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Research Article

Impact of Temperature Variation on Calcium Profiling in a Neuronal Cell Due to Cancer: A Steady-State Case

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Abstract. A crucially vital second messenger for intracellular signaling in the nervous system is Calcium. It regulates the release of synaptic transmitters. The cellular metabolism is monitored by diffusion, the activity of buffering, and influx in the cytoplasm. The temperature of the cellular microenvironment rises as excess energy from cellular metabolism is transformed into heat. The addition of medications or other cancer-curing treatments leads cancer cells to heat up more than normal cells, according to numerous studies. The calcium concentration profile is impacted by the cellular metabolism's elevated temperature. This research aims to examine calcium profiles in neurons brought on by temperature changes brought on by cancer treatment. When there is calcium current input, the Goldman-Hodgkin-Katz (GHK) current equation and mathematical modelling are employed to determine calcium diffusion in neuron cells. Also, the impact of the temperature of the cellular environment on calcium concentration is studied. This model has been proposed for a 1-D steady-state case with the right initial and boundary conditions. To obtain the solution, the finite element method has been used. The simulations have been used to identify the effect of buffers as well as the effect of temperature variation on calcium distribution.

Keywords. Calcium profile, Finite element method, Excess buffering approximation, Variable diffusion coefficient

Mathematics Subject Classification (2020). 65L60, 65M60, 92B05

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1. Introduction

1.1 Calcium Signaling

When it comes to neuronal function, calcium is a fantastic multitasker. Numerous neural processes, including neuronal excitability, synthesis, the release of neurotransmitters, phosphorylation, and many others, are modulated by it. Calcium ensures that long-term processes including metabolism, memory formation, cell growth, and death, operate without interruption (Bong and Monteith [4], Fain [7], and Keener and Sneyd [8]). As an important messenger in signal cascading, Calcium is involved in every part of cellular life. A strictly monitored and systematically driven process like localized calcium entry, binding of buffers, and distribution within neuronal compartments is activated by Calcium. These monitoring processes create different Spatial-temporal domains of the distribution of calcium. Buffers bind free calcium at local sites and release it if required (see Augustine *et al*. [1], Bormann *et al*. [5], Luby-Phelps [9], and McHugh and Kenyon [12]).

We are aware that calcium diffusion is a complicated process that includes a number of different elements, including temperature change, gated channels, receptors, domains, and buffers. The cellular metabolism is significantly impacted by temperature variation in some circumstances, such as fever, chemotherapy, or hyperthermia. The exact effects of temperature vary for presynaptic release and post-synaptic receptors activities; still 'Temperature' is a major modulator of synaptic activity. It is crucial to comprehend how temperature affects cancer cells and their metabolism in an illness like cancer (see Bettaieb *et al*. [3], and Bong and Monteith [4]).

Cancer genetically modifies a cell or group of cells. These modifications disordered the functioning of normal cells which is essential to maintain the regular functioning of tissues, organs, and organ systems. The normal cells stop growing and undergo apoptosis but cancer cells have unstoppable growth that results in tumor formation. Because of genetic changes in cells due to Cancer, these cells do not undergo programmed death (apoptosis)[1].

1.2 Signaling by Calcium in Cancer Cells

Many different biological processes, including proliferation, invasiveness, and apoptosis, are regulated by calcium signaling.

The calcium regulatory mechanism through calcium channels, pumps, and exchangers stringently monitored the activation and execution of many processes like spatial-temporal behavior of calcium signaling. Cancer cells use the same mechanism for proliferation.

Another crucial regulator of cell death in a variety of cell types is the calcium signal (see Augustine *et al*. [1], and Rizzuto *et al*. [21], [2]). Oncogene and/or tumor suppressor-related pathways are either calcium-sensitive or exhibit changes in calcium signaling. It is also observed that cancer is a genetically altered mechanism of cell metabolism. Deviation in calcium profiling, as well as proteins, has been observed (see Monteith *et al*. [13], and Shapovalov *et al*. [23]).

[1] *Cancer Cells vs Normal Cells*, URL: https://www.technologynetworks.com/cancer-research/articles/cancer-cells-vs-normal-cells-307366, accessed October 2021.

[2] *Cytoplasm*, URL: https://biologydictionary.net/cytoplasm/#::text=Cytoplasm%20refers%20to%20the%20fluid, the%20exception%20of%20the%20nucleus, accessed October 2021.

Additionally, there is proof that cancer cells are not likely susceptible to some calcium signal deviations, such as the activation of cell death rather than pro-survival autophagy following IP3R to mitochondrial transfer inhibition in several cancer cell lines (Cárdenas *et al*. [6]). Therefore, research has been going on that included the remodeling of calcium channels, pumps, and signaling that may help in cancer therapy. In the current investigation, proteins that directly influence the calcium signal are taken into account in relation to cancer therapy. We focused on a few calcium signaling-related issues as well as the therapeutic use of hyperthermia to target cancer cells (Bong and Monteith [4], [2]).

To model the diffusion of calcium with mathematical equations, in the current model, we involved boundary conditions, the temperature of neuronal cells, viscosity of the cytosolic fluids, and variable diffusion coefficient. Previous studies have only investigated calcium transport in neuronal cells for either one or two-dimensional steady or unsteady state cases using constant diffusion coefficients (Matthews and Dietrich [11], McHugh and Kenyon [12], and Reddy [20]). The influence of temperature on the viscosity and diffusion coefficient of cytosolic fluid has been investigated in the current work. Similarly, their effect on calcium concentration profile in cytosolic plasma has been studied. Finding changes in a calcium concentration corresponding to distance is done using the finite element approach (Rao [19]).

