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MATHEMATICAL MODELING AND ANALYSIS OF DYNAMICS OF CYTOSOLIC CALCIUM ION IN ASTROCYTES USING FRACTIONAL CALCULUS

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Abstract. Astrocytes actively participate in calcium signaling in nervous system. Calcium signalling depends on cytosolic calcium concentration. Calcium itself is called second messenger. Calcium ions diffuse into the cell due to concentration difference between synapse and cytosol. This process occurs in almost all type of nerve cells. Due to presence of aqua medium and verity of proteins the cross flow of calcium ion takes place using Fick's law of diffusion. In this paper we have studied the concentration profile of Ca^{2+} using fractional calculus. The advantage of using fractional calculus is that next state of the system depends not only upon the current state but also upon all its preceding states. A mathematical model is developed to study the effect of fractional advection diffusion equation (cross flow) for the calcium profile. Analytic solution of the fractional advection diffusion equation, arising in study of diffusion of cytosolic calcium in astrocytes, has been obtained by using integral transform techniques.

1. Introduction

Fractional calculus (FC) is a mathematical approach dealing with derivatives and integrals of arbitrary and complex orders. Therefore, it adds a new dimension to understand and describe basic nature and behavior of complex systems in an improved way. Many applications of fractional calculus can be found in turbulence and fluid dynamics, stochastic dynamical system, plasma physics and controlled thermonuclear fusion, nonlinear control theory, non linear biological system, astro physics, etc. Mathematical models, using ordinary differential equations with integer order, have been proven valuable in understanding the dynamics of physical systems. [27, 6, 7, 5, 22, 16, 30]. The modeling of these systems by fractional order differential equations has more advantages than classical integer-order mathematical modeling. The most important advantage of using fractional order differential equation in mathematical modeling is their non-local property. It is a well-known fact that the integer order differential operator is a local operator whereas the fractional order differential operator is non-local in the sense that the next state of the

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system depends not only upon its current state but also upon all of its proceeding states [26]. Fractional differentiation are generalizations of notions of integer-order differentiation, and include n-th derivatives (n denotes an integer number) as particular cases. Because of this, it would be ideal to have such physical and geometric interpretations of fractional-order operators, which will provide also a link to known classical interpretations of integer-order differentiation and integration. We will derive a new class of generalized models for such physical systems.

Fractional (non-integer order) calculus can provide a concise model for the description of the dynamic events that occur in biological tissues. Such a description is important for gaining an understanding of the underlying multi-scale processes that occur when, for example, tissues are electrically stimulated or mechanically stressed. Fractional calculus also can be apply to build mathematical models in bio-electrodes, bio-mechanics and bio-imaging (Magin [23]). Fractional calculus has recently found applications in the analysis of biological systems. Djordjevic *et al.* [8] developed a rheological model of airway smooth muscle cells using a method incorporating FC and a least-squares data fitting technique. They showed that fractional calculus could be effectively utilized to account for a weak power law frequency dependence of cell rheological behavior. This effect could not be explained with traditional viscoelastic theory. Recently, an FC dynamic model has been applied to generate electrocardiogram (ECG) signals based upon oscillations and a global optimization scheme. This technique subsequently generates a realistic time series, of the ECG signal, and may find potential applications in modeling abnormal and irregular patterns of cardiac conduction (Das and Moharatna [24]). These new models are more adequate than the previously used integer order models, because fractional order derivatives and integrals describe the memory and hereditary properties of different substances. This is the most significant advantage of the fractional order models in comparison with integer order models in which such effects are neglected.

