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An Unsteady State Case: Calcium Profiling Based On Temperature Variation In Neuronal Due To Cancer Cells

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Calcium, is a critically important second messenger in the nervous system. It enters through voltage-gated Ca^{2+} channels and regulates the release of synaptic transmitter. This mechanism is highly complex and very stringently monitored by buffers, gated channels and influxes. This calcium cascading in cytoplasm shows complex spatial- temporal behavior. The major monitoring factor of calcium concentration is buffers but its profiling is also depending on diffusion coefficient of cytoplasmic fluid. Diffusion coefficient is temperature and viscosity dependent quantity, therefore temperature variation and viscosity are also studied.
Calcium signaling is also responsible for long term processes like memory creation, metabolism, growth and death of cells, etc. This signal cascading along with the external exposure to high temperature can be used effectively in cancer treatment therapy like hyperthermia. Effect of raised temperature in calcium profiling in cancer/ tumor cells is studied in this paper. The model is prepared to study unsteady state case that includes diffusion of calcium with respect to variable diffusion coefficient, variable temperature and influx due to potential activity. An analytical solution has been studied and numerical solutions are discussed with the MATLAB software.

Keywords: Calcium profiling, Variable diffusion coefficient, Excess buffering approximation, Influx due to potential activity.

Introduction

Calcium is a neurotransmitter. It modulates synaptic transmitter release by voltage-gated Ca^{2+} channels. This intricate system is monitored by buffers, gated channels, and influxes. This cytoplasmic calcium cascade is spatial-temporal. The major monitoring factor of calcium concentration is buffers but its profiling is also depending on diffusion coefficient of cytoplasmic fluid. Diffusion coefficient is temperature and viscosity dependent quantity, therefore temperature variation and viscosity are also studied. Calcium signaling is also responsible for long term processes like memory creation, metabolism, growth and death of cells, etc. This signal cascading along with the external exposure to high temperature can be used effectively in cancer treatment therapy like hyperthermia. Effect of raised temperature in calcium profiling in cancer/ tumor cells is studied in this paper. The model is prepared to study unsteady state case that includes diffusion of calcium with respect to variable diffusion coefficient, variable temperature and influx due to potential activity. An analytical solution has been studied and numerical solutions are discussed with the MATLAB software.

Calcium Cascading

The calcium is fabulous multitasker, in neuronal functioning. It modulates several neuronal functions, such as neuronal excitability, synthesis and release of neurotransmitters, phosphorylation and many more. The long-term processes like metabolism, formation of memory, cell growth and death are smoothly functioned due to calcium [1,7,11,13,14]. As an important messenger in signal cascading, Calcium involved in every part of cellular life. A strictly monitored and systematically driven processes like localized calcium entry, binding of buffers, distribution within neuronal compartments are activated by Calcium. Calcium in the synaptic cleft is distributed in a variety of spatial and temporal domains due to the many regulatory processes that affect it. Calcium signals are localised to discrete regions of dendrites or include the whole cell at high calcium levels. Complex factors like as gated channels, receptors, domains, buffers, the diffusion coefficient of the cytosolic fluid, temperature change, etc. all play a role in calcium's ability to diffuse from one location to another. In Some cases like fever, chemotherapy or hyperthermia; temperature variation deeply affects cellular metabolism. The exact effects of temperature vary for presynaptic release and post-synaptic receptors activities; still 'Temperature' is a major modulator of synaptic activity. In the disease like cancer, it is essential to understand effect of temperature on cancer cells and their metabolism [1, 2]. Cancer genetically modifies a cell or group of cells. These modifications disordered the functioning of normal cell that are essential to maintain regular functioning of tissues, organs, and organ systems. The normal cells stop growing and undergo apoptosis but cancer cells don't stop growing and dividing them such cell growth results into the tumor formation. Because of genetic changes in cells due to Cancer, these cells do not undergo the programmed death (apoptosis) [33].