In the preliminary part of this paper, numerical results based on the treatment of hyperthermia on cytoplasmic viscosity and the diffusion coefficient are included. Using the finite element method, it is possible to determine how variations in calcium concentration relate to distance (Rao [19], and Reddy [20]).

2. Materials and Methods

2.1 Functioning in Signal Transduction in Cytoplasm

The cytoplasm contains various particles, including ions, small molecules, protein organelles, and multi-protein complexes. The physical properties of the cytosol change due to the transition of all of these particles (Luby-Phelps [9], [2]). The liquid aqueous phase of cytoplasm provides a platform for several metabolic activities and signaling. It contains around 20-30% salts, proteins, and around 70-80% of water (Luby-Phelps [9], and Puchkov [18]). Viscosity is the prime parameter for the liquid medium like cytoplasm. It helps to define the rate of the physicochemical processes involved in the cytoplasm. Viscosity is the friction in fluids that resists the movement of particles from one part to another (Van Hook [28])). The semi-empirical Vogel-Fulcher-Tammann equation is used to find the dynamic viscosity as:

$$\eta = \eta_0 e^{\left(\frac{B}{T-T_{VF}}\right)} \tag{2.1}$$

that supports the fact that viscosity is a temperature-dependent function (Puchkov [18], and Viswanath and Natavajan [29]).

Where η_0, B and T_{VF} are empirical parameters (Van Hook [28], Viswanath and Natavajan [29], [3]). The cytoplasm is an aqueous medium but not like water, so its viscosity is more than water. For simulations, fluids that are more viscous than water are considered to determine friction and further diffusion coefficient which is important in calcium signaling.

[3] *VFT equation*, DOI: https://en.wikipedia.org/wiki/Vogel-Fulcher-Tammann_equation, November 2021.

2.2 Effect of Temperature on Neuronal Functioning

Cancer/tumor cells have slightly high temperatures than normal cells. Similarly, with the manipulation of the cellular processes by cancer/tumor cells, a major change in the temperature within the tumor microenvironment could be observed. The treatment used for cancer/tumor cells also raises the temperature. According to some documentation from earlier researchers, the type of treatment can have an impact on the temperature of tumors (Bettaieb *et al*. [3], [1]).

Over the two decades, the discovery of new strategies for the struggle against cancer has led to the fight against this disease. These new strategies include various therapies including. Chemotherapy, photodynamic therapy, laser treatment, immunotherapy, inhibitors of angiogenesis, hyperthermia, and gene therapy. These therapies target the calcium hemostasis responsible for cancer proliferation. One of the therapies is hyperthermia, which needs optimization and improved equipment. Also, neat understanding of the cellular mechanisms included in cancer treatment. Though hyperthermia needs optimization, is still one of the few strategies that can be accepted as a hopeful therapy in all other therapies to defeat cancer (Bettaieb *et al*. [3], Monteith *et al*. [13], and Shaoivalov *et al*. [23]).

Moderate elevation in temperature is considered as hyperthermia for cancer treatment, hyperthermia is a relatively recent therapy, in which tissues/cells are subjected to high temperatures on a scale of 37 °C to 45 °C. This high temperature can harm or kill cancer cells with little harm to healthy tissues or cells (Bettaieb *et al*. [3], and Cárdenas *et al*. [6]). For the last couple of decades, hyperthermia has been employed as a methodical alternative to other cancer treatments like chemotherapy and radiation therapy (Bettaieb *et al*. [3], and Naraghi and Nehar [14]). Drug-resistant and radio-resistant tumor cells can be eliminated with the use of hyperthermia. Another type of hyperthermia is applied during cancer treatment at temperatures above 60 °C. This high temperature can destroy tumors known as thermal ablation (Bettaieb *et al*. [3]). In the present paper, we will just include moderate hyperthermia that includes a range of temperatures from 37 °C to 45 °C (Bettaieb *et al*. [3]).

Variation in temperature influences Neuronal functioning and synaptic integration. It affects different parts of the cell including cell physiology and calcium channel functioning. The effects of temperature on neuronal function are complex to determine. Still, profiling of calcium can be studied to compare results with earlier research output for different temperatures (Tanimoto *et al*. [25], [2]).

Homogeneous cell homeostasis with variation in temperature 37 °C to 45°C is considered for this paper. Variation in the viscosity of the cytosolic fluid and the diffusion coefficient has been studied with respect to changes in temperature. Temperature based Diffusion coefficient is discussed in a subsequent section.

Considering, $\eta_0 = 0.02939$mPa·s, $B = 507.88$ K, and $T_{VF} = 149.3$ K. For different values of temperatures values of the viscosity are evaluated using equation (2.1). Figure 1 shows the variation in viscosity values for several fluids (more viscous than water). The diffusion coefficient is then calculated using these numerical values.