Astrocytes actively participate in calcium signalling in nervous system. Calcium signalling depends on cytosolic calcium concentration. Calcium Ca^{2+} is an important second messenger, found in almost all cell types. Many theoretical and experimental studies investigated the main characteristics of local Ca^{2+} changes and their possible role in different physiological events. It is used in signal transduction where an electrical signal is converted in the chemical signal. Calcium signals can also mediate inter-cellular communication by eliciting or coordinating calcium signals in surrounding cells, for example in the astrocyte networks of the central nervous system (see for e.g., [18, 11]). Calcium Ca^{2+} oscillations are ubiquitous signals present in all cells that provide efficient means to transmit intracellular biological information. Either spontaneously or upon receptor ligand binding, the otherwise stable cytosolic Ca^{2+} concentration starts to oscillate.
Woods *et al.* [13] discovered the calcium oscillations experimentally in 1986 and large numbers of cells showed calcium oscillations after simulation by an extracellular agonist. Later, the role in calcium signaling by inositol triphosphate was discovered by Berridge [15] from studies of the control fluid secretion by an insect salivary gland. Kummer *et al.* [29] proposed fractional-order Ca^{2+} oscillation model. This mathematical model consists of the four variables as follows: cytosolic

Ca^{2+}, endoplasmic Ca^{2+}, concentrations of active subunits of a G protein, and active PLC (Kummer *et al.* [29]). The model shows good agreement with experimental observations in two respects. First, each oscillation period starts with a large, steep spike followed by a number of pulses of decreasing amplitude around an elevated mean value. Second, varying the model parameters, one finds that the difference in stimulation nature can induce (periodic or aperiodic) bursting or regular oscillations.

Choi [28] studied stochastic hybrid modeling of intracellular calcium dynamics using advection diffusion equation. Schäfer [12] gave a memory-efficient finite volume method for advection-diffusion-reaction systems with non-smooth Sources which is useful for the long time simulation of calcium ion in heart cells and show its parallel scaling. The release of calcium ions in a human heart cell is modeled by a system of reaction-diffusion equations, which describe the interaction of the chemical species and the effects of various cell processes on them. The release is modeled by a forcing term in the calcium equation that involves a superposition of many Dirac delta functions in space; such a non smooth right-hand side leads to divergence for many numerical methods. Hanhart *et al.* [14] studied a memory-efficient finite element method for systems of reaction-diffusion equations with non-smooth forcing. Recently, Agarwal et al. [19] investigated the solutions of generalized space time fractional reaction diffusion equation associated with Hilfer-Prabhakar time fractional derivative and the space fractional Laplacian operator.

The Signalling problem, considered in the domain $x, t \geq 0$, is an initial boundary-value problem (IBVP) when the data are assigned both at $t = 0+$ on the semi-infinite space axis $x > 0$ (initial data) and at $x = 0+$ on the semi-infinite time axis $t > 0$ (boundary data); here, the initial data are assumed to be vanishing (see, for details, Mainardi).

Jha *et al.* [3] found analytic solution of two dimensional advection diffusion equation arising in cytosolic calcium concentration distribution. Jha *et al.* [4] studied effect of voltage-gated calcium channel on cytosolic calcium concentration in astrocytes. Tripathi and Adlakha [1] obtained closed form solution to problem of calcium diffusion in cylindrical shaped neuron cell in terms of modified Bessel function. In physics, fractional derivatives are used to model anomalous diffusion, where the particles spreads differently than the classical Brownian motion model predicts. The fractional order forms of the advection diffusion equation are similarly useful. The mathematical formulation of calcium diffusion in astrocytes yields an initial boundary value problem.
The motive of this paper is to identify the effect of fractional advection and diffusion on cytosolic calcium profile in absence of internal forces. Graphs for the calcium concentration profiles have been simulated for certain values of the parameters.

2. Mathematics Prerequisites

The right-sided Riemann-Liouville fractional integral of order α of function $f(t) \in L_1(a,b)$ (Samko *et. al* [25]) is defined as:

$$I_a^{\alpha}(f(t)) = {}_aD_t{}^{-\alpha}(f(t)) = \frac{1}{\Gamma(\alpha)} \int_a^t (t-\tau)^{\alpha-1} f(\tau)\, d\tau,\ (t > a) \tag{1}$$

where $\Re(\alpha) > 0$.
The right-sided Riemann-Liouville fractional derivative of order α for $f(x) \in AC([a,b])$ can be defined as:

