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## NUMERICAL SOLUTION OF TIME FRACTIONAL DRUG CONCENTRATION EQUATION IN CENTRAL NERVOUS SYSTEM

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**Abstract.** The purpose of this paper is to develop the fractional order explicit finite difference scheme for time fractional drug concentration equation and obtain its numerical solution. Also, we prove that the scheme is conditionally stable and convergent. As an application of this scheme, numerical solutions of fractional order drug concentration equation in the Central Nervous System (CNS) is obtained and these are simulated graphically using Python.

**Keywords:** fractional differential equation; Caputo derivative; numerical method; CNS; python.

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### 1. INTRODUCTION

Pharmacokinetics is the branch of Pharmacology dedicated to study the time course of drug absorption, distribution, metabolism and excretion [1]. Also, it determines how the body affect

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a specific drug/chemical after administration through the mechanism of absorption and distribution, as well as metabolic changes of the drug in the body. Now a days, the treatment of CNS diseases such as Trauma, Expressive aphasia, Alzheimer's disease, Sclerosis, Parkinson's disease etc. are major problem in modern clinical world. There are many drugs available that treat symptoms rather than the disease [2]. Therefore, new drugs and new techniques of treatment are needed. Also, we observed that many new drugs have significant effect in laboratory but that fails in clinical studies. The main reason of this failure is that the drugs are given at the wrong dose or schedule, or they do not reach the target site of CNS in the right concentration because they can not cross the blood-brain-barrier [2, 3]. To reach the concentration of drug to the target site of CNS overdoses must be avoided, since these drugs might have negative effect on healthy cells in the body. Therefore, it is important to predict the drug concentration at the CNS target site, which is the brain Extracellular fluid (ECF), in order to give the right drug at the right time and dose. In human, Cerebrospinal fluid (CSF) is easily accessible fluid which can be used to predict the drug concentration in CNS target site. Recently, many researchers describe the phenomenon of drug distribution, absorption, metabolism and excretion using mathematical modeling with the help of ordinary differential equation [4].

Most of the researchers in pharmacokinetics have studied drug concentration in various compartment namely Blood, Stomach, Neuron, Liver, Gastrointestinal, Astrocyte etc. by integer-order modelling [4]. Furthermore, Westerhout et. al in [5] and [6] has developed the integer-order multi-compartmental model describing the change in concentration over time in CSF system. Also, some of researchers have developed a mathematical model based on partial derivatives describing the change in the drug concentration over time along a CSF system. The main advantage of mathematical modeling involving partial derivatives instead of ordinary derivatives is that it describes the concentration in any point of the CSF system at any time in single equation. Fractional calculus is rapidly developing branch of applied mathematics which deals with the study of non-integer order derivatives and non-integer order integrals. The main reason to choose a fractional order model is its non-local characteristic which describe the drug concentration at CNS target site more preciously [7]. Fractional order model provides better physical interpretation rather than integer order model, because it provides results at any intermediate

stage by considering all the inputs starting from initial stage rather than only previous stage [8]. In last two decades, the fractional differential equation is successfully applied to describe the physical phenomenon in various fields like physics, engineering, finance, bio-medical, thermodynamics, robotics science etc.[9, 10, 8, 11, 7, 12, 13]. There are many definitions of fractional derivatives and different numerical methods are available in literature to solve the fractional differential equations [14, 12, 15, 16]. 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 [17]. Finite difference methods are more effective and commonly used to solve fractional differential equations [18, 19, 20, 21, 22, 23, 24]. In this connection, we study a time fractional drug concentration equation. Furthermore, we develop the fractional order explicit finite difference scheme for time fractional drug concentration equation and obtain its numerical solution.

We organized the paper as follows: In section 2, we develop the fractional order explicit 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, the convergence of the scheme is discussed up to the length. In section 5, the numerical solution of the time fractional drug concentration equation is computed and it is simulated graphically by Python programme.

We consider the time fractional drug concentration equation (TFDCE) with initial and boundary conditions as follows

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

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

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

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 of drug. We discretized time fractional order derivatives in the Caputo sense. Therefore, the Caputo derivative of order  $\alpha$  is defined as follows [15, 23]:

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

where  $\Gamma$  is the gamma function defined as:

