

Finite Volume Model to Study The Effect of Voltage Gated Ca^{2+} Channel on Cytosolic Calcium Advection Diffusion

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Abstract— Mathematical and computational modeling of calcium signalling in nerve cells has produced considerable insights into how the cells contracts with other cells under the variation of biophysical and physiological parameters. The modeling of calcium signaling in astrocytes has become more sophisticated. The modeling effort has provided insight to understand the cell contraction. Main objective of this work is to study the effect of voltage gated (Operated) calcium channel (VOC) on calcium profile in the form of advection diffusion equation. A mathematical model is developed in the form of advection diffusion equation for the calcium profile. The model incorporates the important physiological parameter like diffusion coefficient etc. Appropriate boundary conditions have been framed. Finite volume 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.

Keywords— Ca^{2+} Profile, Advection Diffusion, VOC, FVM.

I. INTRODUCTION

THE problem of neuroscience pose new challenges for mathematics and models of these problems are more interesting. One of the notable examples is of modeling calcium signaling in glial cell like astrocytes. Astrocytes are found the most diverse population of glial cells in nerves system. Twenty years ago, the traditional view of astrocytes as merely supportive cells providing only structural and metabolic support to neurons [18, 28]. Recent 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 [1, 2, 19, 22, 23]. The initial electrophysiological surveys of glial cells did not reveal voltage-sensitive channels [9, 25, 27]. 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 [7, 15, 24]. Astrocytes were shown to express voltage-gated Ca^{2+} channels similar to those found in neurons [4, 15]. Later, it was found that Ca^{2+} influx through voltage-gated ion-channels significantly

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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 [11, 16]. Calcium channels are integral membrane proteins composed of five subunits, each playing a distinct role in channel function. MacVicar [8] 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 [21]. 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. From above literature survey good attempt have been made by scientist on calcium diffusion in neuron cells [3, 10, 23, 25], but very few attempt are reported in the literature on modelling of calcium diffusion in astrocytes. Jha, Adlakha and Mehta studied the calcium profile in the form of advection diffusion [5, 6].

In view of above a mathematical model is developed to study cytosolic calcium profile for Astrocytes. The model has been developed for a one dimension steady state case. The finite volume method [3, 6, 14] is employed to obtain the solution.

II. MATHEMATICAL FORMULATION

The mathematical model consists of a Ca^{2+} flux. The proposed mathematical model can be framed using fickian law, which leads to the following partial differential equations for one dimensional case.

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_{Ca} \nabla^2 [Ca^{2+}] + \sigma_{Ca} + \delta\sigma_x \quad (1)$$

where D_{Ca} is the diffusion coefficient of free calcium, σ_{Ca} is flux of calcium through voltage gated channel. $\delta\sigma_x$ is the source amplitude due to the calcium channel. Here

main objective is to study the calcium distribution in form of advection diffusion equation. Most of the authors studied the buffered calcium concentration in form of reaction diffusion equation. Few attempts are reported which shows that advection diffusion of calcium occurs in the presence of mobile buffer [12, 13, 17].

The advection and diffusion are independent process. Because diffusion is to be random process due to calcium molecular motion. Due to the diffusion each calcium molecule will move one step to the right in given time and due to advection each calcium molecules also move in the cross flow direction. This process is clearly additive and independent. The presence of cross flow does not bias the probability that the molecule will take a diffusion step to the right. It just adds something to the step. The next movement to calcium molecules will be $u\delta t - \delta x$. Thus total flux in x-direction J_x including the advective transport and a Fickian diffusion term will be

$$(J_x) = (uC_a - q_x) \tag{2}$$

Therefore calcium profile has been taken in the form of incompressible fluid flow with advection diffusion of calcium as given below

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_{Ca} \nabla^2 [Ca^{2+}] - u \frac{\partial [Ca^{2+}]}{\partial x} + \sigma_{Ca} + \delta\sigma_x \tag{3}$$

The Ca^{2+} current has been modelled using the Goldman-Hodgkin-Katz (GHK) current equation [7, 12] as given below:

$$I_{Ca} = P_{Ca} z_{Ca}^2 \frac{F^2 V_m}{RT} \frac{[Ca]_i - [Ca]_0 \exp(-z_{Ca} \frac{FV_m}{RT})}{1 - \exp(-z_{Ca} \frac{FV_m}{RT})} \tag{4}$$

