Tutorials in Mathematical Bioscience 2: Mathematical modeling of calcium dynamics and signal transduction; Springer.

[2] Carmignoto G., Pasti L., Pozzan T., (1998), On the role of voltage-dependent calcium channels in calcium signaling of astrocytes in situ, Journal of Neuroscience 18(12) :4637-4645

[3] Catterall W.A., (2011), Voltage gated calcium channels; cold spring Harb Perspect Bio, 1-23

[4] Catterall W.A., Few A.P.,(2008), Calcium channel regulation and presynaptic plasticity. Neuron,59, 882-901.

[5] Christofer P.F., (2002), Computational Cell Biology, Springer-Verlag New York, Vol-20

[6] Dunlap K., Luebke J.I., Turner T.J.,(1995), Exocytotic calcium chanels in mammalian central neurons. Trends Neurosci. 18 : 89-98.

[7] Falvell S.W., Greenberg M.E., (2008), Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system. Annu Rev Neurosci 31:563-590

[8] J. Crank (1975), The mathematics of diffusion, Oxford Univ. Press, London

[9] Jha A. and Adlakha N., (2014), Analytical solution of two dimensional unsteady state problem of calcium diffusion in a neuron; Journal of medical imaging and health informatics, Vol 4(4): 541-553

[10] Jha A. and Adlakha N., (2014), Finite element model to study the effect of exogenous buffer on calcium dynamics in dendrite spines; International Journal of Modeling, Simulation and Scientific Computing, Vol 5(12): 1-12

[11] Jha B.K., Adlakha N. and Mehta M.N., (2011), Finite volume model to study the effect of voltage gated Ca^{2+} channel on cytosolic calcium advection diffusion, International Journal of Mathematical, Computational, Physical, Electrical and Computer Engineering , Vol 5(8): 1379-1383.

[12] Jha B.K., Adlakha N. and Mehta M.N., (2012), Analytical solution of two dimensional advection diffusion equation arising in cytosolic calcium concentration distribution, International Mathematical Forum, Vol 7(3): 135-144

[13] Jha B.K., Adlakha N. and Mehta M.N., (2012), Two dimensional finite element model to study calcium distribution in astrocytes in presence of VGCC and excess buffer, International Journal of Modeling, Simulation and Scientific Computing, Vol 4(2):1-15

[14] Jha B.K., Adlakha N. and Mehta M.N., (2014), Closed form solution to problem of advection diffusion of Ca^{2+} in astrocytes, International Journal of Applied Math and Mech, Vol 10 , 74-81

[15] Kotwani M. and Adlakha N.,(2012), Numerical model to study calcium diffusion in fibroblasts cell for one dimensional unsteady state case , Applied Mathematical Sciences, Vol 6(102), 5063-5072

[16] Naik P. and Pardasani K.R., (2013),Finite element model to study effect of buffers in presence of voltage gated Ca^{2+} channels on calcium distribution in oocytes for one dimensional unsteady state case, International Journal of Modern Biology and Medicine, Vol 4(3): 190-203

[17] Panday S. and Pardasani K.R., (2013), Finite element model to study effect of advection diffusion and Na^{+}/Ca^{2+} exchanger on Ca^{2+} distribution in oocytes; Journal of medical imaging and health informatics, 3(8):374-379

[18] Pathak K, Adlakha N., (2015), Finite element model to study two dimensional unsteady state calcium distribution in cardiac myocytes, Alexandria Journal of Medicine

[19] Smith G.D., Wanger J. and Keizer J., (1996), Validity of the rapid buffering approximation near a point source of Ca^{2+} ions, Biophys-J., 70(6), 2527-2539.

[20] Spiegel M, Laplace Transforms: Schaum's Outlines, 75

[21] Tewari S. and Pardasani K.R., Finite element model to study two dimensional unsteady state cytosolic calcium diffusion in presence of excess buffers, International Journal of Applied Mathematics, Vol 40(3)

[22] Zeng S., Li B., Zeng S., Chen S., (2009), Simulation of spontaneous Ca^{2+} oscillations in astrocytes mediated by voltage-gated calcium channels, Biophys J, 97(9), 2429-37