Calcium signaling in Cancer/Tumor cells

The variety of cellular processes are regulated by calcium signaling out of which some of processes are responsible in cancer progression such as proliferation, invasiveness and apoptosis. The calcium regulatory mechanism through calcium channels, pumps and exchangers stringently monitored activation and execution of many processes like spatial-

temporal behavior of calcium signaling. Cancer cells use the same mechanism for proliferation. The sarco/endoplasmic reticulum ATPase (SERCA) inhibitor thapsigargin may enhance apoptosis in a wide range of cell types [4, 24, 33], demonstrating that Calcium induces and regulates cell death. There is growing evidence that the calcium signal is important in cancer due to the discovery that pathways including oncogenes and tumour suppressors may be calcium sensitive or promote modifications in calcium signalling. It is also observed that as cancer is genetically alters mechanism of cell metabolism. Deviation in calcium profiling as well as proteins has been observed [5, 6]. Cancer cells are not sensitive to various calcium signal deviations, such as the induction of cell death rather than pro-survival autophagy after blocking IP3R to mitochondria transfer in multiple cancer cell lines [30]. Therefore research has been going on that included the remodeling of calcium channels, pumps and signaling that may help in cancer therapy. Within the context of cancer treatment, this study will focus on the calcium signal and the proteins that directly can modulate it. We focused on the connections between calcium signaling and the use of hyperthermia as a therapeutic tool against cancer.[1, 32] In this model, we integrated a variable diffusion coefficient, boundary conditions, and other factors like neuronal cell temperature and cytosolic fluid viscosity to simulate calcium transport using mathematical equations. Most of the previous work on calcium diffusion in neurons has been done for steady or unsteady state instances in one or two dimensions with constant diffusion coefficients for normal cells [8, 10, 17]. In this model, we investigate how changing the temperature of cancer therapy affects the cytosolic fluid's viscosity and diffusion coefficient. Their impact on the cytosolic plasma calcium concentration profile has also been investigated. The temperature and diffusion coefficient in a mathematical model are investigated. Variation in calcium concentration with respect to distance was mapped using a finite element method [10, 23]

Methods

Effect of variable temperature due to therapeutic treatment

The term "cytoplasm" is used to describe the non-nuclear components of eukaryotic cells like neurons. Ions, tiny molecules, proteins, organelles, and multi-protein complexes are all found in the cytoplasm. All of these particle transitions alter the cytosol's physicochemical characteristics [15, 21, 32]. Liquid aqueous phase of cytoplasm content around 80% of water and remaining are above compounds. The pace at which physicochemical processes take place in an aqueous media, such as the cytoplasm, is largely determined by its viscosity. Viscosity is the resistance to the motion of one component against another, and it is described as friction in fluids [28]. The Vogel-Fulcher-Tammann equation provides a semi-empirical method for approximating dynamic viscosity [21,29].

Diffusion Coefficient at different level of temperature

Calcium's diffusion coefficient is based on Boltzmann constant (k), frictional coefficient (f), and absolute temperature (T) as $D = \frac{kT}{f}$ Fig. 4.1. Temperature vs. cytoplasmic viscosity. VFT compares viscosity to water [blue line]. Viscosity vs temperature is shown for

fluids 1 (1.7 times more viscous than water, red line), 2 (3 times more viscous than water, black line), and 3 (4 times more viscous than water, green line). [refer equation 3.2.2]. The diffusion coefficient varies with the temperature of the fluid and the value of the diffusion coefficient for free Ca^{2+} in aqueous solution of physiological ionic strength has been estimated to be $355-424\,\mu m^2/s$.

Mathematical formulation

A bimolicular reaction between Calcium ions and buffer is refered to set up reaction diffusion equations [29, 31, 59].

$$Ca^{2+} + B \underset{k^-}{\overset{k^+}{\square}} CaB \qquad (1)$$

Considering the buffered diffusion equation for Ca^{2+} for single buffer under EBA [ ], we get:

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

where, J represents influx of Ca^{2+} that is considered due to GHK current equation []as:

$$I_{Ca} = P_{\max} V z F \left[\frac{[Ca^{2+}]_\infty - [Ca^{2+}] e^{\varepsilon V}}{1 - e^{\varepsilon V}} \right] \qquad (3)$$

