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Numerical Approach for a Stable Solution of Fractional Order Calcium Diffusion Model

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Abstract— Diffusion is one of the main carrying phenomena which is seen in signaling mechanisms of ions and molecules in living cells, such as neurons. Here we present a one dimensional fractional diffusion model of calcium dynamics in cylindrical dendrites with Dirichlet boundary conditions. Based on shifted Grunwald- Letnikov definition of fractional derivatives, implicit finite difference scheme is used to approximate the solution. The numerical solutions are obtained by using MATLAB programme.

Keywords— *Fractional Fick's law, Fractional Differential equation, Grunwald- Letnikov Derivative, Finite Difference Method, Calcium Diffusion.*

I. INTRODUCTION

In the brain, hundreds of intracellular processes are known to depend on calcium flux; hence any significant variation in external calcium $[Ca^{2+}]$ is likely to generate important functional effects. A pre synaptic action potential has at least two properties on release of transmitter at nerve terminals: (1) Shortly after the action potential invades the terminal, the rate of transmitter discharge rises quickly to a climax for m sec, then drops back to very low levels in the another few milliseconds. (2) The discharge process is facilitated by the action potential; similarly a second action potential arriving after the first will discharge more transmitters. Recent experiments show that the pre synaptic influx of calcium through voltage- dependent channels are liable both for the phasic discharge of transmitter following a spike and for the facilitation of consequent spike- evoked discharge [1].

Calcium diffusion is explained in a form of passive transport by which substances cross membranes. Diffusion of calcium in the dendrite can be considered in two aspects. If Ca^{2+} fluxes are assumed to be uniform across the membrane of a cylindrical compartment, no longitudinal gradients will be treated inside the compartment. As a consequence only radial diffusion needs to be considered. This assumption holds for the case of back propagating action potentials. Fractional Fick's law is used to describe the diffusion between the shells of a cylinder, and number of shells varies with the diameter of the cylinder. This keeps the spatial resolution of diffusion equation continuous. These longitudinal concentration gradients between compartments are much smaller than radial gradients within the compartment; in the case of local calcium signals, it can be neglected. Therefore, if one assumes thin cylindrical dendrites in both the cases, one dimensional approach is sufficient. This model takes into account the diffusion under concentration gradient and voltage gradient and the appropriate fractional partial differential equation is solved by finite difference method.

The structure of this paper is as follows. The first section gives an introduction and second section explains necessary definitions and mathematical preliminaries of the fractional calculus. In section III, we present the fractional diffusion model, and appropriate fractional partial differential equations describing the variation with time of concentration of calcium. In section IV, finite difference method by shifted Grunwald - Letnikov fractional derivative is used to obtain the numerical results with the help of MATLAB .

II. PRELIMINARIES

In this section, it would be useful to introduce some definitions and properties of the fractional calculus theory.

Definition: Grunwald- Letnikov fractional derivative:

Given a function $C(t)$ defined on [a,T] and vanishing for $t < a$ the Grunwald - Letnikov fractional derivative can be written as

$$GLD^{\alpha}C(t) = \lim_{h\to 0}\frac{1}{h^{\alpha}}\sum_{k=0}^{\left[t-\frac{a}{h}\right]} \omega_k^{\alpha}\, C(t- \ kh), \quad \alpha > 0 \qquad (1)$$

where $\omega_k^{\alpha} = (-1)^k\binom{\alpha}{k} = (-1)^k\frac{\Gamma(\alpha+1)}{\Gamma(k+1)\Gamma(\alpha-k+1)}$ is called Grunwald - Letnikov coefficients.