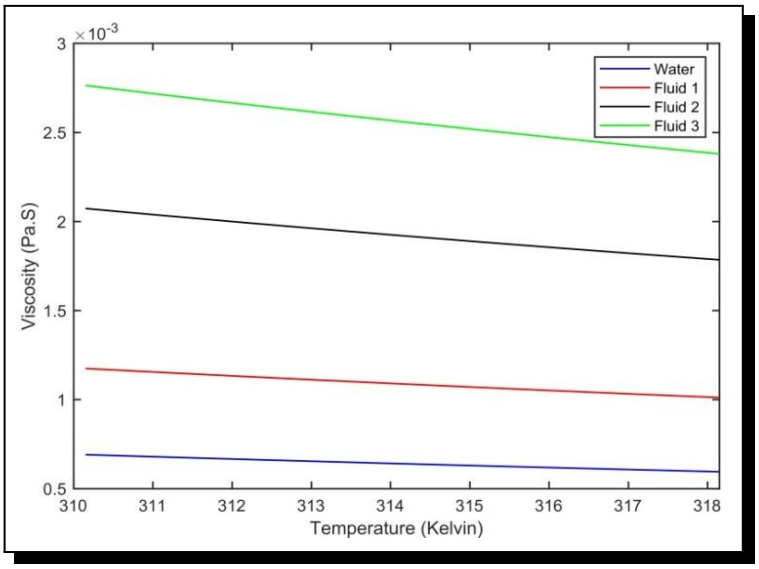


Figure 1. Variation of temperature versus viscosity. The viscosity behavior of water (blue line), Fluid 1, 2 and 3 (1.7, 2, 4 times more viscous than water are considered with redline, black line and green line respectively) in terms of temperature variation

2.3 Mathematical Modeling

In the cytoplasm of neurons, calcium then triggers a large-scale action-reaction (Bertram *et al*. [2], and Tewari and Paradasani [26]). This implies the following bimolecular interaction between calcium and buffer:

$$\mathrm{Ca}^{2+} + \mathrm{B} \underset{\mathrm{k}^-}{\overset{\mathrm{k}^+}{\rightleftarrows}} \mathrm{CaB}, \tag{2.2}$$

where B stands for a free buffer, CaB represents bound buffer of Ca^{2+}, and k^+ and k^- are constants of association and dissociation rate respectively. Taking into account Fickian diffusion in an isotropic, homogeneous medium. The following series of reaction-diffusion equations are written for equation (2.2) (Pathak and Adlakha [16], and Tewari *et al*. [27]).

$$\frac{\partial[\mathrm{Ca}^{2+}]}{\partial t} = D_{Ca}\nabla^2[\mathrm{Ca}^{2+}] + \sum_j R_j + \sum J, \tag{2.3}$$

$$\frac{\partial[\mathrm{B}_j]}{\partial t} = D_{\mathrm{B}_j}\nabla^2\mathrm{B}_j + R_j, \tag{2.4}$$

$$\frac{\partial[\mathrm{CaB}_j]}{\partial t} = D_{\mathrm{CaB}_j}\nabla^2[\mathrm{CaB}_j] - R_j, \tag{2.5}$$

where the terms of reaction $R_j$are given by $R_j = -k_j^+[\mathrm{Ca}^{2+}][\mathrm{B}_j] + k_j^-[\mathrm{CaB}_j]$ and j is an index over Ca^{2+} buffers.

The assumption of the un-saturability of Ca^{2+} buffer is likely to be valid when Ca^{2+} buffer is in excess. Therefore, the process is called *Excess Buffer Approximation* (EBA) (Mantina *et al*. [10]). Considering excess buffering approximation, the steady-state case of buffered calcium diffusion of calcium can be reviewed and generalized.

For bimolecular association reaction between Calcium and buffer, dissociation constant is given by K_j and determined by $K_j = k_j^-/k_j^+$. Therefore, equations for the buffered diffusion of

Ca^{2+} for single buffer become:

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_c\nabla^2[Ca^{2+}] - k^+[B]_\infty([Ca^{2+}] - [Ca^{2+}]_\infty) + J. \tag{2.6}$$

2.4 Inflow Due to Ca^{2+} Current in Response to Potential Activity

According to Goldman-Hodgkin-Katz Equation (Fain [7]), Ca^{2+} current is given by:

$$I_{Ca} = P_{max}VzF\left[\frac{[Ca^{2+}]_\infty - [Ca^{2+}]e^{\varepsilon V}}{1-e^{\varepsilon V}}\right], \tag{2.7}$$

where $\varepsilon = 0.0778491\,\text{mV}^{-1}$, $P_{max} = 5.4\times10^{-6}$ m/s, V is the membrane potential, z is the Calcium valence, and $[Ca^{2+}]_\infty$is the extracellular concentration. Using equation (2.7), influx due to calcium current is calculated by

$$J_{Ca} = \frac{-I_{Ca}}{zF}. \tag{2.8}$$

A finite element model has been derived for Ca^{2+} profiling in the existence of excess buffer approximation in neurons. The current modeling includes the out-turn of influx depending on the potential activity of calcium diffusion in the cytoplasm. Rate of diffusion, association, conductance, and variation in membrane potential are included as parameters. Physical processes related to influx have been used to provide necessary boundary conditions. Numerous parameters have been researched to determine their relationships, and this model has been assessed in order to provide a numerical simulation. A numerical solution to the issue has been found using the FEM (*Finite Element Method*). We conclude with the final differential equation from (2.6) to obtain