Where, $\varepsilon = 0.0778491\, mV^{-1}$, $P_{\max} = 5.4 \times 10^{-6}\, m/s$, V is the membrane/resting potential, z is the valence of Calcium and $\left[Ca^{2+}\right]_\infty$ is the uniform concentration away from the source. Thus, influx due to calcium current is calculated by

$$J_{Ca} = \frac{-I_{Ca}}{zF} \qquad (4)$$

The model in current paper consolidates the effect of potential activity-dependent influx on calcium diffusion process. The parameters like diffusion rate, dissociation rate, conductance and membrane potential are included in this model.. The relationships among various parameters have been studied. Equations (2) and (3) to (4) gives the combined equation as:

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_c \nabla^2 [Ca^{2+}] - k^+ [B]_\infty \left([Ca^{2+}] - [Ca^{2+}]_\infty \right) - P_{\max} V \varepsilon \left[\frac{\left[Ca^{2+}\right]_\infty - \left[Ca^{2+}\right] e^{\varepsilon V}}{1 - e^{\varepsilon V}} \right] \qquad (5)$$

An analytical solution of the equation (5) is obtained and concentration and potential profiles have been determined w.r.t. position and time. The numerical simulations developed with MATLAB

Boundary Conditions

For numerical simulations, a reasonable initial condition of uniform 'background' of Ca^{2+}, profile is considered. Let us assume that all buffers are initially in equilibrium level with Ca^{2+}, and remains same far from the source, at all times.

$$\lim_{r\to\infty}[Ca^{2+}] = [Ca^{2+}]_{\infty} = 0.1\mu M$$
$$\text{and} \quad \lim_{r\to\infty}[B_j] = [B_j]_{\infty} \tag{6}$$

Near the source, we set the boundary conditions as:

$$\lim_{r\to 0}\left[4\pi D_c r^2 \frac{\partial\left[Ca^{2+}\right]}{\partial r}\right] = \sigma \quad \text{and} \quad \lim_{r\to\infty}\left[4\pi D_c r^2 \frac{\partial\left[B_j\right]}{\partial r}\right] = 0 \tag{7}$$

Analytical Solution

To obtain the solution of equation (5) we use the transformation, $u = \left[Ca^{2+}\right] - \left[Ca^{2+}\right]_{\infty}$ and $u_{\infty} = \left[Ca^{2+}\right]_{\infty}$

Therefore, we get,

$$\frac{\partial u}{\partial t} = \mathrm{D_c}\nabla^2 \mathrm{u} \; - \mathrm{k}^{+}\,[\mathrm{B}]_{\infty} u - \varepsilon P_{\max} V\left(\frac{u_{\infty} - \left(u + u_{\infty}\right)e^{\varepsilon V}}{(1 - e^{\varepsilon V})}\right)$$

$$= = \mathrm{D_c}\nabla^2 \mathrm{u} - \left[\mathrm{k}^{+}\,[\mathrm{B}]_{\infty} - \frac{\varepsilon P_{\max} V e^{\varepsilon V}}{(1 - e^{\varepsilon V})}\right] u - \varepsilon P_{\max} V u_{\infty} \tag{8}$$

Let,
$$a = \mathrm{k}^{+}\,[\mathrm{B}]_{\infty} - \frac{\varepsilon P_{\max} V e^{\varepsilon V}}{(1 - e^{\varepsilon V})}, \qquad b = \varepsilon P_{\max} V u_{\infty} \tag{9}$$

So, equation (20) can now be abbreviated as
$$\frac{\partial u}{\partial t} = D_C \nabla^2 u - au - b \tag{10}$$

Applying Laplace transformation to equation (10) we get,

$$L\left(\frac{\partial u}{\partial t}\right) = D_c L\left(\nabla^2 u\right) - a\,L\left(u\right) - b\,L(1) \tag{11}$$

It gives further the differential equation as:

$$\frac{d^2\overline{U}}{dr^2}+\frac{2}{r}\frac{d\overline{U}}{dr}-A\overline{U}=B \tag{12}$$

