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CRANK-NICOLSON METHOD FOR TIME FRACTIONAL DRUG CONCENTRATION EQUATION IN CENTRAL NERVOUS SYSTEM

UTTAM KHARDE, KALYANRAO TAKALE and SHRIKRISHNA GAIKWAD

Department of Mathematics
S.N. Arts, D.J.M. Commerce
and B.N.S. Science College (Autonomous)
Sangamner-422605(M.S.), India

Department of Mathematics
R.N.C. Arts, J.D.B. Commerce
and N.S.C. Science College
Nashik Road, Nashik-422101, (M.S.), India
E-mail: kalyanraotakale1@gmail.com

Department of Mathematics
New Arts, Commerce and Science College
Ahmednagar-414001, (M.S.), India
E-mail: sbgmathsnagar@gmail.com

Abstract

Recently, the treatment of central nervous system (CNS) diseases is a major problem in modern clinical world. Now, there are many drugs available that treat symptoms rather than the disease, therefore, new drugs and new techniques of treatment are needed. In human, cerebrospinal fluid (CSF) is easily accessible fluid that can be used to predict the drug concentration in CNS target site. This process can be represented by mathematical model of drug concentration equation with the help of integer order partial derivatives, but fractional order modeled scribes the drug concentration at CNS target site more precisely. Therefore, the purpose of this paper is to develop the fractional order Crank-Nicolson finite difference scheme to solve the time fractional drug concentration equation, formulated with Caputo fractional derivative. Also, we prove that the scheme is unconditionally stable and convergent. As an application of

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*Corresponding author; E-mail: uttamkharde@gmail.com
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this scheme, numerical solutions of fractional order drug concentration equation in the central nervous system is examined to verify the stability and these solutions are simulated graphically using Python.

1. Introduction

Fractional calculus is a newly developed branch of mathematics which deals with the study of derivatives and integrations of arbitrary order. In recent years, many areas of applied science and technology have used fractional order approach to describe certain phenomena and processes. Fractional order mathematical models describing the physical phenomena are appears in many applications of sciences, such as the fractional diffusion equation [24], fractional subdiffusion equation [31], fractional wave equation [6, 24], fractional Boussinesq's equation [28], fractional heat equation, fractional viscoelastic theory [2], etc. The arbitrary order mathematical model provides better physical analysis rather than integer order model, because it provides results at any inter-mediate stage by considering all the inputs starting from initial stage rather than only previous stage [12]. Many dynamical models of physics, engineering, biomedical, fluid dynamics, hydrology, etc. [4, 3, 7, 12, 15, 18, 19, 21] are modeled by fractional order partial differential equations. Now a days, due to its tremendous applications in various fields, a remarkable attention has been given to find its exact and approximate solution. Due to non-local nature of fractional derivative, many fractional differential equations do not have exact solutions. Therefore, to solve the fractional differential equations, numerical techniques are more demanding. To develop numerical methods for solving fractional differential equations, which are accurate and timely efficient is the primary challenge to researchers. We observed that the fractional derivatives in Caputo sense is more feasible to analyze the physical problem and it allowed to deal with integer-order initial and boundary conditions [7]. Finite difference method is one of the more effective and commonly used method to solve fractional differential equations. In the literature [9, 10, 11, 14, 17, 20, 23, 25, 26, 28], finite difference method is successfully used to obtain the numerical solutions of fractional differential equations.

Now a days, Pharmacokinetics is the branch of Pharmacology which study the drug absorption, distribution, metabolism and excretion in human body [13]. In Pharmacology, one of the significant challenge is the

development of drugs targeting disease of the central nervous system (CNS). Due to medical ethics, direct measurement of brain concentration is restricted and due to presence of bloodbra in barrier (BBB), the prediction of target site concentration of CNS drug is more complicated [32]. Many researchers [9, 29, 30, 32] in pharmacology has developed a physiologically based pharmacokinetics modeling describing a drug concentration in CNS. The Advection-Diffusion equation describes the evolution of a concentration profile due to diffusion and advection simultaneously [1]. A mathematical modeling describing the drug concentration in CNS based on Advection-Diffusion equation is studied in [5]. In this context, we study the fractional order drug concentration equation in the central nervous system. Furthermore, we develop the Crank-Nicolson fractional order finite difference scheme for fractional order drug concentration equation and obtain its approximate solution. There are many numerical techniques developed for solving fractional differential equations using mathematical softwares [6, 10, 16]. We observed that, Python is a high level multi-purpose programming language having large number of mathematical tools. Recently, Python is used for teaching as well as research in various branches of applied mathematics. Therefore, in this connection we develop Python programme to obtain the numerical solution of the drug concentration equation by the proposed scheme.

We organized the paper as follows: In section 2, we develop the fractional order Crank-Nicolson finite difference scheme for time fractional drug concentration equation. Section 3 is devoted for stability of the solution obtained by the scheme. In section 4, convergence of the scheme is discussed up to the length. In section 5, the approximate solution of the time fractional drug concentration equation is computed and it is simulated graphically by Python. We consider the time fractional drug concentration equation with initial and boundary conditions as follows

$$\frac{\partial^{\alpha} c(x,t)}{\partial t^{\alpha}} = -v\frac{\partial c(x,\,t)}{\partial x} + D\frac{\partial^2 c(x,\,t)}{\partial x^2},\ 0 < \alpha \le 1,\ 0 \le x \le L,\ 0 \le t \le T \quad (1.1)$$

$$\text{initial condition: } c(x,\,0) = 0,\ 0 < x < L \quad (1.2)$$

$$\text{boundary conditions: } c(0,\,t) = g(t),\ \frac{\partial c(L,\,t)}{\partial x} = 0,\ t \ge 0 \quad (1.3)$$

where $c(x, t)$ is the drug concentration in CSF space at time t and place x, v is the flow velocity and D is the diffusion coefficient. We discretized time fractional order derivative in the Caputo sense.