Also according to [2], a shifted Grunwald- Letnikov formula is defined as

$$GLD^{\alpha}C(t) = \lim_{h\to 0}\frac{1}{h^{\alpha}}\sum_{k=0}^{\left[t-\frac{a}{h}+p\right]} \omega_k^{\alpha}\, C(t-kh), \quad \alpha > 0 \qquad (2)$$

III. FRACTIONAL DIFFUSION MODEL

The mathematical theory of diffusion in an isotropic environment is based on the Fractional Fick's law which relates the rate of transfer (or ion flux) $C(x,t)$ of a diffusing substance across a surface of unit area to the concentration under the assumption of steady state.

3.1. Fractional Fick's law

Generally, Fick's law is used in normal diffusion for dispersive flux based on empirical observations [3]

$$C(r,t) = -D\frac{\partial C}{\partial r} \qquad (3)$$

Where D is the diffusion coefficient. However, requiring separation of scales, it is not suitable for describing non local transport process. In order to study the diffusion, the fractional Fick's law has been proposed [4], where the gradient of the solute concentration in the empirical flux equation is replaced by a fractional order derivative:

$$C(r,t) = -D\frac{\partial^{1-\lambda}}{\partial t^{1-\lambda}}\left(\frac{\partial^{\alpha-1}C(r,t)}{\partial r^{\alpha-1}}\right) \qquad (4)$$

where $0 < \lambda \leq 1$, $1 < \lambda \leq 2$ and D is the diffusion coefficient $\frac{\partial^{1-\lambda}}{\partial^{1-\lambda}}$ *and* $\frac{\partial^{\alpha}}{\partial r^{\alpha}}$, are Riemann- Liouville operators which are defined as follows.

$$\frac{\partial^{1-\lambda}C(r,t)}{\partial t^{1-\lambda}} = \frac{1}{\Gamma(\lambda)}\frac{\partial}{\partial t}\int_0^t \frac{C(r,\tau)}{(t-\tau)^{1-\lambda}}\,d\tau \qquad (5)$$

$$\frac{\partial^{\alpha}C(r,t)}{\partial r^{\alpha}} = \frac{1}{\Gamma(2-\alpha)}\frac{\partial^2}{\partial r^2}\int_0^r \frac{C(\tau,t)}{(r-\tau)^{\alpha-1}}\,d\tau \qquad (6)$$

where $0 < \lambda \leq 1$, $1 < \lambda \leq 2$.When $\lambda = 1$, $\alpha = 2$, it gives the classical Fick's law. When $\alpha = 2$ it gives time fractional Fick's law, when $\lambda = 1$ it gives space fractional Fick's law.

3.2 .Fractional order Calcium Diffusion Model

Since the flux goes from regions of high concentration to low concentration with a magnitude that is proportional to the concentration gradient (spatial derivative), in spatial dimension, the law is

$$C(x,t) = -D\frac{\partial C(x,t)}{\partial x} \qquad (7)$$

where D is the diffusion coefficient.

Considering the cylindrical compartment fig 1) where the concentration varies along the x dimension, if the concentrations inside of the compartment centered at x and boundaries $x \pm\Delta\, x$ varies by $\frac{\partial C}{\partial t}$.

$$Change\ in\ number\ of\ ions = \frac{\Delta x\pi d^2}{2}\frac{\partial C(x,t)}{\partial t} \qquad (8)$$

$$S(x-\Delta x,t)\ S(x+\Delta x,t)$$

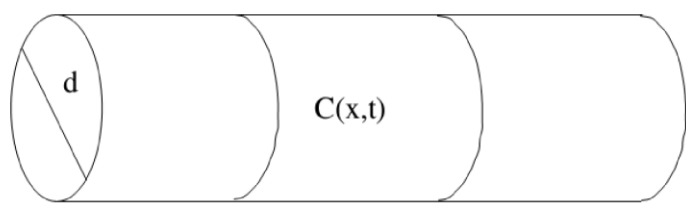

Figure 1: Schematic diagram of a cylindrical compartment of a neuron

This change should be identically equal to the net rate of transfer across one boundary minus the rate of transfer across the other.