Where, $\overline{U}=L(u)$, $A=\frac{s+a}{D_c}$ and $B=\frac{b}{s\,D_c}$

Solution of equation (12) is given as

$$\overline{U}=\frac{c_1e^{\sqrt{A}r}+c_2e^{-\sqrt{A}r}}{r}-\frac{B}{Ar} \tag{13}$$

Using boundary conditions given by equations (6) and (7), we can obtain analytical solution of equation (13) as

$$[Ca^{2+}]=\frac{1}{2}\left(\frac{b}{ar}-\frac{\sigma}{4\pi D_c r}\right)\left\{e^{r\sqrt{a/D_c}}erfc\left(r/2\sqrt{tD_c}+\sqrt{at}\right)+e^{-r\sqrt{a/D_c}}erfc\left(r/2\sqrt{tD_c}-\sqrt{at}\right)\right\}$$
$$-\frac{b}{ar}e^{-at}erfc\left(r/2\sqrt{tD_c}\right)-\frac{b}{ar}+\frac{b}{ar}e^{-at}+0.1 \tag{14}$$

Where, $a=\mathrm{k}^{+}\,[\mathrm{B}]_{\infty}-\frac{\varepsilon P_{\max}Ve^{\varepsilon V}}{(1-e^{\varepsilon V})}$ and $b=\varepsilon P_{\max}Vu_{\infty}$

Results and Discussion

Table 1 shows the various parameters that have been utilized to generate numerical simulations. At various temperatures, the coefficient of diffusion is analyzed for its behavior. Also, the influence of the varied diffusion coefficient on calcium concentration has been examined. Different endogenous buffers and external buffers, as well as the variable diffusion coefficient, are used to solve the equation in (14) The findings have been plotted on every conceivable graph type, and discussed.

Table 1: Numerical Values of Various Endogenous and Exogeneous Buffers

Ca^{2+} buffer	**k^+ $\mu M^{-1}s^{-1}$**	**k^- s^{-1}**	**K** μM	**$[B]_T$** μM
EGTA	1.5	0.3	0.2	113
BAPTA	600	100	0.1-0.7	95
Troponin-C	90-100	7-300	0.05-3 0	50(varied)
Calmodulin D_{28K}	100-500	37-470	0.2-2.0	32

Triponin C	39	20	0.51	70
Parvalbumin	6	1	0.00037	36

Observe Fig.1, EGTA is a slow buffer. For variable diffusion coefficient calcium profiles are traced. Higher is the diffusion coefficient falling in concentration is high. Concentration acquires its steady state $0.1\mu M$ at a position away from the source. Graphs are less sharp comparative to fast buffers like BAPTA. Now, observe the Fig. 2, BAPTA is fast buffer; it has sharp lines comparative to EGTA. Due to higher values of diffusion coefficient, concentrations fall sharply between $0-2\mu m$ and thereafter becomes uniform. Above graph includes calcium profiling with respect to variable diffusion coefficients. For higher values of diffusion coefficient, concentration reduces faster.\\