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_c\nabla^2[Ca^{2+}] - k^+[B]_\infty([Ca^{2+}] - [Ca^{2+}]_\infty) - P_{max}V\varepsilon\left[\frac{[Ca^{2+}]_\infty - [Ca^{2+}]e^{\varepsilon V}}{1-e^{\varepsilon V}}\right]. \tag{2.9}$$

2.5 Diffusion Coefficient for a Range of Values of Temperature

The diffusion coefficient is given by

$$D = \frac{kT}{f}, \tag{2.10}$$

where k is the Boltzmann constant, f is the frictional coefficient and the T is calcium molecule's absolute temperature. The friction coefficient f is computed using the formula: $f = 6\pi\eta R_1$, where R_1 is the Calcium atom's radius equal to 231×10^{-12} pm (Mantina *et al.* [10]). The diffusion coefficients were calculated for the viscosity values as shown in Figure 2 (denoted by D_c for the paper).

2.6 The Solution of Equation (2.18) using the Finite Element Method

Use the transformation, $v = [Ca^{2+}]$ to find the solution to the equation (2.9). We get

$$\begin{aligned}\frac{\partial v}{\partial t} &= D_c\nabla^2 v - k^+[B]_\infty[v - v_\infty] + \left(-\frac{\varepsilon P_{max}V}{(1-e^{\varepsilon V})}\right)[v_\infty - ve^{\varepsilon V}]\\ &= D_c\nabla^2 v - \left[k^+[B]_\infty - \frac{\varepsilon P_{max}Ve^{\varepsilon V}}{(1-e^{\varepsilon V})}\right]v + \left[k^+[B]_\infty - \frac{\varepsilon P_{max}V}{(1-e^{\varepsilon V})}\right]v_\infty.\end{aligned} \tag{2.11}$$

Let

$$a = \frac{\left[k^+[B]_\infty - \frac{\varepsilon P_{\max} V e^{\varepsilon V}}{(1-e^{\varepsilon V})}\right]}{D_c}, \quad b = \frac{\left[k^+[B]_\infty - \frac{\varepsilon P_{\max} V}{(1-e^{\varepsilon V})}\right]}{D_c} v_\infty . \tag{2.12}$$

Thus, equation (2.11) can now be abbreviated as

$$\frac{1}{D_C}\frac{\partial v}{\partial t} = \nabla^2 v - av + b . \tag{2.13}$$

Using spherical coordinates in one dimension, the equation (2.13) for steady-state conditions (setting $\frac{\partial v}{\partial t} = 0$) is represented as:

$$\frac{\partial}{\partial r}\left(r^2 \frac{\partial v}{\partial r}\right) - ar^2 v + br^2 = 0 . \tag{2.14}$$

The research was carried out for the region that is spherical and symmetric as $1 \le r \le 5$. The following boundaries are imposed.

$$v(0) = \alpha\mu M \quad \text{and} \quad v(5) = 0.1\mu M \tag{2.15}$$

Here, at $r = 0$ concentration of calcium is α (referring to free calcium, but can be assigned to a fixed value as per the standard values) and at $r = 5\mu m$, far away from the source calcium concentration converges to $0.1\mu M$.

Using boundary conditions in equation (2.15), the variational form of equation (2.14) is represented as:

$$I[v(r)] = -\frac{1}{2}\int_1^5 \left[r^2\left(\frac{\partial v}{\partial r}\right)^2 + ar^2 v^2 - 2br^2 v\right] dr + \frac{\sigma}{4\pi D_c} v\Big|_{r=r_1} . \tag{2.16}$$

According to our presumption, the functional I can be expressed as the sum of the sub components $I^{(e)}$ as:

$$I[v(r)] = \sum_{e=1}^{M} I^{(e)}, \tag{2.17}$$

where

$$I^{(e)} = -\frac{1}{2}\int_{r_i}^{r_{i+1}} \left[r^2\left(\frac{\partial v^{(e)}}{\partial r}\right)^2 + ar^2[v^{(e)}]^2 - 2br^2[v^{(e)}]\right] dr + \frac{\sigma}{4\pi D_c} v^{(e)}\Big|_{e=1} . \tag{2.18}$$

Equation (2.18) presents equation (2.14) in discretized variational form and r_i, r_{i+1} are extreme points of the typical element e. We take the approximate solution in the form

$$v^{(e)} = M_i v_i + M_{i+1} v_{i+1} = M^{(e)} \phi^{(e)}, \tag{2.19}$$

where

$$M_i = \frac{r_{i+1} - r}{r_{i+1} - r_i} \quad \text{and} \quad M_{i+1} = \frac{r - r_i}{r_{i+1} - r_i}, \tag{2.20}$$

$$M^{(e)} = [M_i, M_{i+1}] \quad \text{and} \quad \phi^{(e)} = [v_i, v_{i+1}]. \tag{2.21}$$

