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RESEARCH ARTICLE

Fractional Order Mathematical Model to Investigate Topical Drug Diffusion in Human Skin

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Abstract

Objectives: The primary objective of this research paper is to gain a comprehensive understanding of drug diffusion within the human dermal region. **Methods:** A temporal fractional-order reaction-diffusion equation with Caputo sense is employed to get mathematical insights on the diffusion of drugs in the human dermal region. The explicit finite difference method is employed to numerically solve the modelled problem. A Python-based algorithm is employed to obtain a numerical solution through the finite difference method. **Finding:** In our research, we focused on examining how fractional-order parameters affect the distribution and concentration profiles of drugs in the dermal region. To convey our findings effectively, we conducted a comprehensive analysis, primarily using graphical representations. These visualizations offer a clear and insightful view of the drug's diffusion rate within the dermal region, taking into account the memory effect associated with the Caputo derivative. In addition to our exploration of fractional-order parameters and drug diffusion profiles, we conducted a comprehensive investigation into the stability and convergence of the explicit finite difference method. **Novelty:** The fractional order explicit finite difference method can be used to estimate drug concentration in the human skin. An algorithm based on Python provides powerful tool for obtaining numerical solution of fractional order differential equations.

Keywords: Drug Diffusion; Numerical Method; Dermal Region; Caputo Derivative; Python

1 Introduction

In modern medical practice, drug delivery predominantly comprises three main methods: topical application, oral ingestion, and injectable administration [1,2]. Each of these methods has some advantages and disadvantages. In oral ingestion, drugs pass through the digestive system before entering the bloodstream, while injection

administration directly enter the bloodstream. Topical medication involves applying drugs directly to the skin's surface. While topical medication offers numerous advantages, the process of drug diffusion from the skin's surface to the desired destination can be complex and time-consuming. It is of utmost importance to comprehend this drug diffusion process to enhance the effectiveness of topical treatments in pharmaceutics and cosmetic. Numerous studies have thoroughly examined the mathematical modeling of drug diffusion within human skin. The detailed review paper published by S. Supe and P. Takudage provides an overview of various methods and techniques used to estimate penetration, permeation and absorption of drugs in transdermal drug delivery systems [3]. Furthermore, it explores the fundamental aspects of skin physiology and the variables that influence drug penetration. F. Jonsdottir, B.S. Snorradottir, S. Gunnarsson, E. Georgsdottir, and S. Sigurdsson conducted a study on a transdermal delivery model describing the parameters that affect drug permeation through the skin layer [4]. They used a multi-compartmental numerical model based on Fickian diffusion to determine the parameters and found that the partition between layers and the mass transfer coefficient are important factors in drug permeation. A. Benslimane, S. Fatmi, L. Taouzinet, and D. Hammiche conducted a study on the unsteady diffusion of transdermal drug delivery with the use of a microneedle inserted into the skin [5]. They explored a mathematical model based on Fick's law to investigate the impact of the diffusion coefficient, initial concentration, and length on drug concentration. S. Mubarak, M. A. Khanday, A. H. Lone, and N. Rasool examined a reaction-diffusion model for dermal drug diffusion [6]. They derived an analytical solution for the model by dividing the dermal region into seven compartments and presented drug concentration and diffusion profiles for each layer. Recently, M. Cukic and S. Galovic conducted a study on a fractional-order mathematical model based on Fick's law, and they presented an analytical solution demonstrating anomalous diffusive behaviour of drugs in the transdermal region [7]. Furthermore, M. Caputo and C. Cametti have authored an informative review paper that centers on modeling drug transportation within human skin while incorporating memory effects [2]. They conducted a comparison between the outcomes produced by the proposed models and experimental results, and they discovered that fractional-order modeling aligns with the experimental data.

