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FINITE ELEMENT MODEL TO STUDY CALCIUM DIFFUSION IN ASTROCYTES

Brajesh Kumar Jha[1 §], Neeru Adlakha[2], M.N. Mehta[3]
[1,2]Department of Applied Mathematics and Humanities
S.V. National Institute of Technology
Surat Gujarat, 395007, INDIA

Abstract: Astrocytes are also known to express voltage-gated Ca^{2+} channels similar to those found in neurons. Calcium $[Ca^{2+}]$ is a second messenger which plays an important role in signal transduction. The main objective of this paper is to study effect of voltage-gated calcium channel on cytosolic calcium concentration in astrocytes. In view of above a mathematical model is developed to study interdependence of all the important parameters like diffusion coefficient and influx over $[Ca^{2+}]$ profile. Finite element method is employed to solve the problem. A program has been developed using in MATLAB 7.5 for the entire problem and simulated on an AMD-Turion 32-bite machine to compute the numerical results.

AMS Subject Classification: 62P10, 80A50
Key Words: Ca2+ profile, potential activity, astrocytes, ion channel, FEM

1. Introduction

Astrocytes compose at least one half of human brain tissue volume. Twenty years ago, the traditional view of astrocytes was as merely supportive cells. It provides only structural and metabolic support to neurons [14, 24, 26]. Recent

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§Correspondence author

studies of astrocytes have suggested that these cells have a more active and direct role in the dynamic regulation of cerebral microcirculation, synaptic transmission and neuronal activation [3, 11, 18, 19]. The initial electrophysiological surveys of glial cells did not reveal voltage-sensitive channels [9, 21, 23]. Due to improved techniques, e.g., voltage clamping and patch clamping, the surprising results were found. It was discovered that some glial cells including astrocytes show a variety of voltage-gated ion channels that were previously believed to be present only in electrically excitable cells [5, 13, 25]. Astrocytes were shown to express voltage- gated $[Ca^{2+}]$ channels similar to those found in neurons [2, 13]. Later, it was found that Ca^{2+} influx through voltage-gated ion-channels significantly increases cytosolic calcium concentration $[Ca^{2+}]_i$ in astrocytes. Voltage-gated Ca^{2+} channels form an important path way for $[Ca^{2+}]$ entry in excitable cells; the latter have been found to express a variety of $[Ca^{2+}]$ channels, differing in their voltage dependence, kinetics, and pharmacological properties [12, 16]. Calcium channels are integral membrane proteins composed of five subunits, each playing a distinct role in channel function. MacVicar [4] first demonstrated Ca^{2+} action potentials in cAMP-treated cultured cortical astrocytes when the K^+ conductance was blocked and 10 mM Ba^{2+} was added.

Calcium $[Ca^{2+}]$ is an important second messenger, found in almost all cell types. The dynamics of calcium Ca^{2+} is very important in cellular physiology because Ca^{2+} regulates their activity and interactions [17]. Waves of elevated cytosolic calcium that travel both within individual astrocytes as well as between the cells. The precise mechanism governing the initiation and propagation of astrocytic Ca^{2+} waves are not completely understood. Ca^{2+} waves are dependent on the diffusion of Ca^{2+} ions both within and possibly between the cells; modulating Ca^{2+} ion diffusion may predictably alter the spatial and temporal character of the Ca^{2+} wave. S. Zeng et al (2009) developed a mathematical model of Simulation of Spontaneous Ca^{2+} Oscillations in Astrocytes Mediated by Voltage-Gated Calcium Channels(VGCC). From above literature survey good attempt have been made by scientist on calcium diffusion in neuron cells [1, 10, 15, 18, 19, 21], but very few attempt are reported in the literature on modelling of calcium diffusion in astrocytes.Jha Adlakha and Mehta have studied the effect of different physiological parameters like advection diffusion, ER fluxes etc over calcium profile using mathematical models [6-8]. In view of above a mathematical model is developed to study cytosolic calcium profile for In view of above a mathematical model is developed to study the effect of VGCC over cytosolic calcium profile in Astrocytes. . The model has been developed for a one dimension steady state case. The finite element method [20, 21,27] is employed to obtain the solution.