Substituting equations (2.19) to (2.21) into (2.16), we obtain

$$I^{(e)} = -\frac{1}{2}\int_{r_i}^{r_{i+1}} \left[r^2\left\{[M_i', M_{i+1}']\begin{bmatrix} v_i \\ v_{i+1}\end{bmatrix}\right\}^2 + ar^2\left\{[M_i \quad M_{i+1}]\begin{bmatrix} v_i \\ v_{i+1}\end{bmatrix}\right\}^2 - 2br^2\left\{[M_i \quad M_{i+1}]\begin{bmatrix} v_i \\ v_{i+1}\end{bmatrix}\right\}\right] dr + \frac{\sigma}{4\pi D_c} v^{(e)}\Big|_{e=1}, \tag{2.22}$$

where dashes denotes derivative with respect to r. The conditions to find extremum of $I^{(e)}$ corresponding to the nodal quantities for an element (e) are:

$$\frac{\partial I^{(e)}}{\partial v_i} = 0 \quad \text{and} \quad \frac{\partial I^{(e)}}{\partial v_{i+1}} = 0. \tag{2.23}$$

In matrix form

$$A^{(e)}\phi^{(e)} = B^{(e)}, \tag{2.24}$$

where

$$\begin{aligned} A^{(e)} &= \int_{r_i}^{r_{i+1}} \left\{ r^2 \begin{bmatrix} M_i' M_i' & M_i' M_{i+1}' \\ M_i' M_{i+1}' & M_{i+1}' M_{i+1}' \end{bmatrix} + ar^2 \begin{bmatrix} M_i M_i & M_i M_{i+1} \\ M_{i+1} M_i & M_{i+1} M_{i+1} \end{bmatrix} \right\} dr, \\ B^{(e)} &= \int_{r_i}^{r_{i+1}} \left\{ r^2 \begin{bmatrix} M_i \\ M_{i+1} \end{bmatrix} \right\} dr - \frac{\sigma}{4\pi D_c} v^{(e)}\Big|_{e=1}. \end{aligned} \tag{2.25}$$

Summing over $e = 1,2,\ldots,n$ and extremization of $I[v(r)]$ we get as:

$$A\Phi = B, \tag{2.26}$$

where A, Φ, and B are global matrices. As a special we consider the region to be divided into four elements as $e = 1,2,3,4$ and the interval $r = [1,5]$ in μm

For $e = 1$, we solve the equation (2.25), we obtain

$$A^{(1)} = \begin{bmatrix} \frac{7}{3} + \frac{8}{15}a & -\frac{7}{3} + \frac{23}{60}a \\ -\frac{7}{3} + \frac{23}{60}a & \frac{7}{3} + \frac{31}{30}a \end{bmatrix} \text{ and } B^{(1)} = \begin{bmatrix} \frac{11}{12}b \\ \frac{17}{12}b \end{bmatrix}.$$

Similarly for $e = 2,3,4$

$$A^{(1)} = \begin{bmatrix} \frac{19}{3} + \frac{81}{10}a & \frac{-19}{3} + \frac{21}{20}a \\ \frac{-19}{3} + \frac{21}{20}a & \frac{19}{3} + \frac{38}{15}a \end{bmatrix} \text{ and } B^{(1)} = \begin{bmatrix} \frac{11}{4}b \\ \frac{43}{12}b \end{bmatrix},$$

$$A^{(3)} = \begin{bmatrix} \frac{37}{3} + \frac{53}{15}a & -\frac{37}{3} + \frac{41}{20}a \\ -\frac{37}{3} + \frac{41}{20}a & \frac{37}{3} + \frac{47}{10}a \end{bmatrix} \text{ and } B^{(3)} = \begin{bmatrix} c\frac{67}{12}b \\ \frac{27}{4}b \end{bmatrix},$$

$$A^{(4)} = \begin{bmatrix} \frac{61}{3} + \frac{181}{30}a & -\frac{61}{3} + \frac{203}{60}a \\ -\frac{61}{3} + \frac{203}{60}a & \frac{61}{3} + \frac{113}{15}a \end{bmatrix} \text{ and } B^{(4)} = \begin{bmatrix} \frac{113}{12}b \\ \frac{131}{12}b \end{bmatrix}.$$

After adding all elements, we deduce equation (2.24) as follows:

$$\begin{bmatrix} \frac{7}{3} + \frac{8}{15}a & -\frac{7}{3} + \frac{23}{60}a & 0 & 0 & 0 \\ -\frac{7}{3} + \frac{23}{60}a & \frac{26}{3} + \frac{517}{60}a & \frac{-19}{3} + \frac{21}{20}a & 0 & 0 \\ 0 & \frac{-19}{3} + \frac{21}{20}a & \frac{56}{3} + \frac{91}{15}a & -\frac{37}{3} + \frac{141}{60}a & 0 \\ 0 & 0 & -\frac{37}{3} + \frac{41}{60}a & \frac{98}{3} + \frac{161}{15}a & -\frac{61}{3} + \frac{203}{60}a \\ 0 & 0 & 0 & -\frac{61}{3} + \frac{203}{60}a & \frac{61}{3} + \frac{113}{15}a \end{bmatrix} \begin{bmatrix} v_0 \\ v_1 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} c\frac{11}{12} \\ \frac{50}{12} \\ \frac{110}{12} \\ \frac{194}{12} \\ \frac{131}{12} \end{bmatrix} b. \tag{2.27}$$

MATLAB programming has been created and implemented to solve (2.27) to obtain various values of v at nodal points. These values of v_i are used in equation (2.18) to find the value of $v^{(e)}$ in each element e (Patil *et al.* [17], and Reddy [20]).

3. Numerical Results and Discussion

Various parameters have been used in previous research papers (Tewari and Pardasani [26]), their values are used to compute the numerical results. For different values of temperature, variation in diffusion coefficient is observed. Also, calcium concentration profiles based on variable diffusion coefficients on has been studied in presence of buffers.