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

## 2. FINITE DIFFERENCE SCHEME

In this section, we develop the fractional order explicit finite difference scheme for time fractional drug concentration equation (1.1) – (1.3). For this, we define  $x_i = i\Delta x$ ,  $i = 0, 1, 2, 3, \dots, M$  and  $t_k = k\Delta t$ ,  $k = 0, 1, 2, 3, \dots, N$ ; where  $\Delta x = \frac{L}{M}$  and  $\Delta t = \frac{T}{N}$ . Let  $c(x_i, t_k)$ ,  $i = 0, 1, 2, 3, \dots, M$  and  $k = 0, 1, 2, 3, \dots, N$ ; be the exact solution of time fractional drug concentration equation (1.1) – (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  $t = t_{k+1}$ , we discretize the space derivatives  $\frac{\partial c}{\partial x}$  and  $\frac{\partial^2 c}{\partial x^2}$  respectively as follows

$$(2.1) \quad \left(\frac{\partial c}{\partial x}\right)_{(x_i, t_{k+1})} = \frac{c_{i+1}^k - c_{i-1}^k}{2\Delta x} + O(\Delta x)$$

and

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

The Caputo time fractional derivative of order  $\alpha$  is discretized as follows

$$\begin{aligned} \left(\frac{\partial^\alpha c}{\partial t^\alpha}\right)_{(x_i, t_{k+1})} &= \frac{1}{\Gamma(1-\alpha)} \int_0^{t_{k+1}} (t_{k+1} - s)^{-\alpha} \frac{\partial c(x_i, s)}{\partial s} ds \\ &= \frac{1}{\Gamma(1-\alpha)} \sum_{j=0}^k \int_{t_j}^{t_{j+1}} (t_{k+1} - s)^{-\alpha} \left[ \frac{c_i^{j+1} - c_i^j}{\Delta t} + O(\Delta t) \right] ds \\ &= \frac{1}{\Gamma(1-\alpha)} \sum_{j=0}^k \left[ \frac{c_i^{j+1} - c_i^j}{\Delta t} + O(\Delta t) \right] \int_{t_j}^{t_{j+1}} (t_{k+1} - s)^{-\alpha} ds \\ &= \frac{1}{\Gamma(1-\alpha)} \sum_{j=0}^k \left[ \frac{c_i^{j+1} - c_i^j}{\Delta t} + O(\Delta t) \right] \left[ \frac{(k-j+1)^{1-\alpha} - (k-j)^{1-\alpha}}{(1-\alpha)(\Delta t)^{\alpha-1}} \right] \\ &= \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^k \left[ c_i^{k-j+1} - c_i^{k-j} + O(\Delta t) \right] \left[ (j+1)^{1-\alpha} - j^{1-\alpha} \right] \end{aligned}$$

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

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

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

$$(2.3) \quad \left( \frac{\partial^\alpha c}{\partial t^\alpha} \right)_{(x_i, t_{k+1})} = \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \left[ c_i^{k+1} - c_i^k \right] + \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=1}^k b_j \left[ c_i^{k-j+1} - c_i^{k-j} \right] + O(\Delta t)$$

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

$$\frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \left[ c_i^{k+1} - c_i^k \right] + \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=1}^k b_j \left[ c_i^{k-j+1} - c_i^{k-j} \right] = -v \left[ \frac{c_{i+1}^k - c_{i-1}^k}{2\Delta x} \right] + D \left[ \frac{c_{i-1}^k - 2c_i^k + c_{i+1}^k}{(\Delta x)^2} \right]$$

$$\left[ c_i^{k+1} - c_i^k \right] + \sum_{j=1}^k b_j \left[ c_i^{k-j+1} - c_i^{k-j} \right] = -v \frac{(\Delta t)^\alpha \Gamma(2-\alpha)}{2\Delta x} \left[ c_{i+1}^k - c_{i-1}^k \right] + D \frac{(\Delta t)^\alpha \Gamma(2-\alpha)}{(\Delta x)^2} \left[ c_{i-1}^k - 2c_i^k + c_{i+1}^k \right]$$

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

$$\left[ c_i^{k+1} - c_i^k \right] + \sum_{j=1}^k b_j \left[ c_i^{k-j+1} - c_i^{k-j} \right] = -\mu \left[ c_{i+1}^k - c_{i-1}^k \right] + r \left[ c_{i-1}^k - 2c_i^k + c_{i+1}^k \right]$$

$$(2.4) \quad c_i^{k+1} = (1 - 2r)c_i^k - \sum_{j=1}^k b_j \left[ c_i^{k-j+1} - c_i^{k-j} \right] + (r + \mu)c_{i-1}^k + (r - \mu)c_{i+1}^k$$

After simplification, for  $k=1, 2, 3, \dots, N$ ; we obtain

$$(2.5) \quad c_i^{k+1} = (r + \mu)c_{i-1}^k + (1 - 2r - b_1)c_i^k + (r - \mu)c_{i+1}^k + \sum_{j=1}^{k-1} \left[ b_j - b_{j+1} \right] c_i^{k-j} + b_k c_i^0.$$