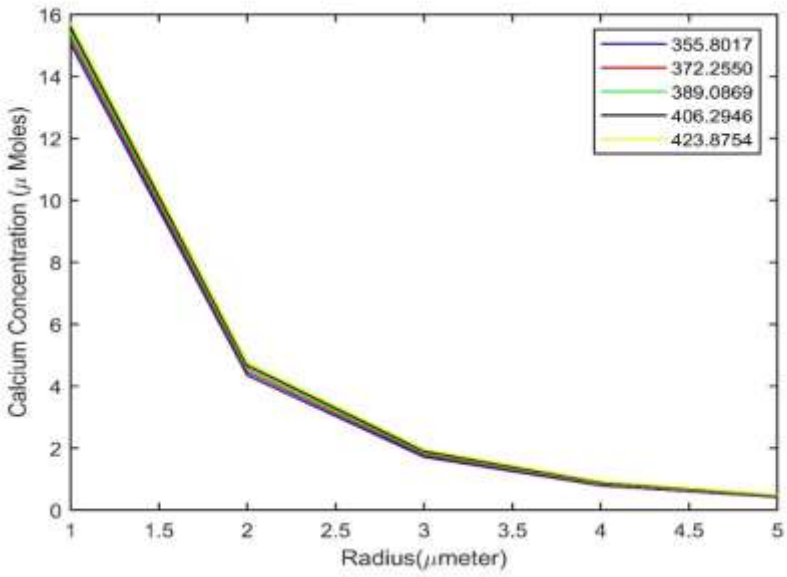

Fig. 1: Calcium concentration profile corresponding to position and fixed time t=1ms, for EGTA : $[B]_T = 113\mu M$, $k^+ = 1.5\mu M^{(-1)}s^{(-1)}$ $for\ \sigma = 1pA$; here diffusion coefficient is considered as variable term, for five different values of diffusion coefficient calcium profile is traced.

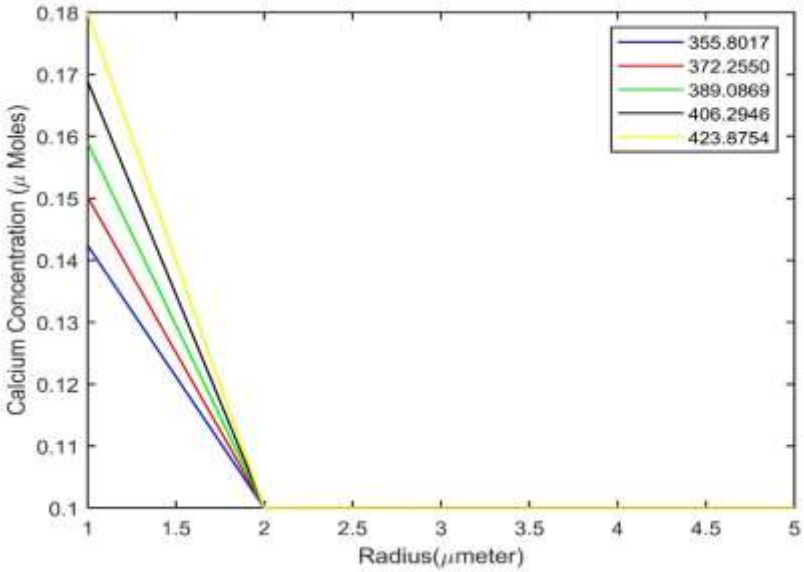

Fig. 2: Calcium concentration profile corresponding to the position and fixed time t=1ms, for BAPTA: $[B]_T = 95\mu M,\ k^+ = 600\mu M^{(-1)}s^{(-1)}\ for\ \sigma = 1pA$, here diffusion coefficient is considered as a variable term, for five different values of diffusion coefficient calcium profile is traced.

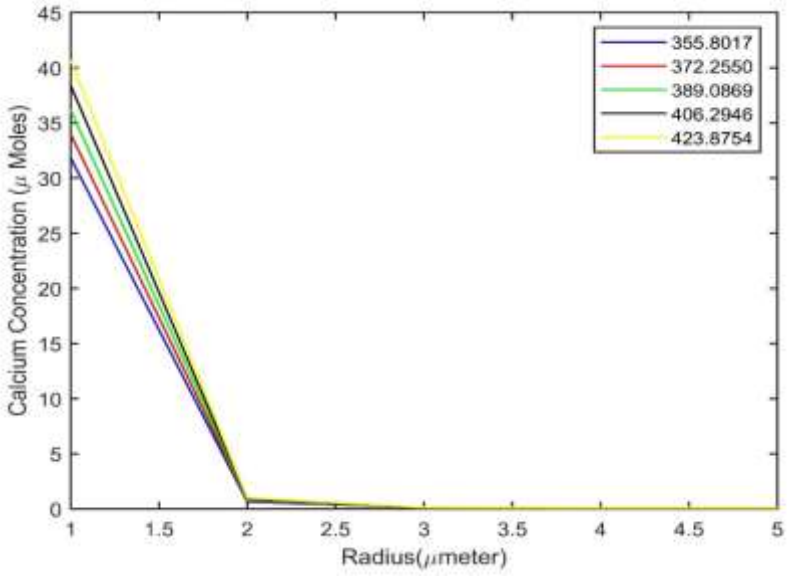

Fig. 3: Calcium concentration profile corresponding to position and fixed time $t=1ms$, for TROPONIN C : $[B]_T = 50\mu M,\ k^+ = 90\mu M^{(-1)}s^{(-1)}\ for\ \sigma = 1pA;$ here diffusion coefficient is considered as variable term, for five different values of diffusion coefficient calcium profile is traced.