The Caputo derivative of order α is defined as follows [22, 23]

$$\frac{\partial^{\alpha} c(x, t)}{\partial t^{\alpha}} = \frac{1}{\Gamma(1-\alpha)} \int_0^t (x-\tau)^{-\alpha} \frac{\partial c(x, \tau)}{\partial \tau} d\tau, \; 0 < \alpha \leq 1 \tag{1.4}$$

where $\Gamma(\cdot)$ is the gamma function defined as

$$\Gamma(\alpha) = \int_0^{\infty} e^{-x} x^{\alpha-1} dx. \tag{1.5}$$

2. Finite Difference Scheme

In this section, we develop the fractional order Crank-Nicolson finite difference scheme for time fractional drug concentration equation (1.1)-(1.3). For this, we define $x_i = i\Delta x$, $i = 0, 1, 2, 3, \ldots, M$ and $t_k = k\Delta t$, $k = 0, 1, 2, 3, \ldots, N$, where $\Delta x = \frac{L}{M}$ and $\Delta t = \frac{T}{N}$. Let $c(x_i, t_k)$, $i = 0, 1, 2, 3, \ldots, M$ and $k = 0, 1, 2, 3, \ldots, N$, be the exact solution of time fractional drug concentration equation (1.2)-(1.3) at mesh point (x_i, t_k) and let c_i^k be the numerical approximation at point (x_i, t_k). The time fractional drug concentration equation with initial and boundary conditions (1.1)-(1.3) is discretized by using the second order accurate central difference formula for space derivative and finite difference formula for the time fractional derivative for each interior grid point $(i\Delta x, k\Delta t)$. At time level $t = t_{k+1}$, the Caputo time fractional derivative of order α is discretized as follows

$$\left(\frac{\partial^{\alpha} c}{\partial t^{\alpha}}\right)_{(x_i, t_{k+1})} = \frac{1}{\Gamma(1-\alpha)} \int_0^{t_{k+1}} (t_{k+1} - s)^{-\alpha} \frac{\partial c(x_i, s)}{\partial s}$$

$$= \frac{1}{\Gamma(1-\alpha)} \sum_{j=0}^{k} \int_{t_j}^{t_{j+1}} (t_{k+1} - s)^{-\alpha} \left[\frac{c_i^{j+1} - c_i^j}{\Delta t} + O(\Delta t)\right] ds$$

$$= \frac{1}{\Gamma(1-\alpha)} \sum_{j=0}^{k} \left[\frac{c_i^{j+1} - c_i^j}{\Delta t} + O(\Delta t) \right] \int_{t_j}^{t_{j+1}} (t_{k+1} - s)^{-\alpha} ds$$

$$= \frac{1}{\Gamma(1-\alpha)} \sum_{j=0}^{k} \left[\frac{c_i^{j+1} - c_i^j}{\Delta t} + O(\Delta t) \right] \left[\frac{(k-j+1)^{1-\alpha} - (k-j)^{1-\alpha}}{(1-\alpha)(\Delta t)^{\alpha-1}} \right]$$

$$= \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^{k} [c_i^{k-j+1} - c_i^{k-j} + O(\Delta t)][(j+1)^{1-\alpha} - j^{1-\alpha}]$$

$$= \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^{k} [c_i^{j+1} - c_i^{k-j} + O(\Delta t)] b_j$$

$$= \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^{k} b_j [c_i^{j+1} - c_i^{k-j}] + \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^{k} b_j O(\Delta t)$$

where $b_j = (j+1)^{1-\alpha} - j^{1-\alpha}$, $j = 0, 1, 2, 3, \ldots, k$.

Since, $k\Delta t \le T$ is finite, the above equation can be written as,

$$\left(\frac{\partial^\alpha c}{\partial t^\alpha} \right)_{(x_i, t_{k+1})} = \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} [c_i^{k+1} - c_i^k] + \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=1}^{k} b_j [c_i^{k-j+1} - c_i^{k-j}] + O(\Delta t). \tag{2.1}$$

Furthermore, the space derivatives $\frac{\partial c}{\partial x}$ is disretized as follows

$$\left(\frac{\partial c}{\partial x} \right)_{(x_i, t_{k+1})} = \frac{c_{i+1}^k - c_{i-1}^k}{2\Delta x} + O(\Delta x) \tag{2.2}$$

The space derivative $\frac{\partial^2 c}{\partial x^2}$ is discretized by using second order central difference scheme as follows

$$\left(\frac{\partial^2 c}{\partial x^2} \right)_{(x_i, t_{k+1})} = \frac{\delta_x^2 c_i^{k+1} + \delta_x^2 c_i^k}{2}$$

$$\therefore \left(\frac{\partial^2 c}{\partial x^2}\right)_{(x_i, t_{k+1})} = \frac{1}{2\Delta x^2}[c_{i-1}^{k+1} - 2c_i^{k+1} + c_{i+1}^{k+1} + c_{i-1}^{k} - 2c_i^{k} + c_{i+1}^{k}] + O(\Delta x^2) \quad (2.3)$$

where δ_x is the central difference operator.

Now, using equations (2.1), (2.2) and (2.3) in equation (1.1), we obtain

$$\frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)}[c_i^{k+1} - c_i^k] + \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)}\sum_{j=1}^{k} b_j[c_i^{k-j+1} - c_i^{k-j}]$$

$$= \frac{-v}{2\Delta x}[c_{i+1}^k - c_{i-1}^k] + \frac{D}{2\Delta x^2}[c_{i-1}^{k+1} - 2c_i^{k+1} + c_{i+1}^{k+1} + c_{i-1}^k - 2c_i^k + c_{i+1}^k]$$

This gives, $[c_i^{k+1} - c_i^k] + \sum_{j=1}^{k} b_j[c_i^{k-j+1} - c_i^{k-j}]$

$$= -v\frac{(\Delta t)^{\alpha}\Gamma(2-\alpha)}{2\Delta x}[c_{i+1}^k - c_{i-1}^k]$$

$$+ D\frac{(\Delta t)^{\alpha}\Gamma(2-\alpha)}{2\Delta x^2}[c_{i-1}^{k+1} - 2c_i^{k+1} + c_{i+1}^{k+1} + c_{i-1}^k - 2c_i^k + c_{i+1}^k]$$

By taking $\mu = v\frac{(\Delta t)^{\alpha}\Gamma(2-\alpha)}{2\Delta x}$ and $r = D\frac{(\Delta t)^{\alpha}\Gamma(2-\alpha)}{2\Delta x^2}$, we get

$$[c_i^{k+1} - c_i^k] + \sum_{j=1}^{k} b_j[c_i^{k-j+1} - c_i^{k-j}] = -\mu[c_{i+1}^k - c_{i-1}^k]$$

$$+ r[c_{i-1}^{k+1} - 2c_i^{k+1} + c_{i+1}^{k+1} + c_{i-1}^k - 2c_i^k + c_{i+1}^k]$$

$$-rc_{i-1}^{k+1} + (1+2r)c_i^{k+1} - rc_{i+1}^{k+1} = (r+\mu)c_{i-1}^k + (1-2r)c_i^k + (r-\mu)c_{i+1}^k$$

$$- \sum_{j=1}^{k} b_j(c_i^{k-j+1} - c_i^{k-j}) \quad (2.4)$$

After simplification, for $k = 0, 1, 2, 3, \ldots, N$, we obtain

$$-rc_{i-1}^{k+1} + (1+2r)c_i^{k+1} - rc_{i+1}^{k+1} = (r+\mu)c_{i-1}^k + (1-2r-b_1)c_i^k + (r-\mu)c_{i+1}^k$$

$$- \sum_{j=1}^{k} (b_j - b_{j+1}) c_i^{k-j} + b_k c_i^0. \tag{2.5}$$

Now, put $k = 0$ in equation (2.4), we get

$$- r c_{i-1}^{k+1} + (1 + 2r) c_i^1 - r c_{i+1}^1 = (r + \mu) c_{i-1}^0 + (1 - 2r) c_i^0 + (r - \mu) c_{i+1}^0. \tag{2.6}$$