Net rate of transfer=

$$\frac{\pi d^2}{2}(C(x-\Delta\, x,t) - C(x+\Delta\, x,t) \qquad (9)$$

Using the concept that the influx and efflux from both sides of the compartments are equal and using Fick's law we get the diffusion equation as

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2} \qquad (10)$$

Now, according to [5] the flux equation can be expressed as in the following time fractional derivative form:

$$\frac{\partial^\alpha C(x,t)}{\partial t^\alpha} = D\frac{\partial^2 C(x,t)}{\partial x^2} \quad \text{for } 0 < x < L \text{ and } t > 0 \quad (11)$$

With boundary conditions

$$C(0,t) = 0, \quad C(1,t) = 0, \qquad \text{for } t > 0 \quad (12)$$

$$C(x,0) = 1 - x^2 \qquad \text{for } 0 \le x \le L \quad (13)$$

IV. THE IMPLICIT FINITE DIFFERRENCE SCHEME FOR TIME FRACTIONAL CALCIUM DIFFUSION MODEL

For the numerical solution of the problem above, we introduce a uniform grid of mesh points (x_m, t_p) with $x_m = mh, m = 0,\ 1,\ 2 \ldots X, t_p = kp, k = 0,\ 1,\ 2 \ldots Y$ where X and Y are two positive integers, $h = \frac{L}{X}$ and $t = \frac{T}{Y}$ are the uniform spatial and temporal mesh size respectively. Then the solution of the point (x_m, t_p) is denoted by $C_{m,p}$.

Let $m-1,\ m,\ m+1$ and and $p-2,\ p-1,\ p$ be the three points in the spatial and time dimension. Then by [5] the solution of the fractional derivative of calcium concentration by time based on Grunwald Letnikov definition is

$$\frac{\partial^\alpha C}{\partial t^\alpha} = \frac{\sum_{j=0}^{N} bc_j C_{m,p-j}}{\Delta t^\alpha} \quad (14)$$

By using the principle of "short memory" where L is the length memory [6], h is the time step and value of N shall be determined by the following relation

$$N = \min\left(\frac{t}{h}, \frac{L}{h}\right)$$

For the calculation of the binomial coefficients bc_j we can use the relation

$$bc_0 = 1, bc_j = \left(1 - \frac{1+\alpha}{j}.bc_{j-1}\right), for\ j \ge 1 \quad (15)$$

Now,

$$\frac{\partial^2 C(m,p)}{\partial x^2} = \frac{C_{m+1,p} - 2C_{m,p} + C_{m-1,p}}{(\Delta x)^2} \quad (16)$$

Applying equations (14) and (16) in equation(11) we get

$$\frac{\sum_{j=0}^{N} bc_j C_{m,p-j}}{\Delta t^\alpha} = D.\frac{C_{m+1,p} - 2C_{m,p} + C_{m-1,p}}{(\Delta x)^2} \quad (17)$$

$$i.e.$$

$$\sum_{j=0}^{N} b\,c_j C_{m,p-j} = \frac{D.\Delta t^\alpha}{(\Delta x)^2}\left[C_{m+1,p} - 2C_{m,p} + C_{m-1,p}\right] \quad (18)$$

$$bc_0 C_{m,p} + \sum_{j=1}^{N} b\,c_j C_{m,p-j} = M\left[C_{m+1,p} - 2C_{m,p} + C_{m-1,p}\right] \quad (19)$$

Where $M = \frac{D\Delta t^\alpha}{(\Delta x)^2}$.