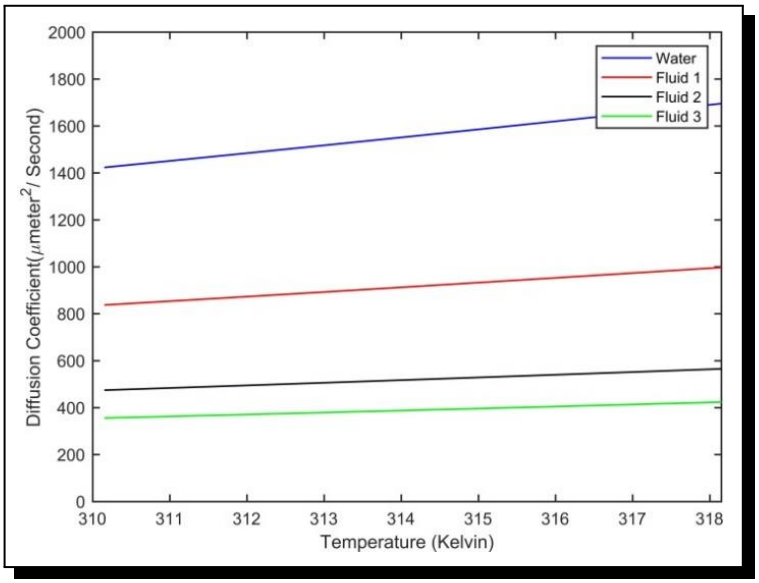


Figure 2. Variation in diffusion coefficient versus temperature. The viscosity behavior of water (blue line), Fluid 1, 2 and 3 (1.7, 2, 4 times more viscous than water are considered with redline, black line and green line, respectively) in terms of temperature variation

For the current work, for current study diffusion coefficient is considered for the fluid that is four-time more viscous than water and these values are in line with biological studies.

Figure 3 shows a graph for fluid, that is four times more viscous than water with respect to variable diffusion coefficient. As the diffusion coefficient increases relative to temperature fluctuation, the concentration of calcium drops in fluid 3 that is more viscous than water. Calcium concentration is reduced, as the diffusion coefficient increases.

In the process of diffusion of calcium in the neuronal cell, many important aspects are involved, and buffers are one of them. The key role of buffers is their binding capacity which maintains the calcium concentration in the intracellular process. Due to the influx activity of gated channels, calcium concentration increased to a great extent. In such cases, buffers are more impactful to modulate free-calcium concentration in intraneuronal activities. In Figures 4(a) and 4(b), calcium profile for the steady-state is plotted corresponding to exogenous buffers EGTA and BAPTA respectively for two values of temperature 37 °C and 44 °C with corresponding diffusion coefficients. The blue line shows the calcium profiling at normal temperature and the red line shows calcium profiling at temperature 44 °C. It is observed that raise in temperature affects the concentration level.

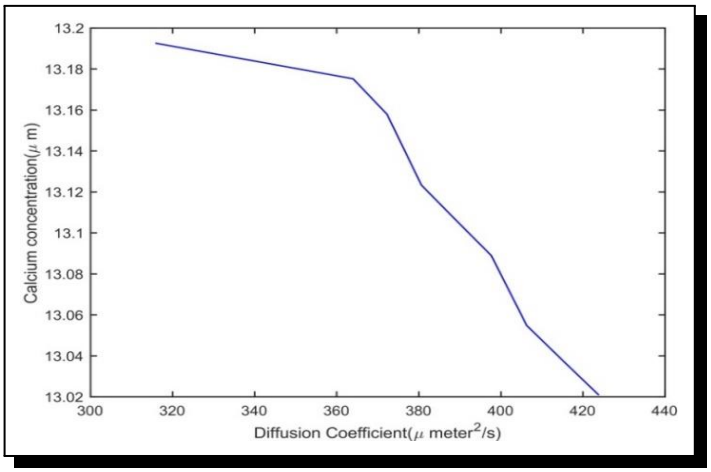
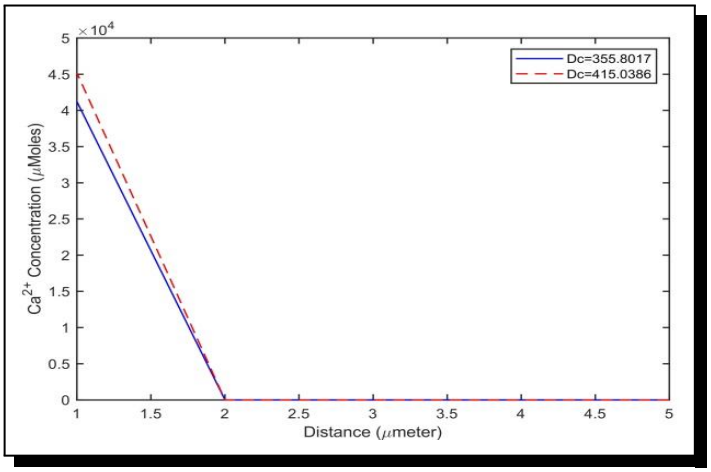
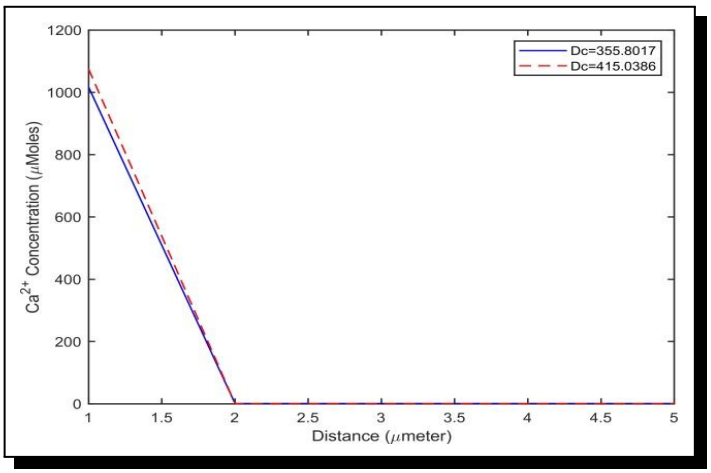