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

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

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

$$(2.7) \quad c_i^0 = 0, i = 1, 2, 3, \dots, M.$$

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

$$(2.8) \quad c(0, t_k) = g(t_k) \text{ implies } c_0^k = g(t_k), k = 0, 1, 2, 3, \dots, N.$$

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,

$$(2.9) \quad c_{M+1}^k = c_{M-1}^k, k = 0, 1, 2, 3, \dots, N.$$

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

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

(2.11)

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

$$(2.12) \quad \text{initial condition: } c_i^0 = 0, i = 1, 2, 3, \dots, M$$

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

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

Therefore, the discretized fractional order explicit finite difference scheme (2.10) – (2.13) can be expressed in matrix form as follows:

$$(2.14) \quad C^1 = AC^0 + S^0, \text{ for } k = 0$$

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

$$(2.16) \quad \text{initial condition: } c_i^0 = 0, i = 1, 2, 3, \dots, M$$

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



are given as

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

where  $a$ ,  $b$  and  $c$  are either real or complex numbers [16].

**Theorem 3.2.** *The solution of the fractional order explicit finite difference scheme (2.10) – (2.13) for time fractional drug concentration equation (1.1) – (1.3) is conditionally stable.*

*Proof.* The eigenvalues of a tri-diagonal matrix  $A$  are given as:

$$\begin{aligned} \lambda_s(A) &= (1 - 2r) + 2\sqrt{(r + \mu)(r - \mu)} \cos\left(\frac{s\pi}{M}\right), \text{ for } s = 1, 2, 3, \dots, M \\ &= (1 - 2r) + 2\sqrt{(r^2 - \mu^2)} \cos\left(\frac{s\pi}{M}\right) \\ &\leq (1 - 2r) + 2r \\ &= 1 \\ \lambda_s(A) &= (1 - 2r) + 2\sqrt{(r + \mu)(r - \mu)} \cos\left(\frac{s\pi}{M}\right), \text{ for } s = 1, 2, 3, \dots, M \\ &\geq (1 - 2r) - 2r \\ &= 1 - 4r \\ &\geq -1 \text{ when } 1 - 4r \geq -1 \Rightarrow r \leq \frac{1}{2}. \end{aligned}$$

Therefore, for matrix  $A$ , we obtain

$$(3.1) \quad |\lambda_s(A)| \leq 1 \text{ for } 0 < r \leq \frac{1}{2}$$

Also, the eigenvalues of tri-diagonal matrix  $B$  are obtained as follows:

$$\begin{aligned} \lambda_s(B) &= (1 - 2r - b_1) + 2\sqrt{(r + \mu)(r - \mu)} \cos\left(\frac{s\pi}{M}\right), \text{ for } s = 1, 2, 3, \dots, M \\ &= (1 - 2r - b_1) + 2\sqrt{(r^2 - \mu^2)} \cos\left(\frac{s\pi}{M}\right) \\ &\leq (1 - 2r - b_1) + 2r \\ &= 1 - b_1 \\ &\leq 1 \end{aligned}$$

$$\begin{aligned} \lambda_s(B) &= (1 - 2r - b_1) + 2\sqrt{(r + \mu)(r - \mu)} \cos\left(\frac{s\pi}{M}\right), \text{ for } s = 1, 2, 3, \dots, M \\ &\geq (1 - 2r - b_1) - 2r \\ &= 1 - 4r - b_1 \\ &\geq -1 \text{ when } 1 - 4r - b_1 \geq -1 \Rightarrow r \leq \frac{2 - b_1}{4}. \end{aligned}$$

Therefore, for matrix B, we obtain

$$(3.2) \quad |\lambda_s(B)| \leq 1 \text{ for } 0 < r \leq \frac{2 - b_1}{4}$$

Hence, from equations (3.1) and (3.2), we see that the solution of the fractional order finite difference scheme (2.10) – (2.13) is stable if  $r \leq \min\{\frac{1}{2}, \frac{2 - b_1}{4}\}$ .

This proves the theorem. □

#### 4. CONVERGENCE

In this section, we discuss the convergence of the scheme. Let  $\Omega$  be the region  $[0, L] \times [0, T]$ . We introduce the vector,  $\bar{C}^k = (\bar{c}(x_0, t_k), \bar{c}(x_1, t_k), \bar{c}(x_2, t_k), \dots, \bar{c}(x_M, t_k))^T$  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  $\tau^k = (\tau_1^k, \tau_2^k, \tau_3^k, \dots, \tau_M^k)^T$  be the vector of truncation error at time level  $t_k$ . Then from finite difference scheme (2.10) – (2.13) we have,

$$\begin{aligned} \tau_i^1 &= c_i^1 - (r + \mu)c_{i-1}^0 - (1 - 2r)c_i^0 - (r - \mu)c_{i+1}^0 = O(\Delta t + (\Delta x)^2), \text{ for } k = 0 \\ \tau_i^{k+1} &= c_i^{k+1} - (r + \mu)c_{i-1}^k - (1 - 2r - b_1)c_i^k - (r - \mu)c_{i+1}^k - \sum_{j=1}^{k-1} [b_j - b_{j+1}]c_i^{k-j} - b_k c_i^0 = \\ &O(\Delta t + (\Delta x)^2), \text{ for } k \geq 1 \end{aligned}$$