2. Mathematical Formulation

The mathematical model consists of a Ca^{2+} flux. We have assumed a cytosol of radius $5\mu m$. The proposed mathematical model can be framed using fickian law, which leads to the following partial differential equations for one dimensional unsteady state case.

$$\frac{\partial \left[Ca^{2+}\right]}{\partial t} = D_{Ca}\frac{\partial^2 \left[Ca^{2+}\right]}{\partial x^2} + \sigma_{Ca} + \delta\sigma(x) \tag{1}$$

Where D_{Ca} is the diffusion coefficient of free calcium is, σ_{Ca} is flux of calcium through voltage gated channel. $\delta\sigma(x)$ is the source amplitude due to the calcium channel. The has been modelled using the Goldman-Hodgkin-Katz (GHK) current equation [10, 15] as given below:

$$I_{Ca} = P_{Ca}z_{Ca}^2\frac{F^2V_m}{RT}\frac{\left[Ca^{2+}\right]_i - [Ca^{2+}]_0 exp(-z_{Ca}\frac{FV_m}{RT})}{1 - exp(-z_{Ca}\frac{FV_m}{RT})} \tag{2}$$

Where $[Ca]_i$ and $[Ca]_0$, are the intracellular and extracellular Calcium concentration respectively. P_{Ca} is the permeability of calcium ion, z_{Ca} is the valency of calcium ion. F is Faradays constant. V_m is membrane potential. R is Real gas constant and T is Absolute temperature. Equation (2) is converted into molar/second by using the following equation

$$\sigma_{Ca} = \frac{-I_{Ca}}{z_{Ca}FV_{Ast}} \tag{3}$$

The negative sign in equation (3) is taken since by convention the inward current is taken to be negative. GHK current equation gives the current density as a function of voltage. The GHK equation is derived from the constant field which assumes that the electric field in the membrane is constant and thus ions move in the membrane as in free solution. Combining equation (1)-(3) we get the proposed mathematical model as given below,

$$\begin{aligned}\frac{\partial \left[Ca^{2+}\right]}{\partial t} &= D_{Ca}\frac{\partial^2 \left[Ca^{2+}\right]}{\partial x^2} + \frac{P_{Ca}z_{Ca}\theta}{V_{Ast}}\frac{\left[Ca^{2+}\right]_i - [Ca^{2+}]_0 exp(-z_{Ca}\theta)}{1 - exp(-z_{Ca}\theta)} \\ &- P_{out}[Ca^{2+}] + \delta\sigma(x)\end{aligned} \tag{4}$$

For the steady state the equation (4) can be written as

$$D_{Ca}\frac{d^2\left[Ca^{2+}\right]}{dx^2}+\frac{P_{Ca}z_{Ca}\theta}{V_{Ast}}\frac{\left[Ca^{2+}\right]_i-[Ca^{2+}]_0 exp(-z_{Ca}\theta)}{1-exp(-z_{Ca}\theta)}$$
$$-\quad P_{out}[Ca^{2+}]+\delta\sigma(x)=0 \tag{5}$$