It has been observed that the majority of mathematical models for drug diffusion in the skin are rooted in ordinary and partial differential equations, with limited emphasis on incorporating memory effects. In recent time, non-integer order differential equations have gained prominence in various fields due to their ability to account for memory effects and long-range dependencies. Fractional order modeling has found successful applications in diverse fields, including physics, engineering [8], economics [9], viscoelasticity [10], medicine [11], heat transfer [12], pharmacokinetics [13] and more, to describe various physical phenomena. The application of fractional differential equations in biology has been widespread, as they demonstrate a capacity to capture memory effects, long-range dependencies, and complex dynamics within biological systems [14]. This advantage arises due to the power-law kernal of the Caputo derivative, where the memory effect become more pronounced at small time values. Drawing from this context and considering the memory effect associated with fractional derivatives, our study extends the conventional model of drug diffusion [15] to a fractional-order mathematical model with the goal of predicting drug diffusion within the human dermal region. Unfortunately, finding exact solutions to most fractional differential equations is a challenging task due to their complex nature and non-linearity. To tackle this issue, numerical methods play a crucial role. Among the various numerical methods available [16], the finite difference method stands out an effective and commonly used approach.

A notable research gap identified in the literature is the prevalent use of integer-order derivatives in mathematical models for drug diffusion in human skin, neglecting memory effects. Given the complex and non-Markovian nature of biological processes, fractional order differential equations are better suited to explain events with persistent effects from the past. In this paper, a fractional-order explicit finite difference method is developed to address the challenge of drug diffusion within the skin. The results obtained from this approach are presented graphically using a Python program, which provides valuable insights into drug diffusion in the dermal region.

2 Methodology

2.1 Preliminaries

Definition 1 The Gamma function is defined as [16]

$$\Gamma(\eta) = \int_0^\infty e^{-t} t^{\eta-1} dt. \tag{1}$$

Definition 2 The fractional order $\alpha \in (0,1]$ derivative of a function $u(x,t)$ in Caputo sense is given as [16]

$$\frac{\partial^\alpha u(x,t)}{\partial t^\alpha} = \begin{cases} \dfrac{1}{\Gamma(1-\alpha)} \displaystyle\int_0^t \frac{u_t(x,s)}{(x-s)^\alpha}\, ds, & for\ \alpha \in (0,1). \\ \dfrac{\partial u(x,t)}{\partial t}, & for\ \alpha = 1. \end{cases} \tag{2}$$

2.2 Mathematical Model

In order to formulate the mathematical model of drug diffusion, we examine a solitary dermal layer within the human body. This skin layer spans a distance of 1 unit length from 0 to 1. The drug is administered onto the skin's outermost surface at spatial point $x = 0$, which corresponds to the epidermis. Subsequently, the drug undergoes a downward diffusion, propagating to locations situated beneath the skin's surface. The outermost layer of the dermal layer corresponds to the epidermis, while the underlying dermal layer possesses an approximate thickness of 2 mm, as referenced in the literature [15]. The domain of interest in this study encompasses the dermal layer, extending up to about 0.1 mm from the epidermis. Recognizing the significant disparity in thickness between the epidermis and the dermal layer, we adopt the assumption that the epidermis is situated at the spatial coordinate $x = 0$. The depth coordinates of the initial dermal layer are modified proportionally, taking into account the maximum achievable depth of the dermal layer. As a result, a length of one unit corresponds to an actual measurement of two millimeters. Considering the provided assumptions and applying scaling, we examine the temporal fractional drug diffusion equation (TFDDE), derived from the classical drug diffusion equation [15]. It is expressed as follows:

$$\frac{\partial^{\alpha} u(x,t)}{\partial t^{\alpha}} = D\frac{\partial^2 u(x,t)}{\partial x^2} - \theta_1 u(x,t) - \theta_2 u(x,t),\ \alpha \in [0,1], x \in [0,1], t \in [0,T]. \tag{3}$$

Here, $u(x,t)$ represents the drug amount in the dermal layer at spatial position x and time t. The parameter D denotes the mass diffusivity, θ_1 and θ_2 are positive constants. The expressions $\theta_1 u(x,t)$ and $\theta_2 u(x,t)$ characterize the rates at which drug is absorbed by the tissue and taken into the bloodstream, respectively. In Equation (3), we use the Caputo sense for the fractional derivative $\frac{\partial^{\alpha} u}{\partial t^{\alpha}}$ to account for non-classical drug diffusion behavior, capturing anomalous diffusion phenomena in specific situations. Indeed, the drug concentration in the dermal layer is initially absent everywhere except on the skin surface, where the drug is applied with a concentration value of a. Therefore, the initial condition is given as follows:

$$u(0,0) = a \quad and \quad u(x,0) = 0, \quad \forall x \in [0,1], \tag{4}$$

and the boundary conditions are:

$$u(0,t) = a \quad and \quad u(1,t) = b, \quad \forall t \in [0,T]. \tag{5}$$

2.3 Numerical Method

In this section, we will outline the development of the proposed finite difference method. This method involves discretizing the domain $[0,1] \times [0,T]$ into mesh points (x_i, t_k) in the following manner.