Figure 3. Relation of calcium Concentration and diffusion coefficient. For source amplitude $\sigma = 1$ pA and fixed radius $r = 1\ \mu$m

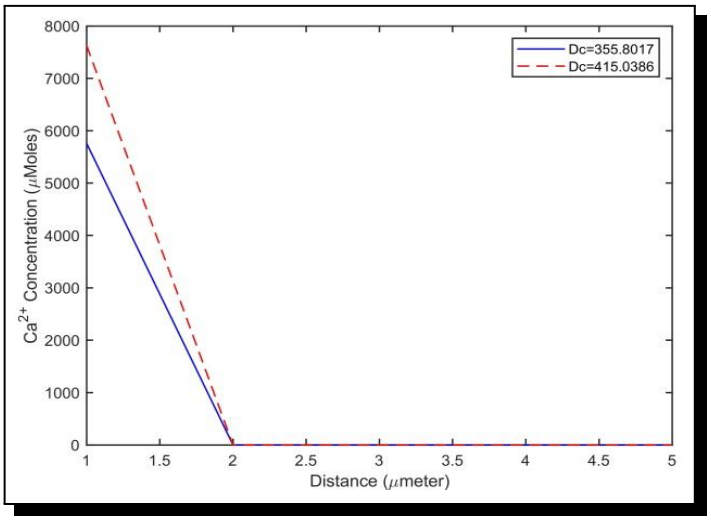


(a)

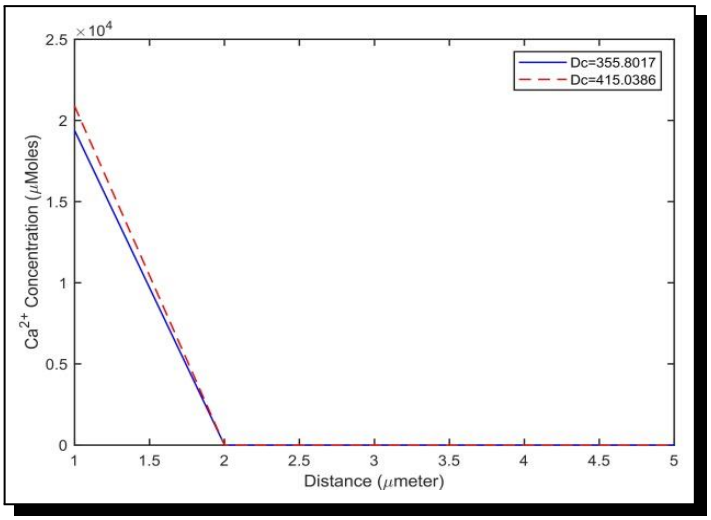


(b)

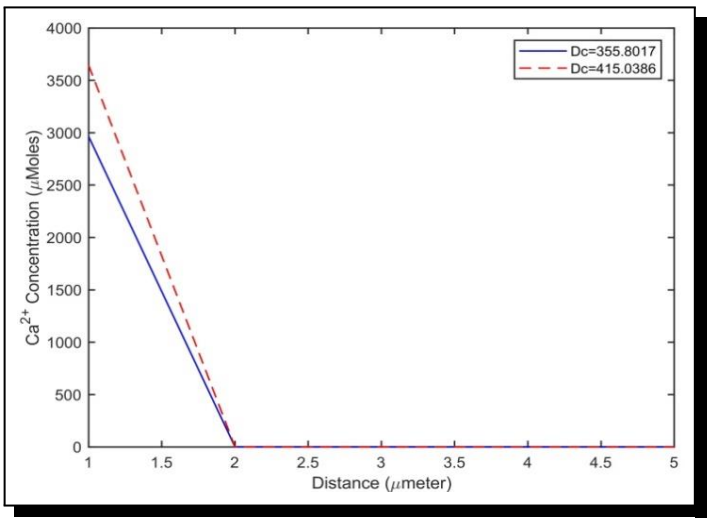
Figure 4. Calcium concentration profile with respect to position for exogenous buffers EGTA and BAPTA respectively for temperature 37 °C and 44 °C, $\sigma = 1$ pA



(a)



(b)



(c)

Figure 5. Calcium concentration profile with respect to distance for endogenous buffers (Troponin C, Triponin C, and Calmodulin, respectively) for temperature 37 °C and 44 °C, $\sigma = 1$ pA

In Figures 5(a), 5(b), 5(c) the steady-state calcium profile is plotted for endogeneous Troponin-C, Triponin-C, and Calmodulin respectively for two values of temperature 37 °C and 44 °C with corresponding diffusion coefficients. The blue line shows the calcium profiling at normal temperature and the red line shows calcium profiling at temperature 44 °C. It is observed that raise in temperature affects the concentration level. At initial distance variation in calcium profiling due to both exogenous and endogenous buffer was observed. This variation in calcium concentration is due to influx activity and raised temperature.