Then the above equation can be re- written as

$$(1+2M)C_{m,p} - MC_{m-1,p} - MC_{m+1,p} = -\sum_{j=1}^{N} b\,c_j C_{m,p-j} \quad (20)$$

4.1 Remark

According to Meerschaert. M. M. and Tadjeran C [7] the implicit finite difference solution to (7) with $1 < \alpha < 2$ on the finite domain $0 \le x \le L$, with Dirichlet boundary conditions for all $t \ge 0$, based on the shifted Grunwald approximation

$$\frac{\partial C(x,t)}{\partial x^\alpha} = \frac{1}{\Gamma(-\alpha)} \lim_{M\to\infty} \frac{1}{h^\alpha} \sum_{k=0}^{M} \frac{\Gamma(k-\alpha)}{\Gamma(k+1)C(x-(k-1)\square,t)} \quad (21)$$

Where $h = x/M$, is consistent and unconditionally stable.

V. NUMERICAL SIMULATIONS

The reaction diffusion equations (11- 13) were solved numerically using MATLAB. The fractional partial differential equations were solved using the implicit finite difference method. Space and time discretization were set to $D = 400\mu m$, $\Delta x = 0.025\mu m$ and $\Delta t = 0.001ms$ respectively. After synaptic inputs calcium remains restricted to a domain of $2.5\mu m$ to each side of the input location independent of the input frequency. The graphs show the concentration of calcium for $0 < x < L$ and $0 < t < T$ for the fractional order 1.75.

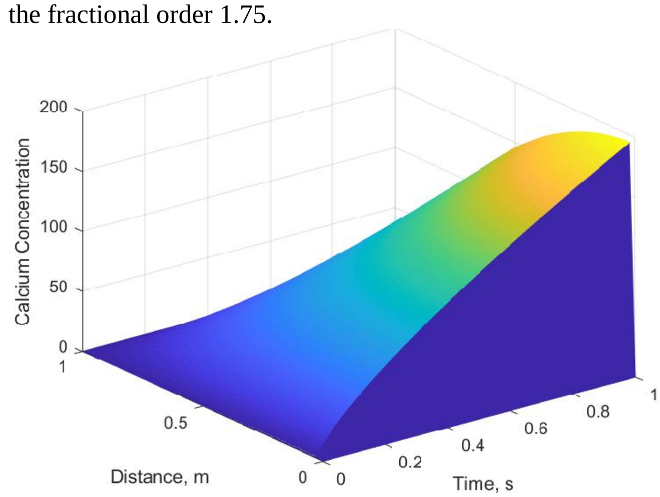

Figure 2: Concentration of calcium for = 1.75 , $D = 400\mu m$ and $L = 1$

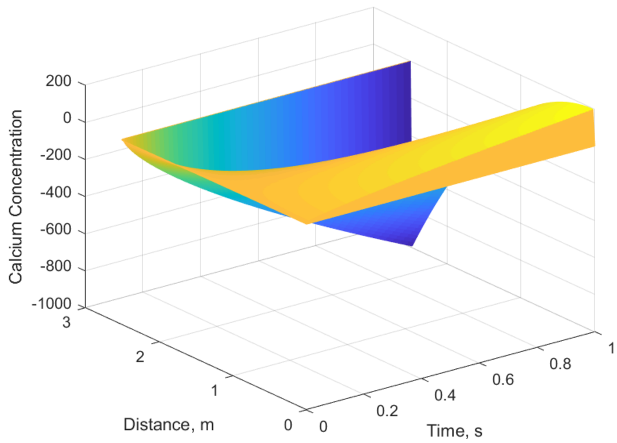

Figure 3: Concentration of calcium for $= 1.75$, $D = 400\mu m$ *and* $L = 2.5$

VI. CONCLUSION

By using Fick's law, a reduced Fractional Diffusion Calcium Model of presynaptic neuron is constructed. From the obtained graphs, we find that calcium spread in dendrites is limited to small micro domains of the order of a few microns $(< 5\mu m)$ .The result is validated through the experimental data given by Biess A, Korkotian E and Holcman D [8]. The method, implicit finite difference scheme, is easy to implement and it also acts as an effective tool to measure changes in presynaptic calcium affecting transmitter release with the desired accuracy, low run time and a minimal number of data points in the required domain.

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