Finally, the initial condition $c(x, 0) = 0 (0 < x < L)$ is approximated as follows:

$$c_i^0 = 0, \; i = 1, 2, 3, \ldots, M. \tag{2.7}$$

Also, the boundary conditions $c(0, t) = g(t)$ and $\frac{\partial c(L, t)}{\partial x} = 0 (t \geq 0)$ are approximated as follows

$$c(0, t_k) = g(t_k) \text{ implies } c_0^k = g(t_k), \; k = 0, 1, 2, 3, \ldots, N \tag{2.8}$$

and

$$\frac{\partial c(L, t_k)}{\partial x} = 0 \text{ implies } \frac{c_{M+1}^k - c_{M-1}^k}{2\Delta x} = 0$$

This gives,

$$c_{M+1}^k = c_{M-1}^k, \; k = 0, 1, 2, 3, \ldots, N. \tag{2.9}$$

Thus, the complete discretized time fractional drug concentration equation with initial and boundary condition is as follows

$$- r c_{i-1}^1 + (1 + 2r) c_i^1 - r c_{i+1}^1 = (r + \mu) c_{i-1}^0 + (1 - 2r) c_i^0 + (r - \mu) c_{i+1}^0, \text{ for } k = 0 \tag{2.10}$$

$$- r c_{i-1}^{k+1} + (1 + 2r) c_i^{k+1} - r c_{i+1}^{k+1} = (r + \mu) c_{i-1}^k + (1 - 2r - b_1) c_i^k + (r - \mu) c_{i+1}^k + \sum_{j=1}^{k} (b_j - b_{j+1}) c_i^{k-j} + b_k c_i^0, \text{ for } k \geq 1 \tag{2.11}$$

$$\text{initial condition: } c_i^0 = 0, \; i = 1, 2, 3, \ldots, M \tag{2.12}$$

$$\text{boundary conditions: } c_0^k = g(t_k), \; c_{M+1}^k = c_{M-1}^k, \; k = 0, 1, 2, 3, \ldots, N \tag{2.13}$$

where $\mu = v\frac{(\Delta t)^{\alpha}\Gamma(2-\alpha)}{2\Delta x}$, $r = D\frac{(\Delta t)^{\alpha}\Gamma(2-\alpha)}{2\Delta x^2}$, $b_j = (j+1)^{1-\alpha} - j^{1-\alpha}$, $j = 1, 2, 3, \ldots$ and $k = 0, 1, 2, 3, \ldots, N$, $i = 1, 2, 3, \ldots, M$.

Therefore, the discretized fractional order Crank-Nicolson finite difference scheme (2.10)-(2.13) can be expressed in matrix form as follows

$$AC^1 = BC^0 + S^0, \text{ for } k = 0 \tag{2.14}$$

$$AC^{k+1} = FC^k + \sum_{j=1}^{k-1}(b_j - b_{j+1})C^{k-j} + b_k C^0 + S^k, \text{ for } k \geq 1 \tag{2.15}$$

$$\text{initial condition: } c_i^0 = 0,\ i = 1, 2, 3, \ldots, M \tag{2.16}$$

$$\text{boundary conditions: } c_0^k = g(t_k),\ c_{M+1}^k = c_{M-1}^k,\ k = 0, 1, 2, 3, \ldots, N \tag{2.17}$$

where $C^k = (c_1^k, c_2^k, c_3^k, \ldots, c_M^k)^T$, $S^k = ((r+\mu)g(t_k) + rg(t_{k+1}), 0, 0, \ldots, 0)^T$ is a constant matrix,

$$A = \begin{pmatrix} 1+2r & -r & & & & & & \\ -r & 1+2r & -r & & & & & \\ & \ddots & \ddots & \ddots & & & & \\ & & -r & 1+2r & -r & & & \\ & & & \ddots & \ddots & \ddots & & \\ & & & & -r & 1+2r & -r & \\ & & & & & -2r & 1+2r & \end{pmatrix}$$

$$B = \begin{pmatrix} 1-2r & r-\mu & & & & & & \\ r+\mu & 1-2r & r-\mu & & & & & \\ & \ddots & \ddots & \ddots & & & & \\ & & r+\mu & 1-2r & r-\mu & & & \\ & & & \ddots & \ddots & \ddots & & \\ & & & & r+\mu & 1-2r & r-\mu & \\ & & & & & 2r & 1-2r & \end{pmatrix}$$

and

$$F=\begin{pmatrix} 1-2r-b_1 & r-\mu & & & & & & \\ r+\mu & 1-2r-b_1 & r-\mu & & & & & \\ & \ddots & \ddots & \ddots & & & & \\ & & r+\mu & 1-2r-b_1 & r-\mu & & & \\ & & & \ddots & \ddots & \ddots & & \\ & & & & r+\mu & 1-2r-b_1 & r-\mu & \\ & & & & & 2r & 1-2r-b_1 \end{pmatrix}$$

3. Stability

In this section, we discuss the stability of solution of the fractional order Crank-Nicolson finite difference scheme (2.10)-(2.13) developed for the time fractional drug concentration equation (1.1)-(1.3) with initial and boundary conditions.

Lemma 3.1. *The eigenvalues of* $M\times M$ *tri-diagonal matrix*

$$\begin{pmatrix} a & b & & & & & \\ c & a & b & & & & \\ & \ddots & \ddots & \ddots & & & \\ & & c & a & b & & \\ & & & \ddots & \ddots & \ddots & \\ & & & & c & a & b \\ & & & & & c & a \end{pmatrix}$$

are given as

$$\lambda_s = a + 2\sqrt{bc}\cos\left(\frac{s\pi}{M+1}\right),\ s = 1, 2, 3, \ldots, M$$

where a, b *and* c *are either real or complex numbers* [25].