$${}_aD_t^{\alpha}(f(t)) = \left(\frac{d}{dt}\right)^n (I_a^{n-\alpha} f(t))\ \ (\Re(\alpha) > 0, n = [\Re(\alpha)] + 1), \tag{2}$$

where $[y]$ represents the integral part of the number y.
The following fractional derivative of order $\Re(\alpha) > 0$ is introduced by Caputo [10] as

$${}_a^C D_t^{\alpha}(f(t)) = \begin{cases} \dfrac{1}{\Gamma(m-\alpha)} \int_a^t \dfrac{f^m(\tau)}{(t-\tau)^{\alpha+1-m}}\, d\tau, & m-1 < \alpha \le m, \Re(\alpha) > 0, m \in N \\ \dfrac{\partial^m}{\partial t^m} f(t), & \text{if } \alpha = m \end{cases} \tag{3}$$

where $f^m(\tau) = \frac{\partial^m}{\partial t^m} f(t)$ is the m-th derivative of the function $f(t)$ with respect to t.
The Laplace transform (see, e.g. Sneddon [9]) of function $f(t)$ with respect to variable t is defined as

$$L\{f(t)\} = \bar{f}(s) = \int_0^{\infty} e^{-st} f(t)\, dt, \quad (\Re(s) > 0, t > 0) \tag{4}$$

The inverse Laplace transform of function $\bar{f}(s)$ defined using Bromwich's integral as

$$L^{-1}\{\bar{f}(s)\} = f(t) = \frac{1}{2\pi i} \int_{\gamma-i\infty}^{\gamma+i\infty} e^{st} \bar{f}(s)\, ds \tag{5}$$

where γ being a fixed real number.

The Laplace transform of the Caputo fractional derivative is given by Podlubny [10]

$$\int_0^{\infty} e^{-st} {}_a^C D_t^{\alpha}(f(t)) dt = s^{\alpha} f(s) - \sum_{j=0}^{n-1} s^{\alpha-j-1} f(0)^j(0)\ \ (n-1 < \alpha < n) \tag{6}$$

Following inversion formula (Povstenko [31, P.4128, Eq. 53]) is required for simplification:

$$L^{-1}\left\{s^{-\beta} \exp(-\lambda s^{\gamma})\right\} = t^{\beta-1} W(-\gamma, \beta; -\lambda t^{-\gamma}) \quad 0 < \gamma < 1, \lambda > 0 \tag{7}$$

Here $W(\alpha, \beta; z)$ is the Wright function (Podlubny [10]) defined by series representation

$$W(\alpha, \beta; z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + \beta) k!} \tag{8}$$

The relationship between the Wright function and the exponential function is given by [21, Eq.27]

$$W\left(-\frac{1}{2},\frac{1}{2};z\right)=\frac{1}{\sqrt{\pi}}e^{z^{2/4}} \tag{9}$$

3. Mathematical Modeling of Time Fractional Advection-Diffusion Equation

Here we consider a chemical species (free calcium ion) Ca^{2+} whose concentration $C(x,t)$ varies in time and space, the spatial variation is considered in one spatial variable x only [18, 11]. This situation is shown in Figure 1, where the chemical species Ca^{2+} is contained in a long, thin tube with constant cross-sectional area A. The conservation of Ca^{2+} can be expressed in words as:

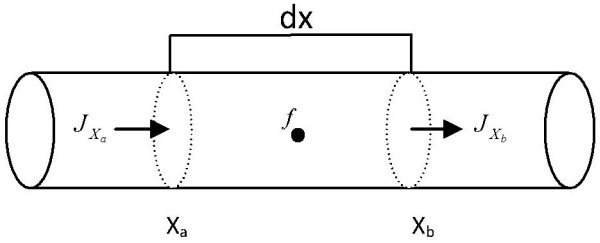

Figure 1. Mass transfer in domain

Rate of change of the total amount of Ca^{2+} within R w. r. t time
= Rate at which Ca^{2+} flows in to R − rate at which Ca^{2+} flows out of R
+ Rate at which Ca^{2+} is generated within R − Rate at which Ca^{2+} is consumed with in R.