Let $x_i = i\Delta x$ for $i = 0,1,2,\ldots,M$, and $t_k = k\Delta t$ for $k = 0,1,2,\ldots,N$, where $\Delta x = \frac{1}{M}$ and $\Delta t = \frac{T}{N}$ represents the space and time step size, respectively. The integers M and N denotes the number of space and time subdivisions, respectively. The approximate solution of TFDDE given by the systemEquations (3), (4) and (5) is denoted as u_i^k, where $1 \le i \le M$ and $1 \le k \le N$. The discretization of the Caputo derivative $\frac{\partial^{\alpha} u}{\partial t^{\alpha}}$ for Equation (3) is given as follows [13]

$$\frac{\partial^{\alpha} u(x_i,t_{k+1})}{\partial t^{\alpha}} = \frac{\tau^{-\alpha}}{\Gamma(2-\alpha)}(u_i^{k+1} - u_i^k) + \frac{\tau^{-\alpha}}{\Gamma(2-\alpha)}\sum_{j=1}^{k}(u_i^{k-j+1} - u_i^{k-j})w_j + O(\Delta t) \tag{6}$$

where $w_j = (j+1)^{1-\alpha} - j^{1-\alpha}$, for $j \ge 1$. The spatial derivative $\frac{\partial^2 u}{\partial x^2}$ is discretized by employing a 2^{nd} order accurate central difference formula, represented as follows [13]

$$\frac{\partial^2 u(x_i,t_{k+1})}{\partial x^2} = \frac{u_{i-1}^k - 2u_i^k + u_{i+1}^k}{\Delta x^2} + O(\Delta x^2). \tag{7}$$

Now, utilizing Equations (6) and (7) in Equations (3), (4) and (5), we can present the complete discretization of the TFDDE as follows:

$$u_i^1 = ru_{i-1}^0 + (1 - \mu - 2r)u_i^0 + ru_{i+1}^0, \quad for\ k = 0, \tag{8}$$

$$u_i^2 = ru_{i-1}^1 + (1 - \mu - 2r - w_1)u_i^1 + ru_{i+1}^1 + w_1 u_i^0, \quad for\ \ k = 1, \tag{9}$$

$$u_i^{k+1} = ru_{i-1}^k + (1-\mu-2r-w_1)\,u_i^k + ru_{i+1}^k + \sum_{j=1}^{k-1}\left(w_j - w_{j+1}\right)u_i^{k-j} + w_k u_i^0,\ \ for k \geq 1, \tag{10}$$

$$I.C.: \quad u_0^0 = a, \quad u_i^0 = 0, \quad (1 \leq i \leq M), \tag{11}$$

$$B.C.: \quad u_0^k = a, \quad u_M^k = b, \quad (1 \leq k \leq N), \tag{12}$$

where $\mu = \Gamma(2-\alpha)\Delta t^2(\theta_1+\theta_2)$, $r = D\frac{\Gamma(2-\alpha)\Delta t^\alpha}{\Delta x^2}$, and $w_j = (j+1)^{1-\alpha} - j^{1-\alpha}$ for all $j \geq 1$.

The system of Equations (8), (9), (10), (11) and (12) represent the discrete version of the TFDDE Equations (3), (4) and (5). By iterating through time steps and employing the provided initial and boundary conditions, the method enables numerical approximation of drug concentration at various spatial grid points x_i and time instances t_k within the discretized dermal region. The numerical implementation of these equations will yield a solution that provides insights into the behavior of the drug concentration over both spatial and temporal domains. The matrix form of the system Equations (8), (9) and (10) is given as follows:

$$U^1 = AU^0 + S^0, \quad for\, k = 0, \tag{13}$$

$$U^2 = BU^1 + w_1U^0 + S^1, \quad for\, k = 1, \tag{14}$$

$$U^{k+1} = BU^k + \sum_{j=1}^{k-1}\left(w_j - w_{j+1}\right)U^{k-j} + w_kU^0 + S^k,\ \ for k \geq 2. \tag{15}$$