Lemma 3.2. *If* $\lambda_j(A)$, $j = 1, 2, 3, 4, \ldots, M-1$ *represent eigenvalues of a matrix* A, *then following conditions are hold*

(i) $\lambda_j(A) \geq 1$

(i) $\| A^{-1} \|_2 \leq 1$, *where* $\| \cdot \|_2$ *is the second norm of matrix.*

Proof. By the Gerschgorin's circle theorem [25], if λ is a eigenvalue of a square matrix $[a_{ij}]$ then λ is in at least one of the following disc

$$| \lambda - a_{ij} | \leq \sum_{l=1,\ l \neq j}^{M} a_{lj},\ l = 1, 2, 3, \ldots, M. \tag{3.1}$$

Thus, each eigenvalue λ of a square matrix $[a_{ij}]$ satisfy at least one of the following inequality

$$| \lambda | \leq \sum_{i=1}^{M} | a_{ij} | \tag{3.2}$$

$$| \lambda | \geq | a_{ij} | - \sum_{i=1,\ i \neq j}^{M} | a_{ij} | \tag{3.3}$$

Now, we use inequality (3.3) to prove the condition (i) for the matrix A as

$$| \lambda_1(A) | \geq | (1 + 2r) + (-r) | = 1 + r \geq 1$$

$$| \lambda_2(A) | \geq | (1 + 2r) + (-r) + (-r) | = 1$$

$$| \lambda_3(A) | \geq | (1 + 2r) + (-r) + (-r) | = 1$$

$$\vdots$$

$$| \lambda_M(A) | \geq | (1 + 2r) + (-r) + (-r) | = 1$$

Thus, $| \lambda_j | \geq 1,\ j = 1, 2, 3, \ldots, M.$

To prove condition (ii), we have

$$\| A \|_2 = \max_{1 \leq j \leq M} | \lambda_j(A) |.$$

Therefore, from condition (i), we get

$$\| A \|_2 \geq 1.$$

Hence,

$$\| A^{-1} \|_2 \leq 1$$

This complete the proof. □

Lemma 3.3. *The discretized fractional order Crank-Nicolson finite difference scheme with initial and boundary conditions* (2.10)-(2.13) *is*

solvable for each time step unconditionally.

Proof. To prove the solvability of equations (2.10) and (2.12), it is enough to prove that matrix A is invertible [8, 27]. We observed that, the first and last row of matrix A is diagonally dominant. For other rows, the diagonal element is $1+2r$ and the sum of the absolute values of the non-diagonal element in the same row is,

$$|(-r)| + |(-r)| = 2r.$$

Hence, for each row, we have $1+2r > 2r$. Thus, matrix A is strictly diagonally dominant. Hence, matrix A is invertible. This shows that the solvability of the finite difference scheme. □

Lemma 3.4. *If* $\lambda_s(B)$ *and* $\lambda_s(F)$ *represents the eigenvalues of B and F respectively*, *then following conditions are hold*

(i) $|\lambda_s(B)| \le 1, |\lambda_s(F)| \le 1, s = 1, 2, 3, \ldots, M$

(ii) $\| B \|_2 \le 1, \| F \|_2 \le 1, s = 1, 2, 3, \ldots, M.$

Theorem 3.5. *The solution of the fractional order Crank-Nicolson finite difference scheme* (2.10)-(2.13) *for time fractional drug concentration equation* (1.1)-(1.3) *is unconditionally stable*.

Proof. To prove the developed finite difference scheme is unconditionally stable, we will prove that

$$\| C^n \|_2 \le K \| C^0 \|_2, n = 1, 2, 3, \ldots$$

where K is positive integer independent of x and t.

For $n = 1,$ from equation (2.14), we obtain

$$C^1 = A^{-1}BC^0 + A^{-1}S^0$$

$$\therefore \| C^1 \|_2 \le \| A^{-1} \|_2 \| B \|_2 \| C^0 \|_2 + \| A^{-1} \|_2 \| S^0 \|_2$$

$$\le \| C^0 \|_2 + \| S^0 \|_2$$

$$\le \| C^0 \|_2 + K_1 \| C^0 \|_2, \text{ where } \| S^0 \|_2 = K_1, \text{ a constant.}$$

Thus, result is true for $n = 1.$

For $n \le k$, let us assume that

$$\| C^k \|_2 \le K \| C^0 \|_2.$$

Now, for $n = k + 1$, from equation (2.15), we obtain

$$C^{k+1} = A^{-1}FC^k + A^{-1}\sum_{j=1}^{k-1}(b_j - b_{j+1})C^{k-j}b_kC^0 + A^{-1}S^K.$$

$$\therefore \| C^{k+1} \|_2 \le \| C^k \|_2 + \sum_{j=1}^{k-1}(b_j - b_{j+1}) \| C^{k-j} \|_2 + b_k \| C^0 \|_2 + \| S^K \|_2$$

$$= \| C^k \|_2 + [(b_1 - b_2) \| C^{k-1} \|_2 + (b_2 - b_3) \| C^{k-2} \|_2 + \ldots + (b_{k-1} - b_k) \| C^1 \|_2]$$

$$+ b_k \| C^0 \|_2 + \| S^k \|_2$$

$$\le K_1 \| C^0 \|_2 + [(b_1 - b_2) + (b_2 - b_3) + \ldots + (b_{k-1} - b_k)]K_2 \| C^0 \|_2 + b_k \| C^0 \|_2 + K_3$$

$$\le [K_1 + b_1 + (1 - K_2)b_k] \| C^0 \|_2 + K_3 \| C^0 \|_2$$

$$= K \| C^0 \|_2.$$

Hence, by induction, for all n, we have

$$\| C^n \|_2 \le K \| C^0 \|_2$$

where K is a positive number independent of x and t.

Therefore, this shows that the scheme is unconditionally stable.

This complete the proof. □

4. Convergence

In this section, we discuss the convergence of the scheme. Let Ω be the region $[0, L] \times [0, T]$. We introduce the vector, $\overline{C}^k = (\bar{c}(x_0, t_k), \bar{c}(x_1, t_k), \bar{c}(x_2, t_k), \ldots, \bar{c}(x_M, t_k))^T$ of size $M + 1$, which represent the exact solution of the time fractional drug concentration equation (1.1)-(1.3) at time level t_k.

Let $\tau^k = (\tau_1^k, \tau_2^k, \tau_3^k, \ldots, \tau_M^k)^T$ be the vector of truncation error at time level t_k. Since $\overline{C}^k$ is the exact solution of the equation (1.1)-(1.3), we have

$$A\overline{C}^1 = B\overline{C}^0 + S^0 + \tau^1, \text{ for } k = 0. \tag{4.1}$$

$$A\overline{C}^{k+1} = F\overline{C}^k + \sum_{j=1}^{k-1}(b_j - b_{j+1})\overline{C}^{k-j} + b_k\overline{C}^0 + S^k + \tau^{k+1}, \text{ for } k \geq 1. \tag{4.2}$$

Lemma 4.1. *The coefficient* b_j, $j = 0, 1, 2, 3, \ldots$ *satisfy the following conditions*

(i) $b_j > 0$

(ii) $b_j > b_j + 1$.