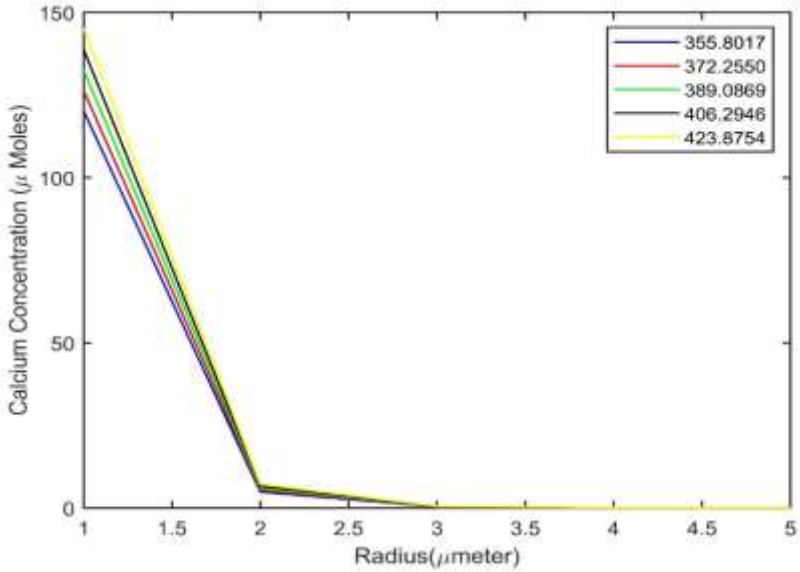

Fig. 4: Calcium concentration profile corresponding to the position and fixed time $t=1ms$, for TRIPONIN C : $[B]_T = 70\mu M$, $k^+ = 39\mu M^{(-1)}s^{(-1)}$ *for* $\sigma = 1pA$; here diffusion coefficient is considered as a variable term, for five different values of diffusion coefficient calcium profile is traced.

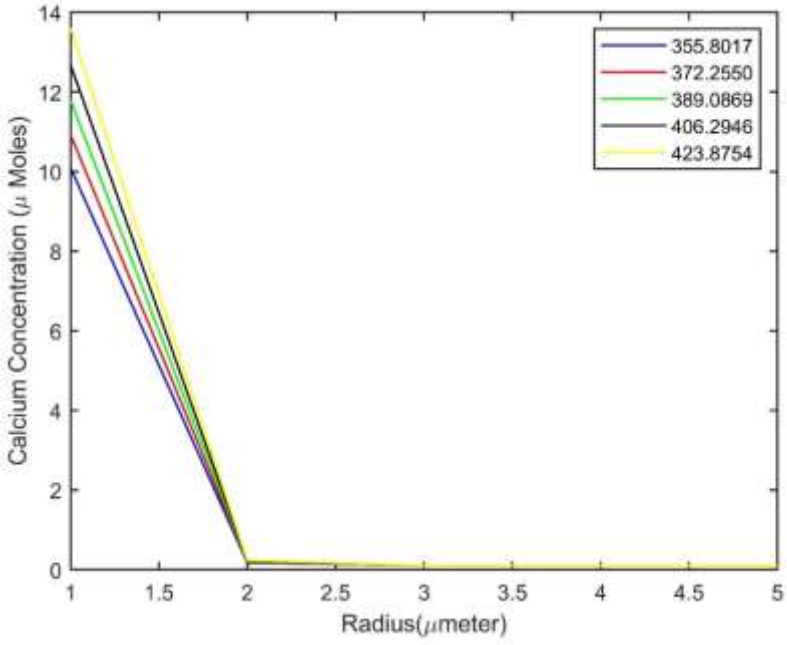

Fig. 5: Calcium concentration profile corresponding to position and fixed time $t=1ms$, for CALMODULIN D_{28K} :$[B]_T = 32\mu M$, $k^+ = 100\mu M^{-1}s^{-1}$ *for* $\sigma = 1pA$; here diffusion coefficient is considered as variable term, for four different values of diffusion coefficient calcium profile is traced