Here, both $U^k = \begin{bmatrix} u_1^k \\ u_2^k \\ \vdots \\ u_M^k \end{bmatrix}$ and $S^k = \begin{bmatrix} ru_0^k \\ 0 \\ \vdots \\ 0 \\ ru_M^k \end{bmatrix}$ represent column vectors of length $M-1$. The matrices

A=$[a_{mn}]$ and $B = [b_{nm}]$ both are square matrices of order $M-1$, where

$$a_{mn} = \begin{cases} 1-\mu-2r\,, & if\ n = m, \\ r\,, & if\ m = n+2, \\ r\,, & if\ n = m+2, \\ 0\,, & otherwise. \end{cases}$$

and

$$b_{mn} = \begin{cases} 1-\mu-2r-w_1\,, & if\ n = m, \\ r\,, & if\ m = n+2, \\ r\,, & if\ n = m+2, \\ 0\,, & otherwise. \end{cases}$$

For numerical simulation and their graphical representation, the Python programming language is used. The Python programming language is a powerful tool for solving a system of equations [17,18].

2.4 Stability of Numerical Solution

In this context, we examine the stability of the solution obtained through the application of the explicit method Equations (8), (9), (10), (11) and (12) to the TFDDE Equations (3), (4) and (5).

Lemma 1 If δ_1, δ_2 and δ_3 are constants, then the eigenvalues of tridiagonal matrix of size (M-1) [13]

$$\begin{pmatrix} \delta_1 & \delta_2 & & & & & \\ \delta_3 & \delta_1 & \delta_2 & & & & \\ & \ddots & \ddots & \ddots & & & \\ & & \delta_3 & \delta_1 & \delta_2 & & \\ & & & \ddots & \ddots & \ddots & \\ & & & & \delta_3 & \delta_1 & \delta_2 \\ & & & & & \delta_3 & \delta_1 \end{pmatrix}$$

are $\lambda_j = \delta_1 + 2\sqrt{\delta_2\delta_3}\, cos\left(\frac{j\pi}{M}\right),\ \ j = 1,2,\ldots,M-1.$

Theorem 1 If $0 < r \leq min\left\{\frac{2-\mu}{4}, \frac{2-\mu-w_1}{4}\right\}$, then numerical solution of fractional order explicit finite difference method described by system of Equations (8), (9), (10), (11) and (12) for TFDDE Equations (3), (4) and (5) is stable.

Proof. According to Lemma 1, the eigen values of the tridiagonal matrix A are given below, for every $i = 1,2,\ldots,M$;

$\lambda_i(A) = (1-\mu-2r) + 2rcos\left(\frac{i\pi}{M}\right) \leq (1-\mu-2r) + 2r = (1-\mu) \leq 1.$

Also, $\lambda_i(A) = (1-\mu-2r) + 2rcos\left(\frac{i\pi}{M}\right) \geq (1-\mu-2r) - 2r = 1-4r-\mu.$

$\therefore \lambda_i(A) \geq -1\ when\ 1-4r-\mu \geq -1 \Rightarrow r \leq \frac{2-\mu}{4}$.

Therefore, for matrix A, for all $i = 1,2,\cdots,M-1$;

$$|\lambda_i(A)| \leq 1\ when\ 0 < r \leq \frac{2-\mu}{4}\ . \tag{16}$$

Similarly, for matrix B, for all $i = 1,2,\ldots,M$,

$\lambda_i(B) = (1-\mu-2r-w_1) + 2rcos\left(\frac{i\pi}{M}\right) \leq 1-\mu-w_1 \leq 1.$

and,

$$\lambda_i(B) = (1-\mu-2r-w_1) + 2rcos\left(\frac{i\pi}{M}\right) \geq (1-\mu-2r-w_1) - 2r = 1-4r-\mu-w_1.$$

$\therefore \lambda_i(B) \geq -1\ \ when\ 1-4r-\mu-w_1 \geq -1 \Rightarrow r \leq \frac{2-\mu-w_1}{4}$.

Therefore,

$$|\lambda_i(B)| \leq 1\ when\ 0 < r \leq \frac{2-\mu-w_1}{4}\ ,\quad \forall\, i = 1,2,\ldots,M-1. \tag{17}$$

Hence, it can be deduced from Equations (16) and (17) that the solution, obtained through the explicit method Equations (8), (9) and (10) for TFDDE Equations (3), (4) and (5), remains stable when $0 < r \leq min\left\{\frac{2-\mu}{4}, \frac{2-\mu-w_1}{4}\right\}$.