The theoretical analysis follow from the derivation of the following conservation law in differential form [11]

$$\frac{\partial C(x,t)}{\partial t}-\frac{\partial J(x,t)}{\partial x}=f(x,t,C) \tag{10}$$

Here $C(x,t)$ is the concentration of Ca^{2+}, $J(x,t)$ is the rate at which Ca^{2+} moves across the boundary at position x from left to right at time t, $f(x,t,C)$ denote the net rate of increase of Ca^{2+} (production-destruction) per unit volume at location x and time t. Here it is supposed that there is a uniform macroscopic flow of the Ca^{2+}, with speed v along the x-axis, which carries additional Ca^{2+} along with it. When both diffusive flux and advective flux is incorporated, then the total flux will be

$$J(x,t)=vC(x,t)-D\frac{\partial C(x,t)}{\partial x} \tag{11}$$

where the proportionality constant D is called the diffusion constant.
Using this constitutive relation is called Fick's law, and states that Ca^{2+} moves from regions of high concentration to regions of low concentration, at a rate proportional

to the concentration gradient. The eq. (10) becomes a reaction advection diffusion equation,

$$\frac{\partial C(x,t)}{\partial t} - \frac{\partial (vC(x,t))}{\partial x} - D\frac{\partial C(x,t)}{\partial x} = f(x,t,C) \tag{12}$$

Therefore the *homogeneous* advection diffusion equation for one dimensional case in Cartesian coordinates is given by:

$$\frac{\partial C(x,t)}{\partial t} + \frac{\partial (uC(x,t))}{\partial x} = D_{ca}\frac{\partial^2 C(x,t)}{\partial x^2} \tag{13}$$

Initial and boundary conditions are given by:

$$\lim_{x\to 0}\left(D_{ca}\frac{dC(x,t)}{dx}\right) = \sigma_{ca} \quad \text{for} \qquad t > 0, \tag{14}$$

$$\lim_{x\to\infty} C(x,t) = 0 \quad \text{for} \qquad\qquad t \geq 0, \tag{15}$$

$$C(x,t)|_{t=0} = 0 \quad \text{for} \qquad\qquad 0 \leq x < \infty. \tag{16}$$

For one-dimension advection diffusion problem we consider without pipe flow of the calcium. The injected tracer calcium spreads equally in both direction describing Gaussian distribution over the time. If calcium is allowed to flow in a pipe then we expect the center of mass of the tracer cloud to move with mean flow velocity in the pipe. If we move our frame of reference with mean velocity and assume inviscid case, then our coordinate transformation for the moving system will be:

$$\eta = x - (x_0 + ut), \tag{17}$$

$$\tau = t, \tag{18}$$

where η is moving reference frame spatial coordinate. For the sake of convenience, we assume origin as the mouth of calcium channel in cytosol (plasma-membrane) i.e. $x_0 = 0$ is the injector point of tracer. u is mean velocity of flow of Ca^{2+} and ut is distance traveled by the center of mass of cloud at time t.
This coordinate transform (17) and (18) can be substituted in (13) using chain rule as follows:

$$\frac{\partial C}{\partial \tau}\frac{\partial \tau}{\partial t} + \frac{\partial C}{\partial \eta}\frac{\partial \eta}{\partial t} + u\left(\frac{\partial C}{\partial \tau}\frac{\partial \tau}{\partial x} + \frac{\partial C}{\partial \eta}\frac{\partial \eta}{\partial x}\right) \tag{19}$$

$$= D_{ca}\left(\frac{\partial}{\partial \tau}\frac{\partial \tau}{\partial x} + \frac{\partial}{\partial \eta}\frac{\partial \eta}{\partial x}\right)\left(\frac{\partial C}{\partial \tau}\frac{\partial \tau}{\partial x} + \frac{\partial C}{\partial \eta}\frac{\partial \eta}{\partial x}\right), \tag{20}$$

which reduces to

$$\frac{\partial C(\eta,\tau)}{\partial \tau} = D_{ca}\frac{\partial^2 C(\eta,\tau)}{\partial \eta^2}, \tag{21}$$