Theorem 4.2. *The fractional order Crank-Nicolson finite difference scheme* (2.10)-(2.13) *for time fractional drug concentration equation* (1.1)-(1.3) *is unconditionally convergent.*

Proof. We set, $E^k = \overline{C}^k - C^k = (e_1^k, e_2^k, e_3^k, \ldots, e_M^k)^T$ be the error vector in the solution at time level t_k. Furthermore, we assume that $| e_l^k | = \max\limits_{1\leq i\leq M} | e_i^k | = \| E^k \|_\infty$ and $\tau_l^k = \max\limits_{1\leq i\leq M} | \tau_i^k |$, for $l = 1, 2, 3, \ldots$

Then, using equation (2.10), we obtain

$$\begin{aligned} | e_l^1 | &= | -re_{i-1}^1 + (1+2r)e_i^1 - re_{i+1}^1 | \\ &\leq (r+\mu)| e_{i-1}^0 | + (1-2r)| e_i^0 | + (r-\mu)| e_{i+1}^0 | + | \tau_l^1 | \\ &\leq (r+\mu+1-2r+r-\mu) \max_{1\leq i\leq M} | e_i^0 | + \max_{1\leq i\leq M} | \tau_i^1 | \\ &= \| E^0 \|_\infty + \max_{1\leq i\leq M} | \tau_i^1 | \end{aligned}$$

$$\therefore \| E^1 \|_\infty \leq \| E^0 \|_\infty + \max_{1\leq i\leq M} | \tau_i^1 |$$

Now, from equation (2.11), we obtain

$$| e_l^{k+1} | = | -re_{i-1}^{k+1} + (1+2r)e_i^{k+1} - re_{i+1}^{k+1} |$$

$$\leq (r+\mu)|\, e_{i-1}^{k} \,| + (1-2r-b_1)|\, e_i^k \,| + (r-\mu)|\, e_{i+1}^{k} \,| + \sum_{j=1}^{k-1}(b_j - b_{j+1})|\, e_i^{k-j} \,|$$

$$+ b_k|\, e_i^0 \,| + |\, \tau_l^{k+1} \,|$$

$$= (r+\mu)|\, e_{i-1}^{k} \,| + (1-2r-b_1)|\, e_i^k \,| + (r-\mu)|\, e_{i+1}^{k} \,| + (b_1 - b_2)|\, e_i^{k-1} \,|$$

$$+ (b_2 - b_3)|\, e_i^{k-2} \,| + \ldots + (b_{k-1} - b_k)|\, e_i^1 \,| + b_k|\, e_i^0 \,| + |\, \tau_i^{k+1} \,|$$

$$= [(r+\mu) + (1-2r-b_1) + (r-\mu)]|\, e_l^k \,| + [(b_1 - b_2) + (b_2 - b_3) + \ldots + (b_{k-1} - b_k)]$$

$$|\, e_l^k \,| + b_k|\, e_l^k \,| + \max_{1\leq i\leq M}|\, \tau_i^{k+1} \,|$$

$$= \|\, E^k \,\|_\infty + \max_{1\leq i\leq M}|\, \tau_i^{k+1} \,|.$$

This is true for every k, therefore we have

$$\|\, E^{k+1} \,\|_\infty \leq \|\, E^k \,\|_\infty + \max_{1\leq i\leq M}|\, \tau_i^{k+1} \,|$$

Hence, by induction, we get

$$\|\, E^{n+1} \,\|_\infty \leq \|\, E^n \,\|_\infty + \max_{1\leq i\leq M}|\, \tau_i^{n+1} \,|$$

As $\|\, E^0 \,\|_\infty = 0$, implies $\|\, E^n \,\|_\infty = 0$.

Therefore, $\|\, E^{n+1} \,\|_\infty \leq \max_{1\leq i\leq M}|\, \tau_i^{n+1} \,|$.

Since $\max_{1\leq i\leq M}|\, \tau_i^{n+1} \,| \to 0$ as $(\Delta x, \Delta t) \to (0, 0)$, implies that $\|\, E^{n+1} \,\|_\infty \to 0$ uniformly on Ω as $(\Delta x, \Delta t) \to (0, 0)$.

Therefore, this shows that for any x and t, as $(\Delta x, \Delta t) \to (0, 0)$, the vector C^n converges to $\overline{C}^n$.

Hence, this complete the proof. □

5. Python Programme

In this section, we develop the algorithm for solving the discretized

scheme (2.10)-(2.13) using Python programme. Here we compute c_i^k at each mesh point (x_i, t_k) using the proposed scheme by Python. The algorithm for the scheme (2.14)-(2.17) is as follows

(i) Define $g(t_k)$ for each $k = 0, 1, 2, 3, \ldots, N$.

(ii) Compute the matrix A, B and F.

(iii) Compute C^0 and S^0, then compute C^1.

(iv) Compute S^1. Then using C^1, compute C^2.

(v) Compute S^k. Then compute C^{k+1} for each $k = 2, 3, 4, \ldots, N$.

Now, we develop the python programme DCE for complete discretized scheme (2.14)-(2.17) as follows:

Inputs:

g - boundary condition at x=0.

C - drug concentration

L - spatial length

T - end time

D - diffusion coefficient of drugs

mu - μ

a - fractional order α of time derivative

t1 - time at which solution to be estimated.