We have assumed that there is a point source of calcium situated at x=0. An appropriate flux condition can be framed as

$$\lim_{x\to 0}(-D_{Ca}\frac{d\left[Ca^{2+}\right]}{dx})=\sigma_{Ca} \tag{6}$$

$$\lim_{x\to 0}\left[Ca^{2+}\right]=0.1\mu M \tag{7}$$

Here $[Ca^{2+}]$ is the background calcium concentration, $P_{Ca}[Ca^{2+}]$ represents the rate of calcium efflux from the cytosol into the extracellular space. σ_{Ca} represents the flux due to Ca^{2+} and incorporated on the boundary. tends to the background concentration of $0.1\mu M$ as $r\to 0$ but the domain taken by us is not infinite but a finite one. Here we are taking the distance required for Ca^{2+} to attain background concentration i.e. $5\mu m$ for Astrocytes. Now our problem is to solve equation (5) with (6)-(7). The discretized variational form of equation (5) is given by [16]

$$I=\frac{1}{2}\int_{x_i}^{x_j}\left[\left(\frac{du}{dx}\right)^2+Au^2+2Bu\right]dx-\mu^{(e)}\left(\frac{\sigma}{2D_{Ca}}u^{(e)}|_{x=0}\right) \tag{8}$$

where

$$A=\frac{1}{D_{Ca}}\left[P_{out}-\frac{P_{max}V_m e^{z_{Ca}\theta}}{1-e^{z_{Ca}\theta}}\right]andB=\frac{P_{max}V_m u_\infty e^{z_{Ca}\theta}}{D_{Ca}\left(1-e^{z_{Ca}\theta}\right)} \tag{9}$$

Here we have used is used in lieu off for our convenience and e = 1, 2 ..... 10. The following linear shape function for the calcium concentration within each element has been taken as:

$$u^{(e)}=c_1+c_2x \tag{10}$$

The thickness of each element is very small, therefore $u^{(e)}$ is assigned linear variation with respect to position as given by (10). In matrix form the equation (10) can be written as:

$$u(e)=P^Tc^e \tag{11}$$

where

$P^T = [1\ x]$ and $c^e = [c_1\ c_2]^T$ also

$$u^{(e)}_{(x_i)} = u_i = c_1 + c_2 x_i \tag{12}$$

$$u^{(e)}_{(x_j)} = u_j = c_1 + c_2 x_j \tag{13}$$

Using equation (11) - (13) we get:

$$\overline{u}_{(e)} = P^{(e)} c^{(e)} \tag{14}$$

where

From equation (11) and (14), we have

$$u^{(e)} = P^T R^{(e)} \overline{u}_{(e)} \tag{15}$$

where $R^{(e)} = P^{(e)-1} = \frac{1}{x_j - x_i}$

here x_i and x_j are boundaries of eth element.K^e, M^e, S^e denote the values of these parameters in the e^{th} elements. Now the integral given in equation (8) can also be put in the form as given below.

$$I^{(e)} = I^{(e)}_k + I^{(e)}_m + I^{(e)}_s - I^{(e)}_p \tag{16}$$

where

$$I^{(e)}_k = \frac{1}{2} \int_{x_i}^{x_j} \left(\frac{du^{(e)}}{dx} \right)^2 dx \tag{17}$$

$$I^{(e)}_m = \frac{A}{2} \int_{x_i}^{x_j} u^{(e)2} dx \tag{18}$$

$$I^{(e)}_s = \frac{B}{2} \int_{x_i}^{x_j} 2u^{(e)} dx \tag{19}$$

$$I^{(e)}_p = \mu^{(e)} \left(\frac{\sigma}{2D_{Ca}} u^{(e)}|_{x=0} \right) \tag{20}$$

Now extremizing I w.r.t. each nodal calcium concentration u_i as given below

$$\frac{dI}{d\overline{u}} = \sum_{e=1}^{N} \overline{M}^{(e)} \frac{dI^e}{d\overline{u}^{(e)}} \overline{M}^{(e)T} = 0 \tag{21}$$

where

$$\overline{M}^{(e)} = \begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix} \begin{matrix} \\ i^{th}row \\ j^{th}row \\ \\ \end{matrix} \quad and\ I = \sum_{e=1}^{10} I^{(e)} \quad \overline{u} = \begin{bmatrix} u_1 \\ u_2 \\ . \\ . \\ . \\ . \\ u_{11} \end{bmatrix} \tag{22}$$

$$\frac{dI^{(e)}}{d\overline{u}^{(e)}} = \frac{dI_k^{(e)}}{d\overline{u}^{(e)}} + \frac{dI_m^{(e)}}{d\overline{u}^{(e)}} - \frac{dI_s^{(e)}}{d\overline{u}^{(e)}} - \frac{dI_p^{(e)}}{d\overline{u}^{(e)}} \tag{23}$$