2.5 Convergence of the Method

Let $\overline{U}^k = \left(\overline{u}_0^k, \overline{u}_1^k, \ldots, \overline{u}_M^k\right)^T$ and $U^k = \left(u_0^k, u_1^k, \ldots, u_M^k\right)^T$ representing the vectors for exact and approximate solutions, respectively, of the drug diffusion model described by Equations (3), (4) and (5).

Define, $\tau^k = (\tau_1^k, \tau_2^k, \ldots, \tau_M^k)^T$ be the truncation error vector at time t_k. By utilizing the finite difference method given by Equations (8), (9) and (10), we can express the following relationship:

$\tau_i^1 = u_i^1 - ru_{i-1}^0 - (1-\mu-2r)u_i^0 - ru_{i+1}^0 = O(\Delta x^2 + \Delta t),\ \ for\ k = 0,$

$\tau_i^2 = u_i^2 - ru_{i-1}^1 - (1-\mu-2r-w_1)u_i^1 - ru_{i+1}^1 - w_1u_i^0 = O(\Delta x^2 + \Delta t),\ \ for\ k = 1,$

$$\tau_i^{k+1} = u_i^{k+1} - ru_{i-1}^k - (1-\mu-2r-w_1)u_i^k - ru_{i+1}^k - \sum_{j=1}^{k-1}(w_j - w_{j+1})u_i^{k-j} - w_ku_i^0$$

$= O\left(\Delta x^2 + \Delta t\right),\ \ for\ k \geq 2.$

Lemma 2 For all $j \geq 0$, the term w_j satisfies the following conditions

(i) w_0=1.

(ii) All w_j are positive.

(iii) $w_j > w_{j+1}$

Lemma 3 The tridiagonal matrices A and B, defined in Equations (13), (14) and (15), satisfies the inequalities $\| A \|_\infty \leq 1$ and $\| B \|_\infty \leq 1$.

Proof. The inequalities $\| A \|_\infty \leq 1$ and $\| B \|_\infty \leq 1$ follow directly from the Equations (16) and (17).

Theorem 2 If $0 < r \leq min\left\{\frac{2-\mu}{4}, \frac{2-\mu-w_1}{4}\right\}$, then the fractional-order explicit method described by the systems Equations (8), (9) and (10), defined for the numerical solution of the TFDDE Equations (3), (4) and (5), is conditionally convergent.

Proof. Let $\overline{U}^k$ and U^k represents the vector corresponding to the exact and approximate solutions, respectively, of the TFDDE governed by Equations (3), (4) and (5) at the time step t_k.

Denote, $E^k = \overline{U}^k - U^k = (e_1^k, e_2^k, \ldots, e_M^k)^T$ be the vector of errors at t_k.

Suppose,

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

and

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

Given that $\overline{U}^k$ represents the exact solution of the TFDDE described by Equations (3), (4) and (5), it satisfies Equations (13), (14) and (15). Therefore,

$$\overline{U}^1 = A\overline{U}^0 + S^0 + \tau^1, \ \ for\ k = 0, \tag{18}$$

$$\overline{U}^2 = B\overline{U}^1 + S^1 + w_1 U^0 + \tau^2, \ \ for\ k = 1, \tag{19}$$

$$\overline{U}^{k+1} = B\overline{U}^k + \textstyle\sum_{j=1}^{k-1}(w_j - w_{j+1})\overline{U}^{k-j} + w_k\overline{U}^0 + S^k + \tau^{k+1}, \ \ for\ k \geq 2. \tag{20}$$

By employing mathematical induction, our objective is to establish that for all $n \geq 1$;

$\| E^n \|_\infty \leq \zeta O((\Delta x)^2 + \Delta t)$,

where ζ is a constant not depends on x and t.

For $n = 1$, the Equations (13) and (18) yield the equation $E^1 = AE^0 + \tau^1$. Therefore, we can derive the following inequality:

$$\| E^1 \|_\infty = \| AE^0 + \tau^1 \|_\infty \leq \| A \|_\infty \| E^0 \|_\infty + \| \tau^1 \|_\infty \leq \| E^0 \|_\infty + \| \tau^1 \|_\infty \leq \zeta O((\Delta x)^2 + \Delta t),$$

where ζ is a constant not dependent on x and t. This establishes the result when $n = 1$.