Where $[Ca^{2+}]_i$ and $[Ca^{2+}]_0$ 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 (3) is converted into molar/second by using the following equation

$$\sigma_{Ca} = \frac{(-I_{Ca})}{(z_{Ca} F V_{Ast})} \tag{5}$$

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,

$$\begin{aligned} \frac{\partial [Ca^{2+}]}{\partial t} &= D_{Ca} \nabla^2 [Ca^{2+}] - u \frac{d [Ca^{2+}]}{dx} \\ &- P_{Ca} z_{Ca}^2 \frac{FV_m}{RT} \frac{[Ca]_i - [Ca]_0 \exp(-z_{Ca} \frac{FV_m}{RT})}{1 - \exp(-z_{Ca} \frac{FV_m}{RT})} \\ &- P_{out} [Ca^{2+}] + \delta\sigma_x \end{aligned} \tag{6}$$

For the steady state the equation (6) can be written as

$$\begin{aligned} D_{Ca} \nabla^2 [Ca^{2+}] - u \frac{d [Ca^{2+}]}{dx} \\ - P_{Ca} z_{Ca}^2 \frac{FV_m}{RT} \frac{[Ca]_i - [Ca]_0 \exp(-z_{Ca} \frac{FV_m}{RT})}{1 - \exp(-z_{Ca} \frac{FV_m}{RT})} \\ - P_{out} [Ca^{2+}] + \delta\sigma_x = 0 \end{aligned} \tag{7}$$

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

$$\lim_{x \rightarrow 0} (-D_{Ca} \frac{\partial [Ca^{2+}]}{\partial x}) = \sigma_{Ca} \tag{8}$$

$$\lim_{x \rightarrow 0} [Ca^{2+}] = 0.1 \mu M \tag{9}$$

Here $[Ca^{2+}]$ is the background calcium concentration, $P_{out} [Ca^{2+}]$ 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. $[Ca^{2+}]$ tends to the background concentration of $0.1 \mu M$ as $r \rightarrow 0$ 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 (7) with (8)-(9).

The finite volume scheme is employed to solve equation (7) together with (8) and (9) [2, 6, 14]. In order to apply the finite volume method the domain is divided into discrete control volumes (Figure 1). taking 20 nodal point in the space between A and B. Each node is surrounded by a control volume or cell. A general nodal point is identified by P and

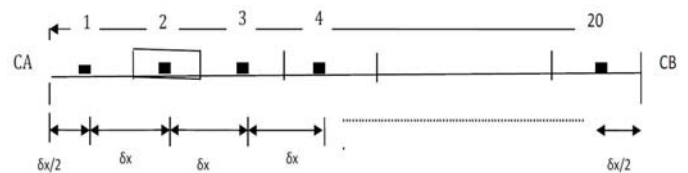


Fig. 1. discretize the domain in 30 nodes

its neighbours in a one-dimensional geometry, the nodes to the west and east, are identified by W and E respectively. The west side face of the control volume is referred to by w and the east side control volume face by e. The distances between the nodes W and P, and between nodes P and E, are identified by δx . Similarly the distance between face w and point P and between P and face e are denoted by $\delta x/2$. Nodal values to the east and west are available at nodal values 2, 3, 4,.....19. Now equation (7) can be written in one dimensional case.

$$\frac{d^2 C}{dx^2} - p \frac{dC}{dx} - qC + r = 0 \tag{10}$$

where

$$\begin{aligned}
 p &= \frac{u}{D_{Ca}} \\
 q &= \frac{P_{Ca} z_{Ca}^2 \frac{FV_m}{RT} e^{(z_{Ca} \frac{FV_m}{RT})}}{D_{Ca} V_{Ast} (1 - e^{(z_{Ca} \frac{FV_m}{RT})})} \\
 r &= \frac{P_{Ca} z_{Ca}^2 \frac{FV_m}{RT} C_0}{D_{Ca} V_{Ast} (1 - e^{(z_{Ca} \frac{FV_m}{RT})})} \quad (11)
 \end{aligned}$$

The calcium concentration is replaced by C for convenience. Integration of equation (10) over control volume gives:

$$\int_{\Delta V} \frac{d^2 C}{dx^2} dV - p \int_{\Delta V} \frac{dC}{dx} dV - q \int_{\Delta V} C dV + \int_{\Delta V} r dV = 0 \quad (12)$$

$$\left[\left(A \frac{dC}{dx} \right)_e - \left(A \frac{dC}{dx} \right)_w \right] - [pAC_e - pAC_w] - qC_p A \delta x + rA \delta x = 0 \quad (13)$$

$$\left[\left(\frac{dC}{dx} \right)_e - \left(\frac{dC}{dx} \right)_w \right] - [pC_e - pC_w] - qC_p \delta x + r \delta x = 0 \quad (14)$$