This leads to a following system of linear algebraic equations.

$$[K]_{11\times 11}\,[\overline{u}]_{11\times 1} = [F]_{11\times 1} \tag{24}$$

Here, $\overline{u} = u_1 u_2 .....u_{11}$, K is the system matrices, and F is system vector. The Gaussian elimination method is employed to solve the system (23). A computer program in MATLAB 7.5 is developed to find numerical solution to the entire problem. The program executed on AMD-Turion 32-bit machine with 3 GB memory.

3. Numerical Results and Discussion

The numerical results for calcium profile against different biophysical parameters have been obtained using numerical values of parameter given in table 1 unless stated along with figures. Figure 1 shows the spatial variation of calcium. We observe that calcium concentration falls down quickly up to $x = 0$ to $x = 1\mu m$ and then gradually converges to $0.1\mu M$.

Figure 2 shows the variation of calcium with the space. Graph is plotted for different values of membrane potential $V_m = -65mV$ and $V_m = -65mV$. It is observed that calcium concentration is higher at lower membrane potential throughout from $x = 0$ to $x = 3\mu m$ and there after converges to $0.1\mu M$ at $x = 5\mu m$ i.e. near the source this difference in calcium concentration is quite significant and decreases gradually as we move away from the source.

Figure 3 shows the spatial variation of calcium concentration for four different values of influx. The four different values of influx are $\sigma_{Ca}, 2\sigma_{Ca}, 3\sigma_{Ca}$ and $4\sigma_{Ca}$. Hence as the value of influx increases more numbers of calcium ions get free, hence the calcium concentration increases. Calcium concentration approaches to $0.1\mu M$ as we move away from the source.

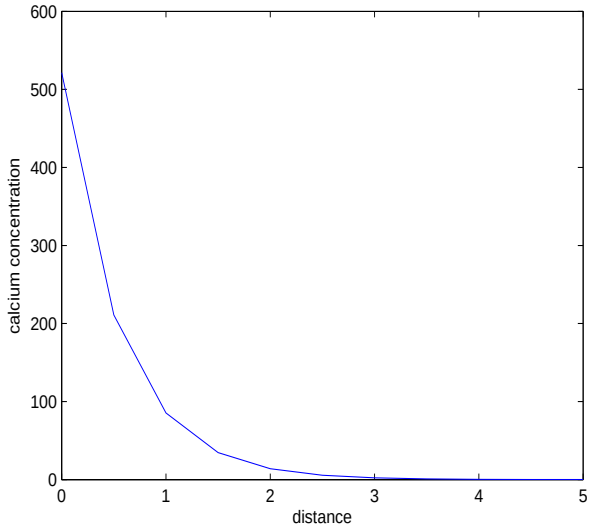

Figure 1: spatial variation of calcium concentration

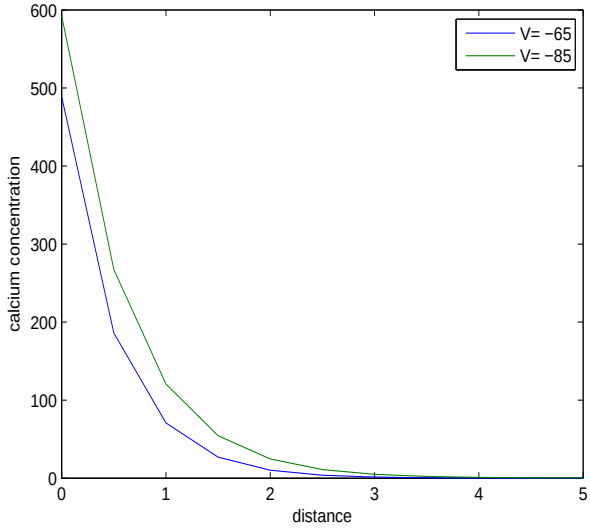

Figure 2: spatial variation of calcium for different values of membrane potential