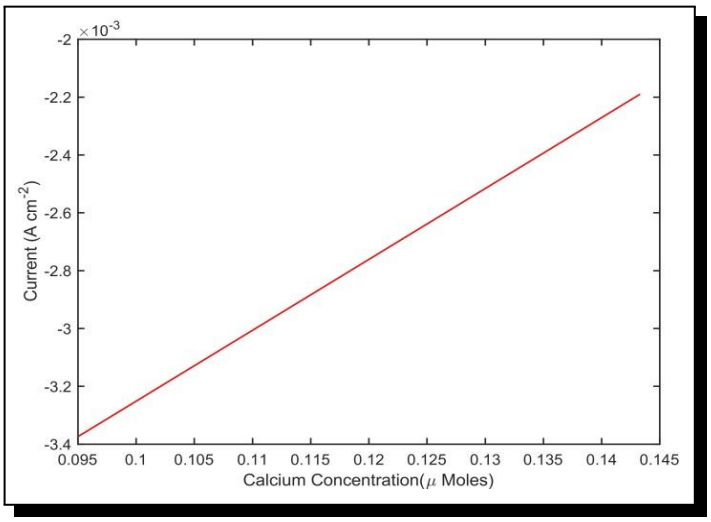


Figure 6. Variation in current and calcium concentration with variable diffusion coefficient and membrane permeability, $P_{\max} = 5.4 \times 10^{-6}$ m/s

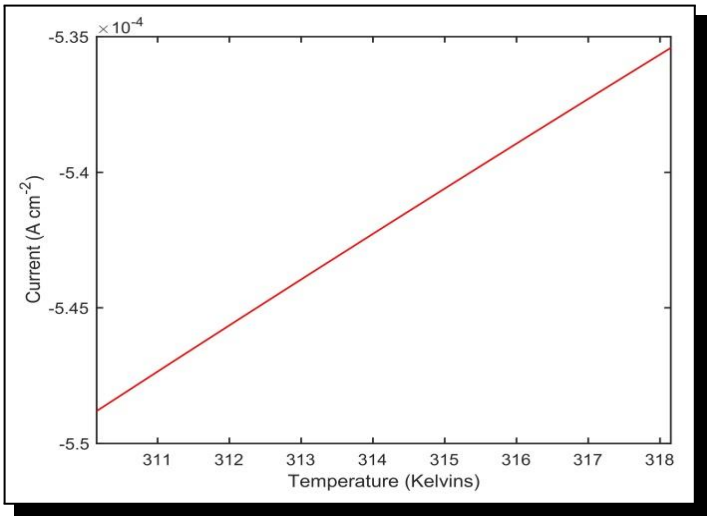


Figure 7. Plot the current as a function of temperature with the permeability constant $P_{\max} = 5.4 \times 10^{-6}$ m/s by using the GHK current equation

To investigate the effect of the diffusion coefficient on the calcium profile and current, the diffusion coefficient and membrane permeability were determined. A graph of current and calcium concentration is shown in Figure 6. A linear graph of calcium concentration versus cytosolic current is observed. Figure 7 depicts a graph of temperature versus current. Research

has evidence of impact of temperature on cytosolic activities (Van Hook [28], and Viswanath and Natavajan [29]). This has been observed through the linear graph between temperature and current (measured in pA).

The current work focuses on two crucial features of calcium profile determination in neuronal cells: buffer activity and changing diffusion coefficient owing to temperature increase. The current study is based on these facts and is, to the best of our knowledge, novel.

Our findings using the suggested model are consistent with prior researchers' biological certainty and experimental findings. For the steady-state instance, the potential activity-based influx and temperature-based variable diffusion coefficient produced results that are consistent with biological realities. Such models can quickly identify correct information about concentration distributions in cells and correlations between numerous factors involved in biological events. Any disruptions in calcium input or potential activity owing to cancer cells or treatment on it (such as hyperthermia) can disrupt calcium concentration profiles. The current study's findings will aid biomedical researchers in understanding cellular processes and building an agreement for cancer treatment.

4. Conclusion

The studies carried in this work, as well as the data acquired, are useful in defining variance in calcium profile in cancer cells. Many scientific researchers are also revealing which calcium channels, pumps, and exchangers will be demonstrated to be the most effective in targeting any given cancer kind. In this study, mathematical modelling was used to monitor the profiling of calcium concentrations as a result of treatment on cancer cells. Although many researchers are interested in the possibilities of integrated therapy, particularly pharmacological inhibitors of a specific calcium channel and pump. Calcium signaling will be accelerated in the context of the tumor microenvironment in the future. The biological facts of calcium profiling in neuronal regions are supported by mathematical modelling in our research. Neuronal activity changes in response to changes in viscosity, temperature, and coefficient of diffusion of Calcium can easily be studied.

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Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All the authors contributed significantly in writing this article. The authors read and approved the final manuscript.

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