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

- (i)  $b_j > 0$
- (ii)  $b_j > b_{j+1}$

**Lemma 4.2.** *If  $\lambda_s(A)$  and  $\lambda_s(B)$  represents the eigenvalues of A and B respectively, then*

- (i)  $|\lambda_s(A)| \leq 1, |\lambda_s(B)| \leq 1, s = 1, 2, 3, \dots, M.$
- (ii)  $\|A\|_\infty \leq 1, \|B\|_\infty \leq 1.$

**Theorem 4.3.** *If  $r \leq \min\{\frac{1}{2}, \frac{2 - b_1}{4}\}$ , then the fractional order explicit finite difference scheme (2.10) – (2.13) for time fractional drug concentration equation (1.1) – (1.3) is convergent.*

*Proof.* Let,  $\bar{C}^k = [\bar{c}_1^k, \bar{c}_2^k, \bar{c}_3^k, \dots, \bar{c}_M^k]^T$  and  $C^k = [c_1^k, c_2^k, c_3^k, \dots, c_M^k]^T$  be the vectors of exact solution and approximate solution of the time fractional drug concentration equation (1.1) – (1.3) respectively at time level  $t_k$ .

Now, we set  $E^k = \bar{C}^k - C^k = [e_1^k, e_2^k, e_3^k, \dots, e_M^k]^T$  be the error vector in the solution at time level  $t_k$ . Suppose,

$$|e_l^k| \leq \max_{1 \leq i \leq M} |e_i^k| = \|E^k\|_\infty, \text{ for } l = 1, 2, 3, \dots$$

and

$$|\tau_l^k| \leq \max_{1 \leq i \leq M} |\tau_i^k| = O(\Delta t + (\Delta x)^2), \text{ for } l = 1, 2, 3, \dots$$

As  $\bar{C}^k$  is the vector of exact solution of the equation (1.1) – (1.3), it will satisfy the equations (2.14) and (2.15) given as

$$(4.1) \quad \bar{C}^1 = A\bar{C}^0 + S^0 + \tau^1, \text{ for } k = 0$$

$$(4.2) \quad \bar{C}^{k+1} = B\bar{C}^k + \sum_{j=1}^{k-1} (b_j - b_{j+1})\bar{C}^{k-j} + b_k\bar{C}^0 + S^k + \tau^{k+1}, \text{ for } k \geq 1$$

By induction, we prove the scheme is convergent. That is to prove,

$$(4.3) \quad \|E^n\|_\infty \leq KO(\Delta t + (\Delta x)^2), n = 1, 2, 3, \dots$$

For  $n=1$ , from equations (2.14) and (4.1), we obtain

$$\begin{aligned} E^1 &= AE^0 + \tau^1 \\ \therefore \|E^1\|_\infty &= \|AE^0 + \tau^1\|_\infty \\ &\leq \|AE^0\|_\infty + \|\tau^1\|_\infty \\ &\leq \|A\|_\infty \|E^0\|_\infty + \|\tau^1\|_\infty \\ &\leq \|E^0\|_\infty + \|\tau^1\|_\infty \\ &\leq KO(\Delta t + (\Delta x)^2) \end{aligned}$$

where  $K$  is independent of  $x$  and  $t$ . Thus, result is true for  $n = 1$ .