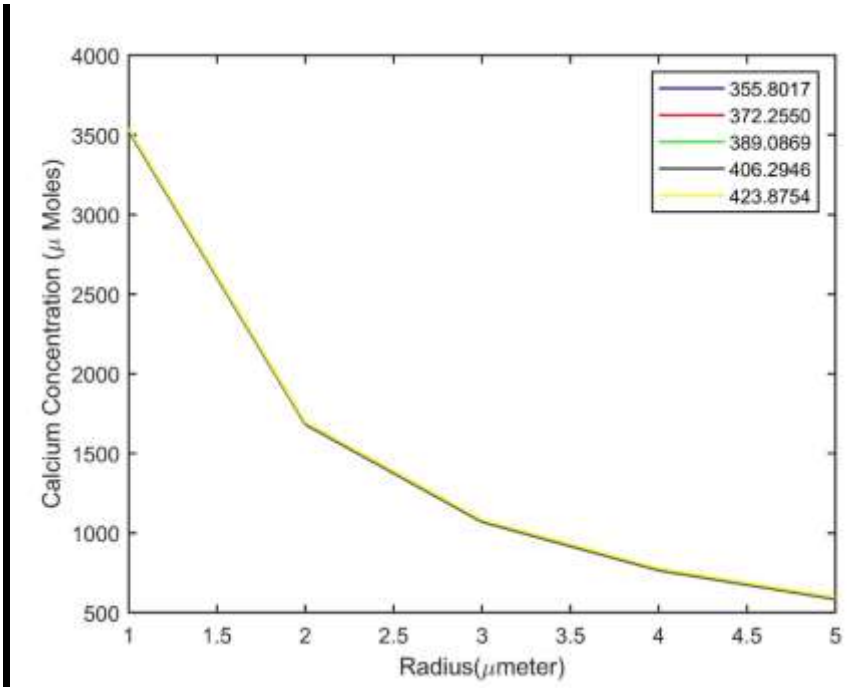

Fig 6: Calcium concentration profile corresponding to position and fixed time $t=1ms$, for PARVALBUMIN : $[B]_T = 36\mu M$, $k^+ = 6\mu M^{-1}s^{-1}$ *for* $\sigma = 1pA$; here diffusion coefficient is considered as variable term, for four different values of diffusion coefficient calcium profile is traced.

Fig.s 3, 4, 5 and 6 represents graphs for different endogenous buffers like Troponin C, Triponin C, Calmodulin D_{28k} and Pavalbumin. Here, also variable values of diffusion coefficients are considered to trace the profiling of calcium concentration with respect to distance (r). In all graphs, it is observed that for higher values of diffusion coefficient, concentration reduces faster. The concentrations fall sharply between $0-2\mu m$, then slowly decreases between $2-3\mu m$ and thereafter becomes uniform. Sharpness of fall in calcium concentration increases with increase in values of diffusion coefficients.

For all buffers either Endogenous or Exogenous, fall of concentration becomes sharp as diffusion coefficient increases. This indicates loss of functioning of cell subjected to hyperthermia. So, as temperature increases diffusion coefficient increases which affects the calcium profiling under different buffers.

Conclusion

Findings and references of this study aid in defining calcium profile variance in cancer cells. The finest calcium channels, pumps, and exchangers to target various cancer types are also being revealed by several scientific investigations. In this work, a mathematical model was used to profile the concentration of calcium in cancer cells as a result of therapy. Despite the fact that many scientists are interested in the possibilities of combined therapy, especially pharmacological inhibitors of a specific calcium channel and pump. Calcium signaling in the setting of the tumor microenvironment will surely speed up in the future. We show that the scientific facts of calcium profiling in neuronal region may be rationalized by mathematical modelling, and we present this work. Likewise, the impact of changes in viscosity, temperature, and diffusion coefficient on calcium signaling may provide light on a variety of biological facts.

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