Where A is a cross section area. Subsequent division by cross sectional area A .Equation (14) becomes

$$\left(\frac{C_E - C_P}{\delta x} \right) - \left(\frac{C_P - C_W}{\delta x} \right) - p \left[\left(\frac{C_E + C_P}{2} \right) - \left(\frac{C_P + C_W}{2} \right) \right] - q(C_p \delta x) + r \delta x = 0 \quad (15)$$

This can be rearranged as

$$\left[\left(\frac{1}{\delta x} + \frac{p}{2} \right) + \left(\frac{1}{\delta x} - \frac{p}{2} \right) + q \delta x \right] C_P = \left(\frac{1}{\delta x} + \frac{p}{2} \right) C_W + \left(\frac{1}{\delta x} - \frac{p}{2} \right) C_E + r \delta x \quad (16)$$

The general form for the interior nodal point 2, 3, 4.....19 is given by:

$$a_P C_P = a_W C_W + a_E C_E + S_u \quad (17)$$

where

$$\begin{aligned}
 a_W &= \left(\frac{1}{\delta x} + \frac{p}{2} \right), \\
 a_E &= \left(\frac{1}{\delta x} - \frac{p}{2} \right) \\
 a_P &= a_W + a_E - S_P, \\
 S_P &= -q \delta x \\
 S_u &= r \delta x \quad (18)
 \end{aligned}$$

We apply the boundary conditions at node points 1 and 20. At node 1 west control volume boundary is kept at specified concentration.

$$\begin{aligned}
 a_W &= 0, a_E = \left(\frac{1}{\delta x} - \frac{p}{2} \right), \\
 a_P &= a_E - S_P, S_P = -\left(\frac{2}{\delta x} + p + q \delta x \right) \text{ and} \\
 S_u &= \left(\frac{2}{\delta x} + p \right) C_A + r \delta x \quad (19)
 \end{aligned}$$

TABLE I
VALUES OF BIOPHYSICAL PARAMETER USED

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+} efflux	$0.5 s^{-1}$
z_{Ca}	valance of calcium ion	2

m=meter, s= second, M= Mole

Similarly at node 20 east control volume boundary is at specified concentration.

$$\begin{aligned}
 a_W &= \left(\frac{1}{\delta x} + \frac{p}{2} \right), a_E = 0, \\
 a_P &= a_W + a_E - S_P, S_P = -\left(\frac{2}{\delta x} - p + q \delta x \right) \text{ and} \\
 S_u &= \left(\frac{2}{\delta x} - p \right) C_B + r \delta x \quad (20)
 \end{aligned}$$

In equation (17), putting all values of equation (18-20) we have a system of algebraic equations as given below. Where C_A and C_B be the specified boundary conditions in terms of calcium concentration.

$$AX = B \quad (21)$$

Here, $X = C_1, C_2, C_3, \dots, C_{20}$ represents the calcium concentration, A is system matrices and B is the system vector.