Output of Python programme DCE is the approximate value of vector $C(x_i, t_k)$.

```
import scipy
from scipy import *
import math
from math import *
```

```
def g(k):
    return(c(0,t))
import numpy as np
def DCE(g,v,L,T,dx,dt,D,a,t1):
    r=dt**a*D*math.gamma(2-a)/(2*dx**2)
    mu=v*dt**a*math.gamma(2-a)/(2*dx)
    N=int(round(T/dt))
    M=int(round(L/dx))
    t=np.linspace(0,N*dt,N+1)
    x=np.linspace(0,M*dx,M+1)
    A = np.zeros((M+1, M+1))
    A[0, 0] = 1+2*r
    A[0, 1]=-r
    A[M,M-1]=-2*r
    A[M, M] = 1+2*r
    for i in range(1, M):
        A[i, i-1] = -r
        A[i, i] = 1+2*r
        A[i, i+1] = -r
B=np.zeros((M+1,M+1))
B[0,0]=1-2*r
B[0,1]=r-mu
B[M,M-1]=2*r
B[M,M]=1-2*r
for i in range(1,M):
   B[i, i-1] = r+mu
```

```
    B[i, i] = 1-2*r
    B[i, i+1] = r-mu
F=np.zeros((M+1,M+1))
F[0,0]=1-2*r-((1+1)**(1-a)-1**(1-a))
F[0,1]=r-mu
F[M,M-1]=2*r
F[M,M]=1-2*r-((1+1)**(1-a)-1**(1-a))
for i in range(1,M):
    F[i, i-1] = r+mu
    F[i, i] = 1-2*r-((1+1)**(1-a)-1**(1-a))
    F[i, i+1] = r-mu
C=np.zeros((N+1,M+1))
S0=np.zeros(M+1)
S0[0]=(r+mu)*g(t[0])+r*g(t[1])
b0=B@C[0]+S0
C[1]=scipy.linalg.solve(A,b0)
S1=np.zeros(M+1)
S1[0]=(r+mu)*g(t[1])+r*g(t[2])
b1=F@C[1]+S1
C[2]=scipy.linalg.solve(A,b1)
for k in range(2,N):
    ek=(k+1)**(1-a)-k**(1-a)
    Sk=np.zeros(M+1)
    Sk[0]=(r+mu)*g(t[k])+r*g(t[k+1])
    sum=np.zeros(M+1)
    for j in range(1,k):
```

```
        sum=sum+((j+1)**(1-a)-j**(1-a)-(j+2)**(1-a)+(j+1)**(1-a))*C[k-j]
    bk=F@C[k]+sum+ek*C[0]+Sk
    C[k+1][:]=scipy.linalg.solve(A,bk)
t1=int(t1/dt)
return(x,C[t1])
```

6. Numerical Solutions

In this section, we obtain the approximate solution of time fractional drug concentration equation (1.1)-(1.3) by a developed fractional order Crank-Nicolson finite difference scheme (2.10)-(2.13).

6.1 Test Problem 1. Steady State Concentration

In pharmacology, the steady state of drug is an important fundamental concept. Steady-state is a situation during which the concentration of drug in the body is stable. In the treatment of CNSdisease, understanding of steady-state is important for choosing the right dose and determining the dosing interval to achieve a desire steady-state concentration. This is the situation corresponds to where maintenance dose is given in order to keep the drug concentration constant in the brain ECF [5]. If the concentration in brain ECF remains constant, then we will obtain the drug concentration in the CSF changes along the CSF space by the following drug concentration equation

$$\frac{\partial^{\alpha} c(x,\, t)}{\partial t^{a}} = -v\,\frac{\partial c(x,\, t)}{\partial x} + D\,\frac{\partial^{2} c(x,\, t)}{\partial x^{2}},\ 0 < \alpha \le 1,\ 0 \le x \le 8,\ t \ge 0$$

$$\text{initial condition: } c(x,\, 0) = 0,\ 0 \le x < 8$$

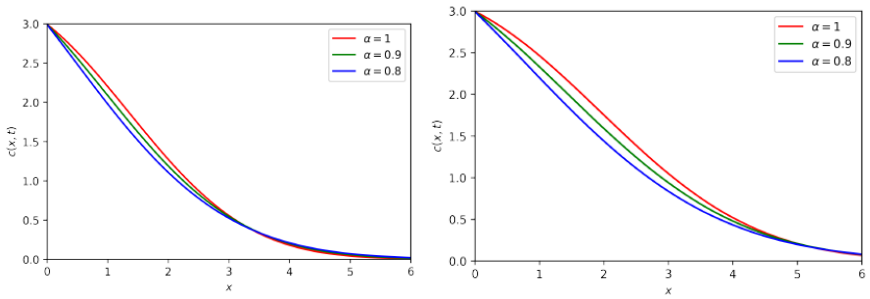
$$\text{boundary conditions: } c(0,\, t) = 3,\ \frac{\partial c(8,\, t)}{\partial x} = 0\,(t \ge 0).$$

The exact solution of the problem for $\alpha = 1$ is given as [5]

$$c(x,\, t) = \frac{3}{2}\left(erfc\left(\frac{x - vt}{2\sqrt{Dt}}\right) + e^{\frac{vx}{D}} erfc\left(\frac{x + vt}{2\sqrt{Dt}}\right)\right).$$

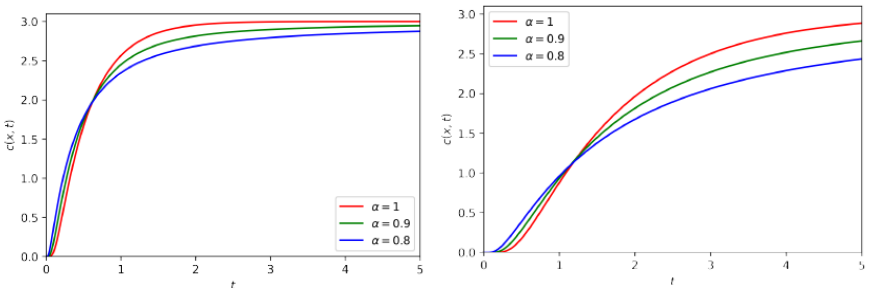
With the help of Python programme DCE, we calculate the drug concentration $c(x,\, t)$ for anytime t_k. The numerical solutions of the time

fractional drug concentration equation obtained by developed scheme for $\alpha = 1.0, 0.9, 0.8$ with the parameters $v = 0.5$, $D = 0.7$, $\Delta x = 0.01$ and $\Delta t = 0.001$ is represented graphically in Figure 1. Furthermore, we simulate the numerical solution of the time fractional drug concentration equation for different values of x in Figure 2. The exact solution and numerical solution for $\alpha = 1$ with the parameters $v = 0.5$, $D = 0.7$, $\Delta x = 0.01$ and $\Delta t = 0.001$ at time $t = 2$ are shown in Table 1. We observed that the magnitude of the error of exact solution and numerical solution is of $O(\Delta t + (\Delta x)^2)$.



(a) $t = 2$ (b) $t = 3$

Figure 1. Drug concentration profile with the parameters $v = 0.5$, $D = 0.7$, $\Delta x = 0.01$, $\Delta t = 0.001$ and $\alpha = 1.0, 0.9, 0.8$.



(a) $x = 1$ (b) $x = 2$

Figure 2. Numerical solution of steady state concentration for $x = 1$ and $x = 2$ with the parameters $v = 0.5$, $D = 0.7$, $T = 5$, $\Delta x = 0.01$ and $\Delta t = 0.001$.