subject to the initial and boundary conditions:

$$\lim_{\eta\to 0}\left(D_{ca}\frac{\partial C(\eta,\tau)}{\partial \eta}\right) = \sigma_{ca} \qquad \tau \geq 0, \tag{22}$$

$$\lim_{\eta\to\infty} C(\eta,\tau) = C_\infty \quad \tau \geq 0 \tag{23}$$

and

$$C(\eta,\tau)_{\tau=0} = C_\infty \qquad 0 \leq \eta < \infty. \tag{24}$$

Note that the standard version of advection-diffusion equation does not allow for predicting the the concentration on cytosolic calcium profile in absence of internal force accurately. It is then important to investigate a possible analytical partial differential equation that can describe better this problem.

In present work, we consider a new model in the form of fractional partial differential equation

$$ {}_a^C D_t^\alpha C(\eta,\tau) = D_{ca}\frac{\partial^2 C(\eta,\tau)}{\partial \eta^2}, \quad 0<\alpha\leq 1, \;\; \tau\geq 0, \;\; \eta\geq 0 \tag{25}$$

where ${}_a^C D_t^\alpha$ is Caputo derivative given in (3). The relevant initial and boundary conditions are as follows:

$$\lim_{\eta\to 0}\left(D_{ca}\frac{\partial C(\eta,\tau)}{\partial \eta}\right) = \sigma_{ca}, \qquad \tau\geq 0, \tag{26}$$

$$\lim_{\eta\to\infty} C(\eta,\tau) = C_\infty \quad \tau\geq 0 \tag{27}$$

and

$$C(\eta,\tau)_{\tau=0} = C_0 \qquad 0\leq \eta<\infty. \tag{28}$$

Here C_∞ is calcium concentration at infinity. We assume that at initial state of time and at a long distance calcium concentration vanishes or becomes zero. The integro-differential equation does contain the additional parameter α, which can be viewed as new physical parameters that characterize the cytosolic calcium ion in astrocytes. If we consider $\alpha = 1$ then equation (25) reduces to the classical heat equation (21).

Remarks: 1. The Riemann-Liouville definition (1) could lead to unphysical results when applied to simulate dynamics of cytosolic calcium ion. To overcome this problem, a modified method is presented to define the fractional diffusion with the Caputo derivatives (3).

2. The fractional derivatives are considered in Caputo sense. Many numerical solutions of the fractional advection diffusion equation were derived from a fractional derivative based on the Riemann-Liouville or the Grünwald-Letnikov definitions. Podlubny [10], Gorenflo et al. [20], and Butzer and Westphal [17] have pointed out that the Caputo fractional derivative represents a short of regularization in the time origin for the Riemann-Liouville fractional derivative and satisfies the requirements of being zero when applied to a constant. Besides, the Caputo definition does not use the fractional order derivative in the initial condition, thus is convenient in physical and engineering applications where the initial conditions are usually given in terms of the integer-order derivatives.

4. Solution of the Problem

Applying Laplace transform (6) for $n = 1$ to (25), yields

$$s^\alpha \bar{C}(\eta,s) - s^{\alpha-1}C(\eta,0) = D_{ca}\frac{\partial^2}{\partial\eta^2}\bar{C}(\eta,s). \tag{29}$$

Using the initial condition $C(\eta,0)=0$ in (29), we get

$$\frac{\partial^2}{\partial\eta^2}\bar{C}(\eta,s)-\frac{s^\alpha}{D_{ca}}\bar{C}(\eta,s)=0. \tag{30}$$

Applying Laplace transform on the boundary conditions, (26) and (27) we get:

$$\frac{\partial}{\partial\eta}\bar{C}(0,s)=\frac{\sigma_{ca}}{D_{ca}s^\alpha}, \tag{31}$$

$$\lim_{n\to\infty}\bar{C}(\eta,s)=0. \tag{32}$$

The solution of equation (30) is given by:

$$\bar{C}(\eta,s)=C_1e^{\sqrt{s^\alpha/D_{ca}}\eta}+C_2e^{-\sqrt{s^\alpha/D_{ca}}\eta}. \tag{33}$$