III. 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 2 shows the spatial variation of calcium. It is

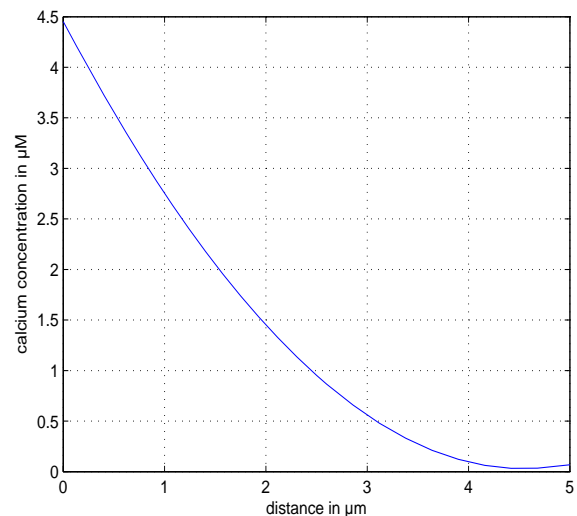


Fig. 2. Spatial variation of calcium concentration

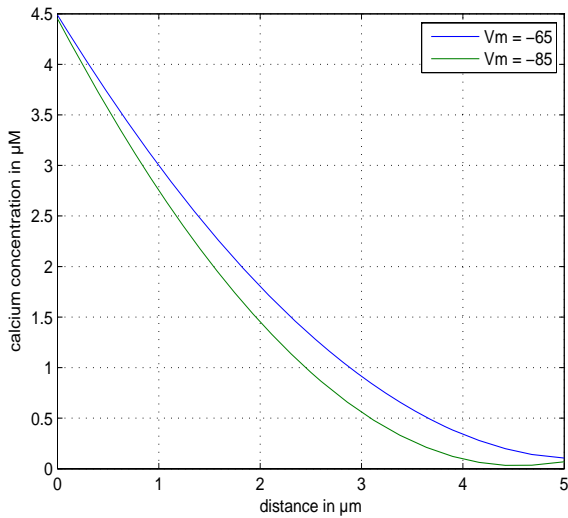


Fig. 3. Spatial variation of calcium for different values of membrane potential

observed that calcium concentration falls down quickly up to $x=0$ to $x=4\mu m$ and then gradually converges to $0.1\mu M$.

Figure 3 shows the variation of calcium with the space. Graph is plotted for different values of membrane potential $V_m = -65mV$ and $V_m = -85mV$. It is observed that calcium concentration is higher at lower membrane potential throughout from $x=0$ to $x=4.5\mu m$ 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.

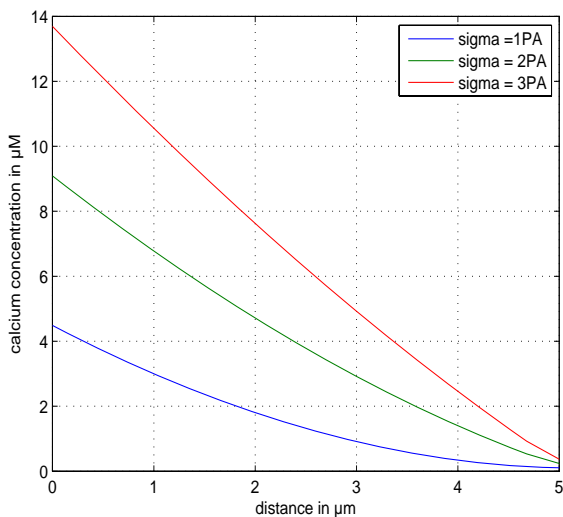


Fig. 4. Spatial variation of calcium for different values of influx at boundary

Figure 4 shows the spatial variation of calcium concentration for four different values of influx. The four different values of influx are 1PA, 2PA and 3PA. 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.

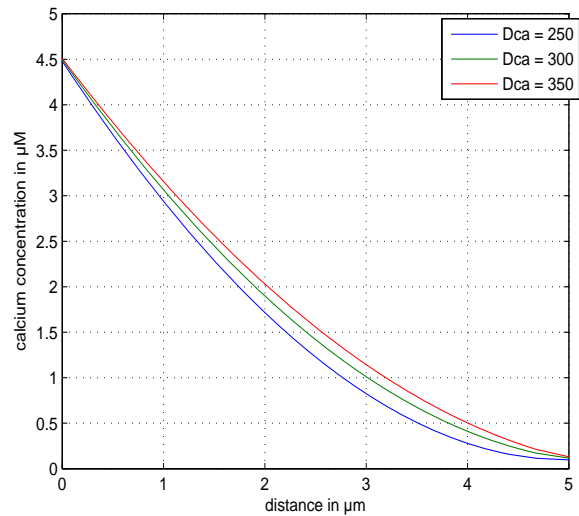


Fig. 5. Spatial variation of calcium for different values of Dca

Figure 5 shows the variation of calcium concentration with different values of diffusion constants. We have considered three different values of $D_{Ca} = 250, D_{Ca} = 300$ and $D_{Ca} = 350$. Hence as the diffusion coefficient increases more numbers of calcium ions get free as lesser number of calcium ions bind, hence the calcium concentration increases. Calcium concentration approaches to $0.1\mu M$. as we move away from the source.