Table 1. Comparision of exact solution and numerical solution for $\alpha = 1$, $t = 2$, $v = 0.5$, $D = 0.7$, $\Delta x = 0.01$ and $\Delta t = 0.001$.

x	Exact Solution	Numerical Solution	Error $e_i^k = \| \bar{c}_i^k - c_i^k \|$
0.0	3.0	2.993907278649013	0.006092721350987151
0.5	2.6456568378800114	2.637640626024081	0.0080162118559306
1.0	2.210862045444807	2.2016244916677286	0.009237553777078578
1.5	1.7395672793993147	1.7300687648213946	0.009498514577920059
2.0	1.2820481022496093	1.2732489286656066	0.008799173584002729
2.5	0.8812918247063797	0.8739078798391523	0.007383944867227377
3.0	0.5631456958949884	0.5575140861890188	0.0056316097059696535
3.5	0.33360708628476354	0.3296952147891131	0.003911871495650421
4.0	0.1828205165043782	0.1803422974511022	0.0024782190532759985
4.5	0.09251994640668684	0.0910867844617443	0.0014331619449425431
5.0	0.04317739107570287	0.042420349641816124	0.0007570414338867459
5.5	0.018560555515715397	0.01819513741539206	0.00036541810032333574
6.0	0.007342283849504758	0.007181092835093199	0.00016119101441155938

6.2 Test Problem 2. Elimination Phase

The elimination phase of drug is the case corresponds to the drug being present in the CSF in the lateral ventricles at some concentration c_0 [5]. At $t = 0$, the injection is stopped and the elimination begins. This case is relevant for concentration-time profile on coarse time scale. Since the drug aggregation happens quite fast in the case of intravenous injection, it will not visible on such a time-scale and we will see only elimination phase in the plot. This phenomenon is study by the following time-fractional drug concentration equation

$$\frac{\partial^\alpha c(x, t)}{\partial t^\alpha} = -v \frac{\partial c(x, t)}{\partial x} + D \frac{\partial^2 c(x, t)}{\partial x^2}, \; 0 < \alpha \le 1, \; x \le 6, \; t \ge 0$$

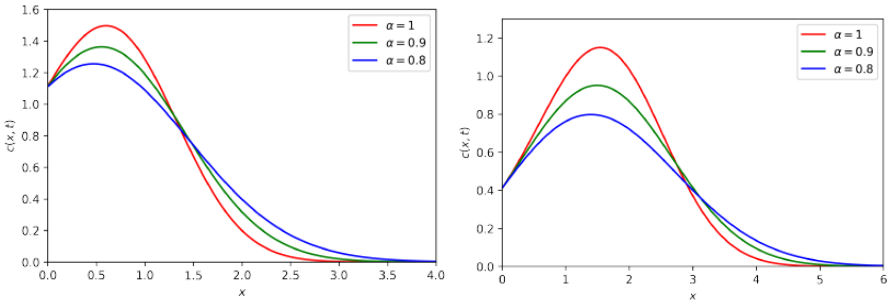
$$\text{initial condition: } c(x, 0) = 0, \; 0 < x < 6$$

$$\text{boundary conditions: } c(0, t) = 3e^{-t}, \frac{\partial c(6, t)}{\partial x} = 0 (t \geq 0).$$

The exact solution of the problem for $\alpha = 1$ is given as [5]

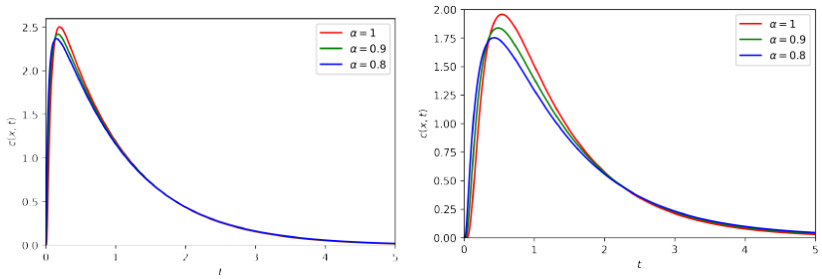
$$c(x, t) = \frac{3}{2} e^{-t} \left(e^{\frac{(v-y)x}{2D}} erfc\left(\frac{x - yt}{2\sqrt{Dt}}\right) + e^{\frac{(v+y)x}{2D}} erfc\left(\frac{x + yt}{2\sqrt{Dt}}\right) \right)$$

where $y = \sqrt{v^2 - 4D}$. The numerical solutions of the time fractional drug concentration equation obtained by developed scheme for $\alpha = 1.0, 0.9, 0.8$ with the parameters $v = 1$, $D = 0.2$, $\Delta x = 0.01$ and $\Delta t = 0.001$ are represented graphically in Figure 3 by Python programme DCE. Furthermore, we simulate the numerical solutions of the time fractional drug concentration equation for different values of x in Figure 4. In Table 2, we compare the exact solution and numerical solution of the time fractional drug concentration equation for $\alpha = 1$ with the parameters $v = 1$, $D = 0.2$, $\Delta x = 0.01$ and $\Delta t = 0.001$ at time $t = 2$. Moreover, we observe that the error in the calculation is of $O(\Delta t + (\Delta x)^2)$.



(a) $t = 1$ (b) $t = 2$

Figure 3. Drug concentration profile with the parameters $v = 1$, $D = 0.2$, $\Delta x = 0.01$, $\Delta t = 0.001$ and $\alpha = 1.0, 0.9, 0.8$.



(a) $x = 0.2$ (b) $x = 0.5$

Figure 4. Numerical solution for drug elimination for $x = 0.2$ and $x = 0.5$ with the parameters $v = 1$, $D = 0.2$, $t = 5$, $\Delta x = 0.01$ and $\Delta t = 0.001$.