Assume the condition is true for all $n \leq k$. That means,

$\| E^k \|_\infty \leq \zeta O((\Delta x)^2 + \Delta t),\ \forall n \leq k$.

Then, for $n = k+1$, we can utilize Equations (15) and (20) to derive the following expression:

$$E^{k+1} = BE^k + \sum_{j=1}^{k-1}(w_j - w_{j+1})E^{k-j} + w_k E^0 + \tau^{k+1}.$$

$$\therefore \| E^{k+1} \|_\infty \leq \| B \|_\infty \| E^k \|_\infty + \sum_{j=1}^{k-1} |(w_j - w_{j+1})| \ \| E^{k-j} \|_\infty + |w_k| \ \| E^0 \|_\infty + \| \tau^{k+1} \|_\infty$$

$$\leq \| B \|_\infty \| E^k \|_\infty + |(w_1 - w_2)|. \| E^{k-1} \|_\infty + |(w_2 - w_3)|. \| E^{k-2} \|_\infty$$
$$+ |(w_3 - w_4)|. \| E^{k-3} \|_\infty + \cdots + |(w_{k-1} - w_k)|. \| E^1 \|_\infty + |w_k|. \| E^0 \|_\infty + \| \tau^{k+1} \|_\infty$$
$$\leq [1.\zeta_k + (w_1 - w_2)\zeta_{k-1} + (w_2 - w_3)\zeta_{k-2} + (w_3 - w_4)\zeta_{k-3}$$
$$+ \cdots + (w_k - w_{k-1})\zeta_1]O((\Delta x)^2 + \Delta t) + \| \tau^{k+1} \|_\infty$$
$$\leq \zeta^*[1 + w_1 - w_k]O((\Delta x)^2 + \Delta t) + \zeta_0 O((\Delta x)^2 + \Delta t),\ where\ \zeta^* = max\{\zeta_1, \zeta_2, \cdots, \zeta_k\}$$
$$\leq \zeta O((\Delta x)^2 + \Delta t)\ where,\ \zeta > 0\ is\ a\ constant\ not\ dependent\ on\ x\ and\ t.$$

So, by principle of mathematical induction, for all $n \geq 1$,

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

Hence, when $0 < r \leq min\left\{\frac{2-\mu}{4}, \frac{2-\mu-w_1}{4}\right\}$, as $(\Delta x, \Delta t)$ approach $(0,0)$, the vector U^n approaches the vector $\overline{U}^n$. This shows that scheme is conditionally convergent.

3 Result and Discussion

The proposed study utilizes a time fractional drug diffusion problem described by Equations (3), (4) and (5) to evaluate the diffusion of drug within the human dermal layer. To accomplish this, we employ a fractional-order explicit finite difference method, as developed in Equations (8), (9), (10), (11) and (12), to predict drug diffusion at specific grid points (x_i, t_k) within the discretized dermal region. The simulation employs dimensionless quantities. In our model problem, we employ the physiological parameters, provided in the literature[15] as: $L = 1$, $D = 0.00068$, $\theta_1 = 0.02$, $\theta_2 = 0.002$, $a = 5$, and $b = 0$. We develop following Python program "DDE" to solve the system of Equations (8), (9) and (10) with the values $\Delta x = 0.05$ and $r = 0.2$.

Inputs:

dx=Δx, dt=Δt, mu=μ, D=Diffusion coefficient, theta1=θ_1, theta2=θ_2, L=Spacial length, T=Time for estimating the solution, aa=Fractional order α, and U= Solution matrix.