IV. CONCLUSION

It is observed that potential activity has significant effect calcium concentration gives better central regions little away from the source. The FVM 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. C. Charles, J.E. Merrill, E.R. Ditzsen, M.J. Sanderson, 1991. Intercellular signaling in glial cells: calcium waves and oscillations in response to mechanical stimulation and glutamate. *Neuron* 6, 983-992.
- [2] A. Tripathi and 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
- [3] A.H. Cornell-Bell, S.M. Finkbeiner, M.S. Cooper, S.J. Smith, 1990. Glutamate induces calcium waves in cultured astrocytes: long range glial signaling. *Science* 247, 470-473.
- [4] A. Verkhratsky, R. K. Orkand, and H. Kettenmann, Glial Calcium: Homeostasis and Signaling Function, *Physiological Reviews* 78 (1998)
- [5] 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 (6): 72-79, 2011
- [6] B.K. Jha, N. Adlakha, M.N. Mehta, Finite Volume Model to Study the Effect of Buffer on Cytosolic Ca²⁺ Advection Diffusion *International Journal of Engineering and Natural Sciences, WASET*, 4(3):160-163 2010
- [7] B. A. Barres, L. L. Chun, And D. P. Corey. Ion channel expression by white matter glia. I. Type 2 astrocytes and oligodendrocytes. *Glia* 1 (1988) 1030

- [8] B. A. Macvicar, Voltage-dependent calcium channels in glial cells. *Science* 226 (1984) 1345-1347
- [9] B. R. Ransom and S. Goldring. Ionic determinants of membrane potential of cells presumed to be glia in cerebral cortex of cat. *J. Neurophysiol.* 36 (1973) 855-868
- [10] E. Neher, Concentration profiles of intracellular Ca^{2+} in the presence of diffusible chelator. *Exp. Brain Res. Ser.* 14 (1986) 80-96
- [11] F. Hofmann, M. Biel and V. Flockerzi, Molecular basis for Ca^{2+} channel diversity. *Annu. Rev. Neurosci.* 17 (1994) 399-418
- [12] G.D. Smith, L. Dai, R. M. Miura, and A. Sherman, Asymptotic analysis of buffered calcium diffusion near a point source, *SIAM J. Of Applied of Math*, vol.61, pp.1816-1838.2000
- [13] G.D. Smith, Analytical steady-state solution to the rapid buffering approximation near an open Ca^{2+} channel, *Biophysical Journal*, vol.71, pp.3064-3072,1996.
- [14] H. K. Versteeg, W. Malalasekera, An introduction to computational fluid dynamics the finite volume method, Longman Scientific and Technical, 1995
- [15] H. Sontheimer, J. A. Black, and S. G. Waxman. Voltage-gated Na^+ channels in glia: properties and possible functions. *Trends Neuroscience* 19 (1996) 325-331
- [16] J. R. Huguenard, Low threshold calcium currents in central nervous system. *Annu. Rev. Physiol.* 58 (1996) 329-348
- [17] J. Wagner and J Keizer, Effect of rapid buffers on Ca^{2+} diffusion and Ca^{2+} oscillations, *Biophysical Journal*, vol.67, pp. 447-456,1994.
- [18] J.W. Deitmer, A.J. Verkhratsky, C. Lohr, Calcium signalling in glial cells, *Cell Calcium* (1998) 24 (5/6), 405-416
- [19] J.W. Dani, A. Chernavsky, S.J. Smith, 1992. Neuronal activity triggers calcium waves in hippocampal astrocytic networks. *Neuron* 8, 429-440.
- [20] J. Keener and J. Sneyd, *Mathematical Physiology*, Springer 8 (1998) 53-56
- [21] M. J. Berridge Elementary and global aspects of calcium signalling, *J. physiol.* 499 (1997) 291-306
- [22] Q. S., Liu, Q. Xu, J. Kang, and M. Nedergaard, Astrocyte activation of presynaptic metabotropic glutamate receptors modulates hippocampal inhibitory synaptic transmission. *Neuron Glia Biol.* 1 (2004).307-316
- [23] S. Nadkarni, P. Jung, and H. Levine. 2008. Astrocytes optimize the synaptic transmission of information. *PLOS Comput. Biol.* 4:e1000088.]
- [24] S. Bevan, S. Y. Chiu, P. T. Gray, and 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
- [25] S. Tiwari, and K. R. Pardasani, Finite difference model to study the effects of Na^+ influx on cytosolic Ca^{2+} diffusion, *International journal of Biological and Medical Sciences* (2009) 205-209.
- [26] S. Zeng, B. Li, S. Zeng, and S. Chen, Simulation of Spontaneous Ca^{2+} Oscillations in Astrocytes Mediated by Voltage-Gated Calcium Channels, *Biophysical Journal* 97 (2009) 2429-2437
- [27] S. W. Kuffler and D. D. Potter. Glia in the leech central nervous system: physiological properties and neuron-glia relationship *J. Neurophysiol.* 27 (1964) 290-320
- [28] T. Fellin, communication between neuron and astrocytes: relevance to the modulation of synaptic and network activity, *Journal of Neurochemistry*, (2009) 533-544,