Table 2. Comparision of exact solution and numerical solution for $\alpha = 1$, $t = 2$, $v = 1$, $D = 0.2$, $\Delta x = 0.01$ and $\Delta t = 0.001$.

x	Exact Solution	Numerical Solution	Error $e_i^k = \| \bar{c}_i^k - c_i^k \|$
0.0	0.40600584970983805	0.4108789821823356	0.004873132472497543
0.5	0.690643252642077	0.6969777675627705	0.006334514920693479
1.0	0.9910421336946248	0.9965539539700895	0.005511820275464707
1.5	1.147116277674832	1.1484516174662687	0.0013353397914366294
2.0	1.0385500472139912	1.0343063307369158	0.004243716477075443
2.5	0.72077795551975	0.7133503723003761	0.007427583219373868
3.0	0.37847592991323475	0.3718015170776765	0.006674412835558252
3.5	0.14906463756342395	0.14515526386486594	0.003909373698558011
4.0	0.04377805649358062	0.04219236700542997	0.0015856894881506461
4.5	0.009547713552140515	0.009091836821831855	0.0004558767303086599
5.0	0.0015417744244616016	0.001447866329388511	9.390809507309065e-05
0.0	0.40600584970983805	0.4108789821823356	0.004873132472497543
0.5	0.690643252642077	0.6969777675627705	0.006334514920693479

6.3 Test Problem 3. Drug Aggregation

The drug aggregation corresponds to the case in which drug is given continuously over a longer period of time [5]. The drug reaches the CSF at time $t = 0$ and no drug was present in the brainECF and CSF before that. The injection is continued long enough in order to reach the steady state

concentration and is not stopped within the period of time considered. This phenomenon is study by the following time-fractional drug concentration equation

$$\frac{\partial^{\alpha} c(x, t)}{\partial t^{\alpha}} = -v \frac{\partial c(x, t)}{\partial x} + D \frac{\partial^2 c(x, t)}{\partial x^2}, \; 0 < \alpha \leq 1, \; x \leq 5, \; t \geq 0$$

$$\text{initial condition: } c(x, 0) = 0, \; 0 < x < .$$

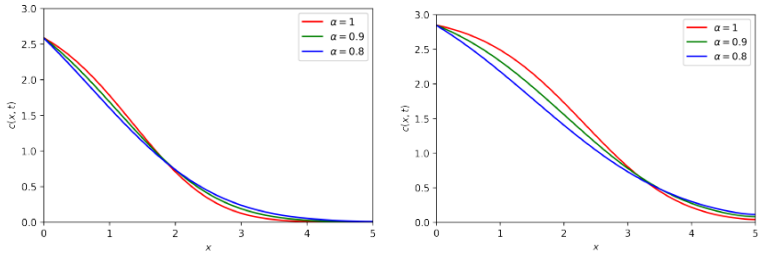
$$\text{boundary conditions: } c(0, t) = 3e^{-t}, \; \frac{\partial c(5, t)}{\partial x} = 0 (t \geq 0).$$

The exact solution of the problem for $\alpha = 1$ is given as [5]

$$c(x, t) = \frac{3}{2}\left(erfc\left(\frac{x - vt}{2\sqrt{Dt}}\right) + e^{\left(\frac{vx}{D}\right)} erfc\left(\frac{x + vt}{2\sqrt{Dt}}\right) \right.$$

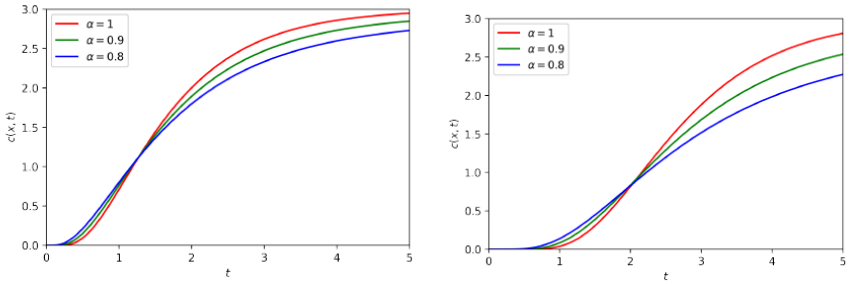
$$\left. - e^{-t}\left(e^{\frac{(v-y)x}{2D}} erfc\left(\frac{x - yt}{2\sqrt{Dt}}\right) + e^{\frac{(v+y)x}{2D}} erfc\left(\frac{x + yt}{2\sqrt{Dt}}\right)\right)\right)$$

where $y = \sqrt{v^2 - 4D}$. With the help of developed python programme DCE, the numerical solutions of the time fractional drug concentration equation for $\alpha = 1.0, 0.9, 0.8$ with the parameters $v = 1, D = 0.2, \Delta x = 0.01$ and $\Delta t = 0.001$ is represented graphically in Figure 5. Furthermore, we simulate the numerical solutions of the time fractional drug concentration equation for different values of x in Figure 6. In the Table 3, we compare the exact solution and numerical solution at time $t = 3$ for $\alpha = 1$ with the parameters $v = 1, D = 0.2, \Delta x = 0.01$ and $\Delta t = 0.001$. We observe that the magnitude of the error between the exact solution and numerical solution is of $O(\Delta t + (\Delta x)^2)$.



(a) $t = 2$ (b) $t = 3$

Figure 5. Drug concentration profile with the parameters $v = 1$, $D = 0.2$, $\Delta x = 0.01$, $\Delta t = 0.001$ and $\alpha = 1.0, 0.9, 0.8$.



(a) $x = 1$ (b) $x = 2$

Figure 6. Numerical solution for drug aggregation for $x = 1$ and $x = 2$ with the parameters $v = 1$, $D = 0.2$, $\Delta x = 0.01$ and $\Delta t = 0.001$.

Table 3. Comparision of exact solution and numerical solution for $\alpha = 1$, $t = 3$, $v = 1$, $D = 0.2$, $\Delta x = 0.\ 01$ and $\Delta t = 0.001$.

x	Exact Solution	Numerical Solution	Error $e_i^k = \| \bar{c}_i^k - c_i^k \|$
0.0	2.8506387948964083	2.8486584009974187	0.0019803938989895187
0.5	2.717400152250943	2.7140190061622556	0.003381146088687448
1.0	2.495369092986084	2.490061111986018	0.005307981000065798
1.5	2.1654336714236244	2.157966519981535	0.007467151442089204
2.0	1.7376742713960167	1.7284649530934093	0.009209318302607405
2.5	1.2617161036485738	1.251930562993927	0.009785540654646763

3.0	0.8126564196023055	0.8038171392485197	0.008839280353785783
3.5	0.4565234712200368	0.44980441741804056	0.006719053801996222
4.0	0.22062447196653884	0.21636491470986893	0.004259557256669905
4.5	0.09072778152906447	0.08873837701972355	0.001989404509340917
5.0	0.03147838582653009	0.040396872611049295	0.008918486784519203

7. Conclusion

(i) We successfully develop the fractional order Crank-Nicolson finite difference scheme for the time fractional drug concentration equation in the central nervous system.

(ii) The stability and convergence of the developed scheme are both investigated.

(iii) Furthermore, we successfully develop the Python programme for the time fractional drug concentration equation in the central nervous system.

(iv) The performance and efficiency of the developed scheme is numerically tested using some numerical experiments. We observe that the error in the calculation is $O((\Delta t)^{2-\alpha} + (\Delta x)^2)$.

(v) Finally, we conclude that Python is a very powerful tool for obtaining the numerical solutions of the time fractional drug concentration equation.

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