The C_1 and C_2 are obtained by using the relations (31) and (32) as given below:

$$C_1=0 \quad \text{and} \quad C_2=\frac{\sigma_{ca}}{\sqrt{D_{ca}}}\frac{1}{s^{\alpha/2}} \tag{34}$$

and hence (33) becomes

$$\bar{C}(\eta,s)=\frac{\sigma_{ca}}{\sqrt{D_{ca}}}\frac{1}{s^{\alpha/2}}e^{-\sqrt{s^\alpha/D_{ca}}\eta}. \tag{35}$$

Taking inverse Laplace transform of equation (35) and using eq. (7) therein, we get

$$C(\eta,\tau)=\frac{\sigma_{ca}}{\sqrt{4D_{ca}}}\tau^{\frac{\alpha}{2}-1}W\left[-\frac{\alpha}{2},\frac{\alpha}{2};-\frac{\eta}{\sqrt{D_{ca}}}\tau^{-\frac{\alpha}{2}}\right]. \tag{36}$$

Transforming variables back to original variables using (17) and (18) in equation (36), we get

$$C(x,t)=\frac{\sigma_{ca}}{\sqrt{4D_{ca}}}t^{\frac{\alpha}{2}-1}W\left[-\frac{\alpha}{2},\frac{\alpha}{2};-\frac{(x-ut)}{\sqrt{D_{ca}}}t^{-\frac{\alpha}{2}}\right]. \tag{37}$$

In particular, with the help of (9), for $\alpha=1$ (37) reduces to the following result obtained by Jha et al. [3].

$$C(x,t)=\frac{\sigma_{ca}}{\sqrt{4D_{ca}\pi t}}exp\left[-\frac{(x-ut)^2}{4D_{ca}t}\right]. \tag{38}$$

5. Result and Discussion

From the past observations [3, 2, 4] the range for the numerical values of bio-physical parameters used for computation of results, are given below in Table 1.

Table 1

Symbol	**Parameter**	**Values**
D_{ca}	Diffusion Coefficient	200-300 $\mu m^2/s$
σ_{ca}	Source Amplitude	1.5 $\mu M^{-1}s^{-1}$
u	Velocity of Flux	10-40 $\mu m/s$

The solution (37) represents the variation in calcium concentration due to time fractional advection diffusion in cytosol, which represent the calcium concentration at distance x in the positive direction from mouth of the channel for any time $t>0$.

The solution is in the form of Wright function given by eq. (8), which is generalization of exponential function.

The concentration profile simulated with the values $D_{ca} = 225\mu m^2/s$, $\sigma_{ca} = 1.5\mu M^{-1}s^{-1}$, $u = 25\mu m/s$ and for the different values of α $(0 < \alpha \leq 1)$ as shown in Figures 2 and 3 below

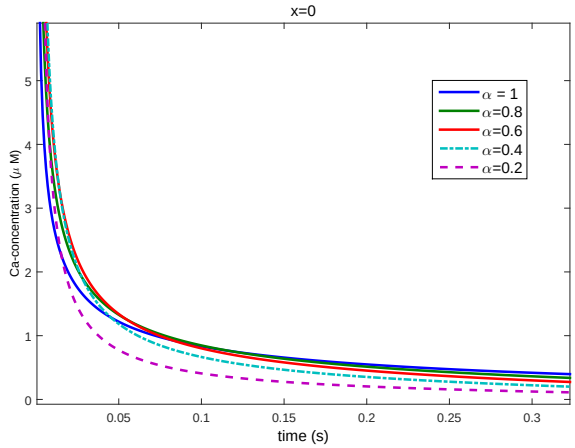

FIGURE 2. Calcium distribution in cytosol with respect to time at the source $x = 0$ for different values of α.