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

$$\|E^k\|_\infty \leq KO(\Delta t + (\Delta x)^2).$$

Now, for  $n = k + 1$ , from equations (4.2) and (2.15), we obtain

$$\begin{aligned} E^{k+1} &= BE^k + \sum_{j=1}^{k-1} (b_j - b_{j+1})E^{k-j} + b_k E^0 + \tau^{k+1} \\ \therefore \|E^{k+1}\|_\infty &\leq \|BE^k\|_\infty + \left\| \sum_{j=1}^{k-1} (b_j - b_{j+1})E^{k-j} \right\|_\infty + \|b_k E^0\|_\infty + \|\tau^{k+1}\|_\infty \\ &\leq \|B\|_\infty \|E^k\|_\infty + |(b_1 - b_2)| \cdot \|E^{k-1}\|_\infty + |(b_2 - b_3)| \cdot \|E^{k-2}\|_\infty + |(b_3 - b_4)| \cdot \|E^{k-3}\|_\infty \\ &\quad + \dots + |(b_{k-1} - b_k)| \cdot \|E^1\|_\infty + |b_k| \cdot \|E^0\|_\infty + \|\tau^{k+1}\|_\infty \\ &\leq [1 + (b_1 - b_2) + (b_2 - b_3) + (b_3 - b_4) + \dots + (b_k - b_{k-1})] K_1 O(\Delta t + (\Delta x)^2) + \|\tau^{k+1}\|_\infty \\ &\leq [1 + b_1 - b_k] K_1 O(\Delta t + (\Delta x)^2) + K_2 O(\Delta t + (\Delta x)^2) \\ &= KO(\Delta t + (\Delta x)^2) \end{aligned}$$

where  $K = \max\{K_1, K_2\}$  is the positive number independent of  $x$  and  $t$ . Hence, by induction, for all  $n$ , we prove

$$\|E^n\|_\infty \leq KO(\Delta t + (\Delta x)^2).$$

Therefore, this shows that if  $r \leq \min\{\frac{1}{2}, \frac{2-b_1}{4}\}$ , then as  $(\Delta x, \Delta t) \rightarrow (0, 0)$ , the vector  $C^n$  converges to  $\bar{C}^n$ .

Hence, this complete the proof. □

### 5. 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 explicit finite difference scheme (2.10) – (2.13).

**5.1. Test Problem 1: Stable Concentration.** In this case we consider a stable concentration level in the brain ECF. Therefore, this situation corresponds to where the steady state has been reached and maintenance dose is given in order to keep the drug concentration constant in the

brain ECF [2]. 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

$$\frac{\partial^\alpha c(x,t)}{\partial t^\alpha} = -v \frac{\partial c(x,t)}{\partial x} + D \frac{\partial^2 c(x,t)}{\partial x^2}, \quad 0 < \alpha \leq 1, 0 \leq x \leq 8, t \geq 0.$$

initial condition:  $c(x,0) = 0$  ( $0 < x < 8$ ).

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

The exact solution of the problem for  $\alpha = 1$  is given as [2]

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

Using python programme, we estimate the drug concentration  $c(x,t)$  for any time level  $t_k$ . In Figure 1, we simulate 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  $v=1, D=0.2, r=0.4$  and  $\Delta x=0.05$ . Futhermore, we simulate the numerical solution of the time fractional drug concentration equation for different values of  $x$  in Figure 2.

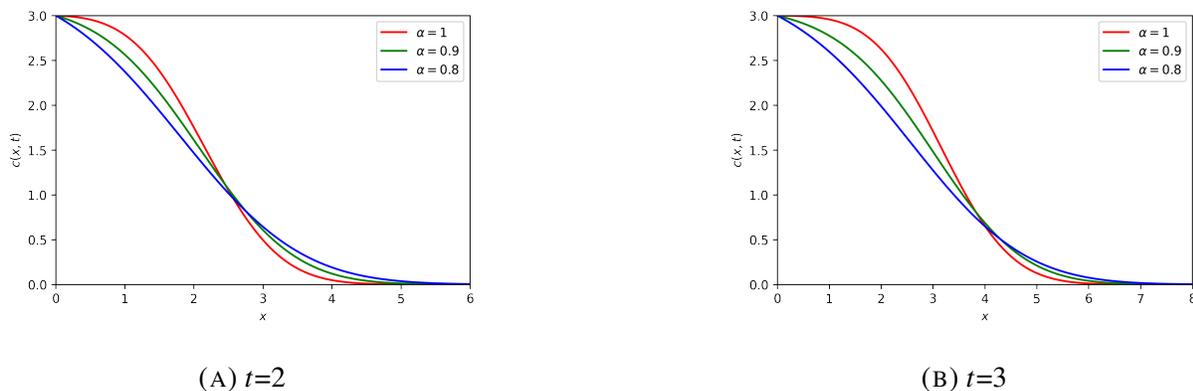


FIGURE 1. Drug concentration profile with the parameters  $v=1, D=0.2, r=0.4, \Delta x=0.05$  and  $\alpha = 1.0, 0.9, 0.8$ .