3.1 Python Program DDE

```
import numpy as  np
  from math  import*
  def DDE(D,theta1,theta2,r,dx,L,T,aa):
  dt=((r*dx**2)/(D*gamma(2-aa)))**(1/aa)
  mu=(theta1+theta2)*gamma(2-aa)*(dt**aa)
  M=int(round(L/dx))
  N=int(round(T/dt))
  x=np.linspace(0,L,M+1)
  t=np.linspace(0,T,N+1)
  w=np.zeros(N+1)
  for k in range(0,N+1):
    w[k]=(k+1)**(1-aa)-k**(1-aa)
  U=np.zeros((N+1,M+1))
  for i in range(1,M):
    U[0][i]=0
    U[0][0]=5; U[0][M]=0
  for i in range(1,M):
    U [1] [i]=r*U[0][i-1]+(1-2*r-mu)*U[0][i]+r*U[0][i+1]
    U [1][0]=5; U [1][M]=0
  for i in range(1,M):
    U [3][i]=r*U [1] [i-1]+(1-2*r-mu-w [1])*U [1][i]+r*U [1][i+1]-w [1]*U[0][i]
    U [3][0]=5; U [3][M]=0
  for k in range(2,N):
    for i in range(1,M):
     S=0
     for j in range(1,k):
      S=S+(w[j]-w[j+1])*U[k-j][i]
     U[k+1][i]=r*U[k][i-1]+(1-2*r-mu-w(1))*U[k][i]+r*U[k][i+1]+S-w[k]*U[0][i]
     U[k+1][0]=5; U[n+1][M]=0
  T=int(T/dt)
  return(x, U[T])
```

The output of the **DDE** is the approximate value of the vector $u(x_i, T)$. The simulations are conducted for various time levels t and various α values. The results have been graphically represented in Figures 1, 2 and 3. These graphs represent the drug concentration profile in the human dermal region over its length. In Figure 2, we have plotted the drug concentration in the dermal region at a time $t = 1$ second for different values of α. The graph shows that at the start of the drug diffusion process in the dermal layer (i.e., at $x = 0$), the drug concentration is high on the skin's surface. However, as the distance from the surface increases, the drug concentration gradually decreases and eventually reaches zero. Furthermore, we observed that,

for different value of α, the concentration profile follows the same pattern. This suggests that the diffusion process exhibits consistent behavior irrespective of the fractional order α used in the model.

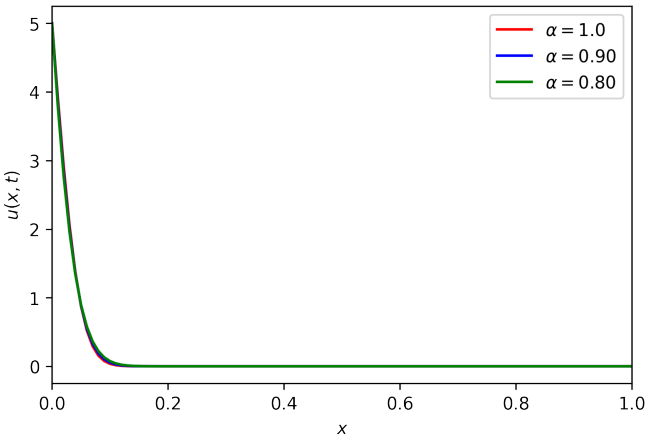

Fig 1. Drug diffusion in the skin at time $t = 1$ second and for α=1.0,0.90,0.8

Figure 2 illustrates the concentration profile of drug diffusion in the skin at four different time points: $t = 60$ seconds, $t = 600$ seconds, $t = 1800$ seconds, and $t = 3600$ seconds, each corresponding to distinct values of α. In Figure 2, we observed that the concentration of the drug in the skin decreases slowly compared to Figure 1. This observation is attributed to the increase in time. As time progresses, the drug diffuses further into the skin, leading to a gradual decrease in its concentration. Finally, based on the observations from Figure 2, we can conclude that after $t = 600$ seconds, the drug concentration profile remains the same for different values of α.