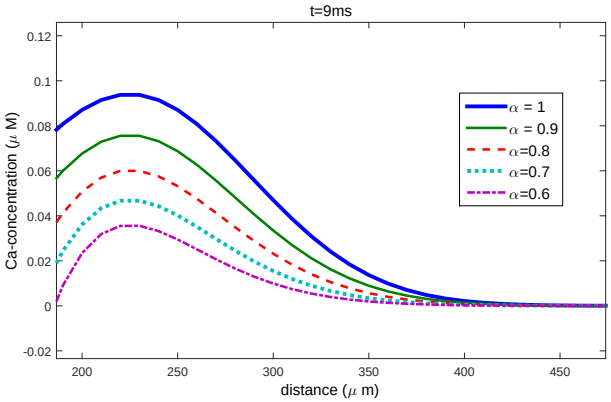

FIGURE 3. Calcium distribution in cytosol along x direction specified point of $t = 9$ms for different values of α.

Figure 2 shows the variation at different values of α in calcium concentration near the source $x = 0$ with respect to time. It is observed that the calcium concentration is high initially at the mouth of the channel then it falls sharply and there after it achieves steady state.

Figure 3 shows the calcium distribution at different values of α along X- direction at the time $t = 9$ms. Here calcium concentration Ca^{2+} decreases and tend to $0.1\mu M$ for $x > 400\mu$m which is independent of α.

To access the effect of the fractional order derivative into the solution of the advection-diffusion equation, we compare both solutions (37) and (38) with the theoretical values. We note that the solution of the model, with various values of α, continuously depends on the time-fractional derivative but achieves steady state. We should also note that although the steady state points are very near for both integer-order and fractional-order models, the solution of the fractional order model tends to the steady state over a longer period of time. From the graphs, we can see that fractional order differential equations have rich dynamics and are better descriptors of physical systems than traditional integer-order mode.
The solutions of fractional advection diffusion are not only function of time and space but also a function of the order of the derivative. If these orders are integer, we recover the standard advection diffusion equation. Figures show that the order of the derivative can be used to simulate the real-world problem and this makes the fractional version of advection diffusion equation better than the advection diffusion equation.

6. Conclusion

The mathematical modeling plays very important role for signal transduction in astrocytes. Fractional advection diffusion is new invention in mathematical model for astrocytes cell. Efficient model can be developed further to study the relationship among various biophysical parameters like buffers, pumps, leaks, gates, source in flux, diffusion, coefficients etc and the effect of fractional advection diffusion on calcium distribution in presence of internal process.

Formally, fractional diffusion equations are obtained from their ordinary counterparts by replacing the first order time derivatives, by derivatives of fractional order with $0 < \alpha < 1$ for fractional diffusion.

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References

[1] A. Tripathi and N. Adlakha, Closed Form Solution to problem of Calcium Diffusion in Cylindrical Shaped Neuron Cell, International Journal of Mathematical, Computational, Physical, Electrical and Computer Engineering, 5(8), 2011.
[2] B. Jha and A. Jha, Two Dimensional Finite Volume Model to Study the Effect of ER on Cytosolic Calcium Distribution in Astrocytes, Procedia Computer Science, 46, 1285-1293, 2005.
[3] B. Jha, N. Adlakha and M. N. Mehta, Closed form of advection diffusion of Ca2+ in astrocytes, International Journal of Applied Mathematics and Mechanics, 10, 74-81, 2014.
[4] B. K. Jha, N. Adlakha and M. N. Mehta, Finite element model to study calcium diffusion in astrocytes, International Journal of Pure and Applied Mathematics, 78(7), 945-955, 2012.
[5] D. Baleanu, J. Machado and A. Luo, Fractional Dynamics and Control, Springer-Verlag New York, 2012.