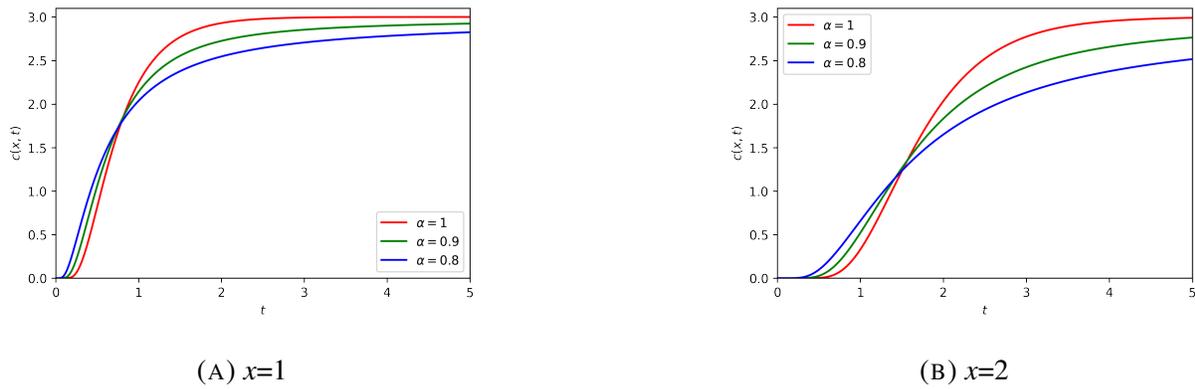


FIGURE 2. Numerical solution for stable concentration for  $x=1$  and  $x=2$  with the parameters  $\nu=1, D=0.2, r=0.4, T=5$  and  $\Delta x=0.05$ .

The magnitude of the error at time  $t = 2$  between the exact solution and numerical solution for  $\alpha=1$  with the parameters  $\nu=1, D=0.2, r=0.4$  and  $\Delta x=0.05$  is of  $O(\Delta t + (\Delta x)^2)$  shown in Table 1.

$x$	Exact Solution	Numerical Solution	Error $e_i^k = \ \bar{c}_i^k - c_i^k\ $
0.0	3.0	3.0	0.0
0.5	2.9545165012221775	2.9550346065996917	0.0005181053775142885
1.0	2.781927833666733	2.7831694361237376	0.0012416024570045536
1.5	2.3828753300625687	2.3834477931821696	0.0005724631196009078
2.0	1.7558665774889595	1.752867295242055	0.002999282246904489
2.5	1.0604625214137187	1.0528067809291066	0.007655740484612039
3.0	0.506563971783521	0.4972097212100896	0.009354250573431366
3.5	0.1868227657214106	0.17975752668707443	0.007065239034336174
4.0	0.05236011642197146	0.048816957626405165	0.003543158795566298
4.5	0.011036284861671741	0.009820254467711441	0.0012160303939603
5.0	0.0017372826433866826	0.0014472590555545842	0.00029002358783209847

TABLE 1. Comparison of exact solution and numerical solution for  $\alpha=1, t=2, \nu=1, D=0.2, r=0.4, \Delta x=0.05$ .

**5.2. 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  $c_0$  [2]. 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 be visible on such a time-scale and we will see only the elimination phase in the plot. This phenomenon is studied by the following time-fractional drug concentration equation

$$\frac{\partial^\alpha c(x,t)}{\partial t^\alpha} = -v \frac{\partial c(x,t)}{\partial x} + D \frac{\partial^2 c(x,t)}{\partial x^2}, \quad 0 < \alpha \leq 1, 0 \leq x \leq 6, t \geq 0.$$

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

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

The exact solution of the problem for  $\alpha = 1$  is given as [2]

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

where  $y = \sqrt{v^2 - 4D}$ . The numerical solutions of the time fractional drug concentration equation obtained by the developed scheme for  $\alpha=1.0, 0.9, 0.8$  with the parameters  $v=1, D=0.2, r=0.4$  and  $\Delta x=0.05$  are represented graphically by a python programme in Figure 3. Furthermore, we simulate the numerical solutions of the time fractional drug concentration equation for different values of  $x$  in Figure 4.

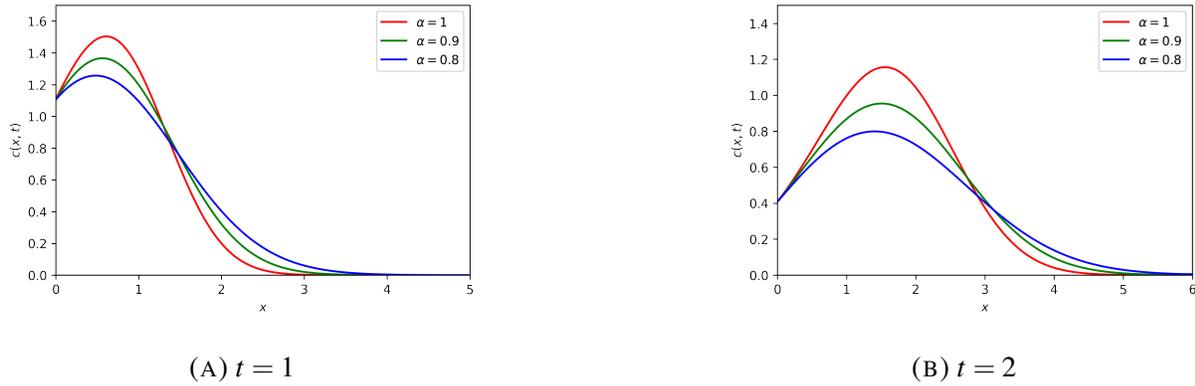


FIGURE 3. Drug concentration profile with the parameters  $v=1, D=0.2, r=0.4, \Delta x=0.05$  and  $\alpha= 1.0, 0.9, 0.8$ .