Symbol	Parameter	Values
D_{Ca}	diffusion coefficient	250-350 $\mu m^2/s$
σ_{Ca}	Source Amplitude	1.5 $\mu M^{-1}s^{-1}$
V_{Ast}	Volume of the Cytosol	5.233×10^{-13}
u	velocity of calcium flux	10-20$\mu m/s$
F	Faraday's Constant	96,485 Coul/mole
R	Ideal Gas Constant	8.31 J/(mole.K)
T	Absolute Temperature	300 K
P_{out}	rate of Ca^{2+} eflux	$0.5s^{-1}$
z_{Ca}	valance of calcium ion	2

m=meter,
s= second,
M= Mole

Table 1: Values of biophysical parameter

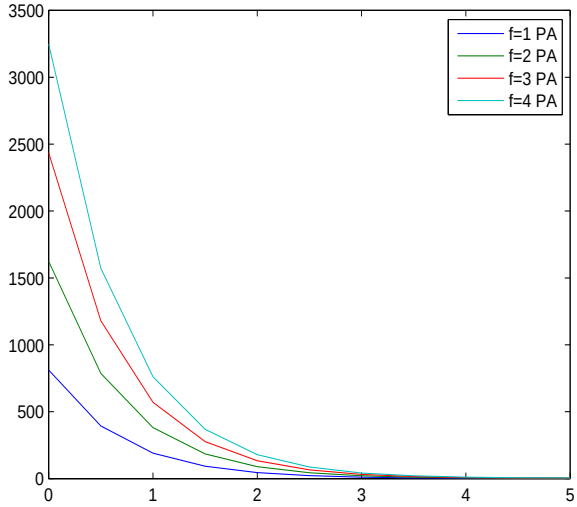

Figure 3: spatial variation of calcium for different values of influx at boundary

4. Conclusion

It is observed that potential activity has significant effect calcium concentration gives better central regions little away from the source. The FEM developed

here gives us quite interesting results as such models can be developed to generate information about relationship among physical and physiological parameter in word in the problem and give us better insights and understanding of the chemical signaling phenomena in Astrocytes.

References

[1] A. Tripathi, N. Adlakha, Finite volume model to study calcium diffusion in neuron cell under excess buffer approximation, *International J. of Math. Sci. and Engg. Appls. (IJMSEA)*, **5** (2011), 437-447.

[2] A. Verkhratsky, R. K. Orkand, H. Kettenmann, *Glial Calcium: Homeostasis and Signaling Function*, Physiological Reviews, **78** (1998).

[3] A.D. Garbo, M. Barbi, S. Chillemi, S. Alloisio, M. Nobile, Calcium signalling in astrocytes and modulation of neural activity, *Bio System*, **89** (2007), 74-83.

[4] B.A. Macvicar, Voltage-dependent calcium channels in glial cells, *Science*, **226** (1984), 13451347.

[5] B.A. Barres, L.L. Chun, D.P. Corey, Ion channel expression by white matter glia, I, Type 2 astrocytes and oligodendrocytes, *Glia*, **1** (1988), 1030.

[6] B.K. Jha, N. Adlakha, M.N. Mehta, Solution of advection diffusion equation arising in cytosolic calcium concentration distribution, *Int. J. of Appl. Math and Mech.*, **7**, No. 6 (2011), 72-79.