[6] D. Baleanu, K. Diethelm, E.Scalas and J. Trujillo, Fractional Calculus Models and Numerical Methods, World scientific pub., 2012.
[7] D. Baleanu, Z. Guvenc and J. Machado, New Trends in Nanotechnology and Fractional Calculus Applications, Springer Netherlands, 2010.
[8] D. Djordjevic, J. Jaric, B. Fabry, J. J. Fredberg and D. Stamenovic, Fractional derivatives embody essential features of cell rheological behavior, Annals of Biomedical Engineering, 31, 692-699, 2003.
[9] I. N. Sneddon, Fourier Transform, MacGraw-Hill, New York, 1951.
[10] I. Podlubny, Fractional differential equations, Academic Press, 1999.
[11] J. P. Keener, Spatial Modeling, Computational Cell Biology, Springer, 171-197, 2002.
[12] J. Schäfer, X. Huang, P. Birken, Gobbert Matthias K. and Andreas M., Numerical Methods for Partial Differential Equations, 31(1), 143-167, 2015.
[13] K. S. R. Kuthbertson and P. H. Cobbold, Agonist-induced oscillations in hepatocytes, Cells Calcium, 8, 79-100, 1987.
[14] L. A. Hanharta, K. Gobberta Matthias and T. Izub Leighton, A memory-efficient finite element method for systems of reactiondi)usion equations with non-smooth forcing, Journal of Computational and Applied Mathematics, 169(2), 431-458, 2004.
[15] M. J. Berridge, Unlocking the secrets of cell signaling, Annual Review of Physiology, 67, 1-21, 2005.
[16] M. Ortigueira, Fractional Calculus for Scientists and Engineers, Springer Netherlands, 2011.
[17] P. L. Butzer and U. Westphal, An Introduction to Fractional Calculus, World Scientific, Singapore, 2000.
[18] P. M. Conn, Neuroscience in Medicine, Third Edition, Humana Press, 2008.
[19] R. Agarwal, S. Jain and R. P. Agarwal, Analytic Solution of Generalize Space Time fractional Reaction Diffusion Equation, Fractional Differential Calculus, Fractional Differential Calculus, 7(2), 169-184, 2017.
[20] R. Gorenflo, G. de Fabritiis, F. Mainardi, D. Moretti, G. Pagnini and P. Paradisi, Discrete random walk models for space-time fractional diffusion, Chem. Phys., 284, 521-541, 2002.
[21] R. Gorenflo, Y. Luchko and F. Mainardi, Analytical properties and applications of the Wright function, Fract. Calc. Appl. Anal., 2(4), 383-414, 1999.
[22] R. Herrmann, Fractional Calculus An Introduction for Physicists, 2nd Edition, World scientific pub., 2014.
[23] R. L. Magin, Fractional calculus models of complex dynamics in biological tissues, Computers and Mathematics with Applications, 59(5), 1586-1593, 2010.
[24] S. Das and K. Moharatna, Fractional dynamical model for the generation of ECG like signals from filtered coupled Van-der Pol oscillators, Computer Methods and Programs in Biomedicine, 112, 490-507, 2013.
[25] S. G. Samko, A. A. Kilbas and O. I. Marichev, Fractional Integrals and derivatives-Theory and applications, Gordan and Breach, Linghorne, P.A, 1993.
[26] S. Panday and K. Pardasani, Finite element model to study the mechanics of calcium regulation in oocyte, Journal of Mechanics in Medicine and Biology, 14(2), 1450022, 2014.
[27] T. Atanackovic, S. Pilipovic, B. Stankovic and D. Zorica, Fractional Calculus with Applications in Mechanics: Wave Propagation, Impact and Variational Principles, Wiley-ISTE, 2014.
[28] T. Choi, Stochastic Modeling of Advection-Diffusion-Reaction Processes in Biological Systems, Ph. D. thesis, University of California, San Diego, 2013.
[29] U. Kummer, L. Olsen, C. Dixon, A. Green, E. Bornberg-Bauer and G. Baier, Switching from simple to complex oscillations in calcium signaling, Biophysical Journal, 79(3), 1188-1195, 2000.
[30] V. Uchaikin, Fractional Derivatives for Physicists and Engineers, Springer-Verlag Berlin Heidelberg, 2013.
[31] Y. Povstenko, Fractional Heat Conduction in an Infinite Medium with a Spherical Inclusion, Entropy, 4122-4133, 2013.

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