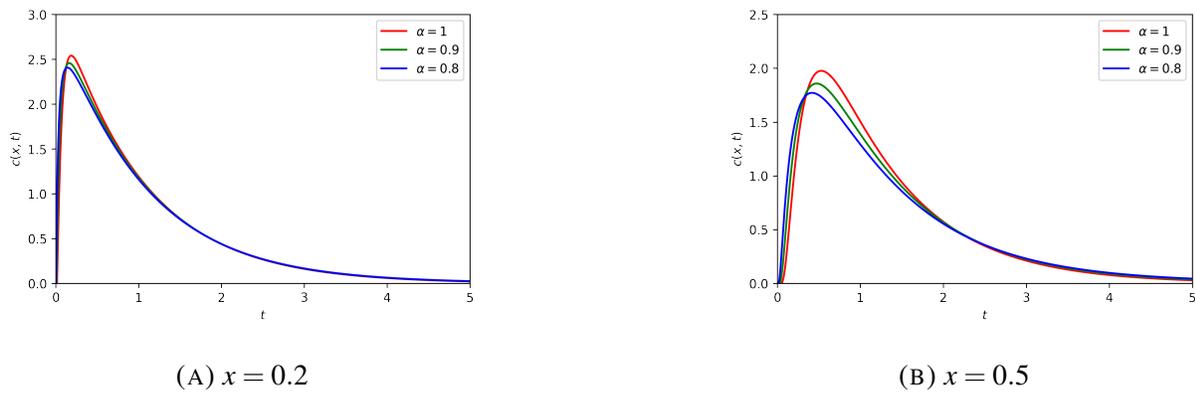


FIGURE 4. Numerical solution for drug elimination for  $x=0.2$  and  $x=0.5$  with the parameters  $v=1, D=0.2, r=0.4, T=5$  and  $\Delta x=0.05$ .

In Table 2, we observe that the magnitude of the error at time  $t=2$  between the exact solution and numerical solution for  $\alpha=1$  with the parameters  $v=1, D=0.2, r=0.4$  and  $\Delta x=0.05$  is of  $O(\Delta t + (\Delta x)^2)$ .

$x$	Exact Solution	Numerical Solution	Error $e_i^k = \ \bar{c}_i^k - c_i^k\ $
0.0	0.40600584970983805	0.4080409625005474	0.002035112790709337
0.5	0.690643252642077	0.6940200639691858	0.003376811327108764
1.0	0.9910421336946248	0.9967578907395134	0.005715757044888581
1.5	1.147116277674832	1.1543669003231574	0.007250622648325322
2.0	1.0385500472139912	1.0436653435335776	0.005115296319586404
2.5	0.72077795551975	0.7205672911170007	0.00021066440274930542
3.0	0.37847592991323475	0.37414081806396726	0.004335111849267492
3.5	0.14906463756342395	0.14446196927369298	0.004602668289730966
4.0	0.04377805649358062	0.04111085110562339	0.0026672053879572277
4.5	0.009547713552140515	0.008557105946725596	0.0009906076054149188
5.0	0.0015417744244616016	0.001293652834574765	0.00024812158988683666

TABLE 2. Comparison of exact solution and numerical solution for  $\alpha=1$ ,  $t=2$ ,  $v=1$ ,  $D=0.2$ ,  $r=0.4$ ,  $\Delta x=0.05$ .