[7] B.K. Jha, N. Adlakha, M.N. Mehta, Finite volume model to study the effect of ER flux on cytosolic calcium distribution in Astrocytes, *Journal of Computing*, **3**, No. 11 (2011).

[8] B.K. Jha, N. Adlakha, M.N. Mehta, Analytic solution of two dimensional advection diffusion equation arising in cytosolic calcium concentration distribution, *International Mathematical Forum*, **7**, No. 3 (2012), 135-144.

[9] B.R. Ransom, S. Goldring, Ionic determinants of membrane potential of cells presumed to be glia in cerebral cortex of cat, *J. Neurophysiol.*, **36** (1973), 855868.

[10] E. Neher, Concentration profiles of intracellular Ca2+ in the presence of diffusible chelator, *Exp. Brain Res. Ser.*, **14** (1986), 80-96.

[11] E. Scemes, Components of astrocytic intercellular calcium signaling, *Molecular Neurobiology*, **22** (2000), 167-179.

[12] F. Hofmann, M. Biel, V. Flockerzi, Molecular basis for Ca2/channel diversity, *Annu. Rev. Neurosci.*, **17** (1994), 399418.

[13] H. Sontheimer, J.A. Black, S.G. Waxman. Voltage-gated Na/channels in glia: Properties and possible functions, *Trends Neuroscience*, **19** (1996), 325331.

[14] J.W. Deitmer, A.J. Verkhratsky, C. Lohr, Calcium signalling in glial cells, *Cell Calcium*, **24** (1998), 405-416.

[15] J. Keener, J. Sneyd, *Mathematical Physiology*, Springer, **8** (1998), 53-56.

[16] J.R. Huguenard, Low threshold calcium currents in central nervous system, *Annu. Rev. Physiol.*, **58** (1996), 329348.

[17] M.J. Berridge, Elementary and global aspects of calcium signalling, *J. Physiol.*, **499** (1997), 291-306.

[18] Q.S. Liu, Q. Xu, J. Kang, M. Nedergaard, Astrocyte activation of presynaptic metabotropic glutamate receptors modulates hippocampal inhibitory synaptic transmission, *Neuron Glia Biol.*, **1** (2004)307316.

[19] S. Nadkarni, P. Jung, H. Levine, Astrocytes optimize the synaptic transmission of information, *PLOS Comput. Biol.*, **4** (2008.), e1000088.

[20] S.S. Rao, *Finite Element Method in Engineering*, Elsevier Science and Technology (2004).

[21] S. Tiwari, K.R. Pardasani, Finite difference model to study the effects of Na+ influx on cytosolic Ca2+ diffusion, *International Journal of Biological and Medical Sciences* (2009), 205-209.

[22] S.W. Kuffler, J.G. Nicholls, R.K. Orkand, Physiological properties of glial cells in the central nervous system of amphibia, *J. Neurophysiol*, **29** (1966), 768787.

[23] S.W. Kuffler, D.D. Potter. Glia in the leech central nervous system: physiological properties and neuron-glia relationship, *J. Neurophysiol.*, **27** (1964), 290320.

[24] S. Zeng, B. Li, S. Zeng, S. Chen, Simulation of spontaneous Ca2+ oscillations in astrocytes mediated by voltage-gated calcium channels, *Biophysical Journal*, **97** (2009), 24292437.

[25] S. Bevan, S.Y. Chiu, P.T. Gray, J.M. Ritchie, The presence of voltage-gated sodium, potassium and chloride channels in rat cultured astrocytes, *Proc. R. Soc. Lond. B Biol. Sci.*, **225** (1985), 299-313.

[26] T. Fellin, Communication between neuron and astrocytes: relevance to the modulation of synaptic and network activity, *Journal of Neurochemistry* (2009), 533-544.

[27] V.P. Saxena, K.R. Pardasani, Effect of dermal tumours on temperature distribution in skin with variable blood flow, *Bulletin of Mathematical Biology*, **53** (1991), 525-536.