**5.3. Test Problem 3: Drug Aggregation.** The drug aggregation corresponds to the case in which drug is given continuously over a longer period of time [2]. The drug reaches the CSF at time  $t=0$  and no drug was present in the brain ECF 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

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

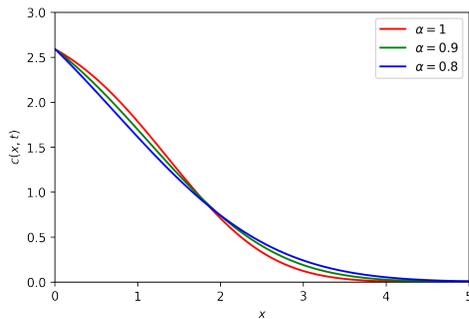
$$\text{initial condition: } c(x,0) = 0, \quad 0 < x < 5.$$

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

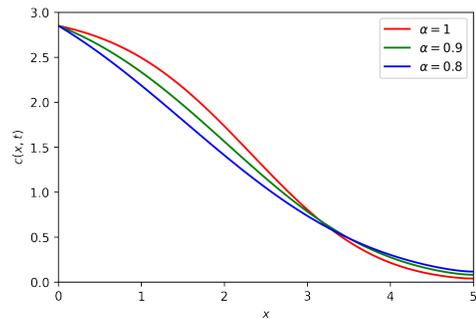
The exact solution of the problem for  $\alpha = 1$  is given as [2]

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

where  $y = \sqrt{v^2 - 4D}$ . By using python, 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  $v=1, D=0.2, r=0.4$  and  $\Delta x=0.05$  are represented graphically in Figure 5. Furthermore, we simulate the numerical solutions of the time fractional order drug concentration equation for different values of  $x$  in figure 6.

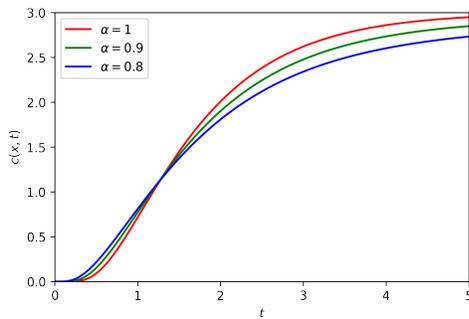


(A)  $t = 2$

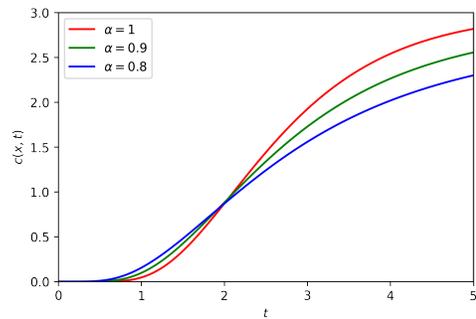


(B)  $t = 3$

FIGURE 5. Drug concentration profile with the parameters  $v=1, D=0.2, r=0.4, \Delta x=0.05$  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  $v=1, D=0.2, r=0.4, T=5$  and  $\Delta x=0.05$ .

In the Table 3, we compare the exact solution and numerical solution at time  $t=3$  for  $\alpha=1$  with the parameters  $\nu=1$ ,  $D=0.2$ ,  $r=0.4$  and  $\Delta x=0.05$ . Furthermore, we observe that the magnitude of the error in the calculation is of  $O(\Delta t + (\Delta x)^2)$ .

$x$	Exact Solution	Numerical Solution	Error $e_i^k = \ \bar{c}_i^k - c_i^k\ $
0.0	2.8506387948964083	2.849890118740241	0.0007486761561672495
0.5	2.717400152250943	2.716481674246823	0.000918478004119816
1.0	2.495369092986084	2.494071604980657	0.001297488005426839
1.5	2.1654336714236244	2.163208367038135	0.0022253043854894017
2.0	1.7376742713960167	1.7337657640134156	0.0039085073826010674
2.5	1.2617161036485738	1.255732029905071	0.005984073743502849
3.0	0.8126564196023055	0.8051728160752607	0.007483603527044802
3.5	0.4565234712200368	0.44901165243300384	0.007511818787032942
4.0	0.22062447196653884	0.21459328651648493	0.006031185450053905
4.5	0.09072778152906447	0.08707831854784201	0.0036494629812224566
5.0	0.03147838582653009	0.03891973887140211	0.0074413530448720205

TABLE 3. Comparison of exact solution and numerical solution for  $\alpha=1$ ,  $t=3$ ,  $\nu=1$ ,  $D=0.2$ ,  $r=0.4$ ,  $\Delta x=0.05$ .

## 6. CONCLUSION

- (i) We successfully developed the fractional order explicit finite difference scheme for the time fractional drug concentration equation in central nervous system and obtain its numerical solution.
- (ii) Also, we prove the developed scheme is conditionally stable and the bound of stability is  $0 \leq \min\{\frac{1}{2}, \frac{2-b_1}{4}\}$ , where  $0 \leq b_1 < 1$ .
- (iii) In all cases, we obtain the numerical solutions by Python and these solutions are represented graphically, we observe that the error in the calculation is  $O(\Delta t + (\Delta x)^2)$ .

- (iv) Finally, we conclude that Python is a very powerful tool for obtaining the numerical solutions of the time fractional drug concentration equation in central nervous system and represent the solutions graphically.

## CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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