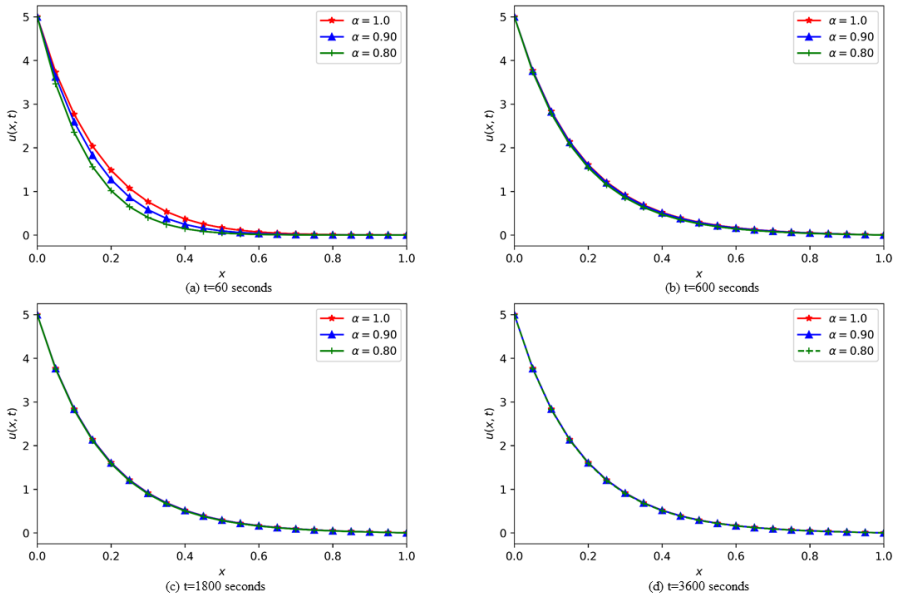

Fig 2. Simulation of drug diffusion in the skin at time$t = 60,600,1800$ *and* 3600

In Figure 3, the concentration profile is presented for different time levels with $\alpha = 1.0$ and $\alpha = 0.90$. From these representations, we observe that the rate of diffusion of drug in the skin decreases rapidly for $\alpha = 0.9$ compared to $\alpha = 1.0$. The results demonstrate excellent agreement with those reported by S. Mungkasi [15]. This consistency further validates the reliability of the proposed fractional-order explicit finite difference method and reinforces its capability to accurately predict drug diffusion in the human dermal layer.

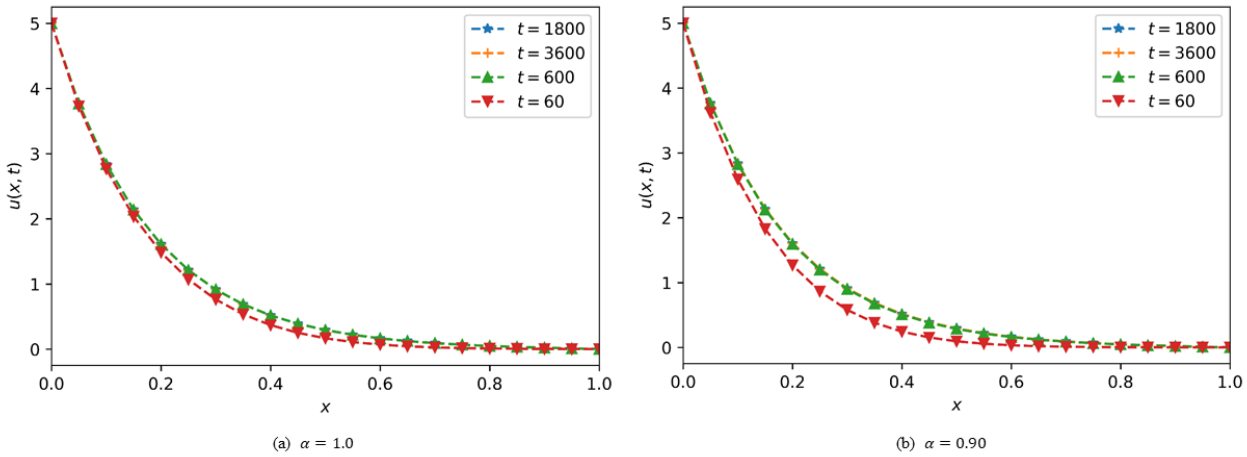

Fig 3. Simulation of drug diffusion in the skin at parameter $\alpha = 1.0$ *and* 0.90

4 Conclusion

The application of the time fractional drug diffusion equation in the Caputo sense, coupled with the fractional order finite difference technique, represents a significant advancement in the field of drug delivery and mathematical modeling of drug concentration within the dermal region of the human body. The numerical solution of the modelled problem, obtained through the developed scheme, remains stable under the condition $0 < r \leq min\left\{\frac{2-\mu}{4}, \frac{2-\mu-w_1}{4}\right\}$. In addition, the Python programming language has shown to be an efficient tool for producing numerical outcomes and simulating them across a range of α values. We employed parameter values from existing literature to conduct numerical simulations for the model. The graphical visualization reveals that, for various values of the parameter α, drug diffusion in the dermal region remains constant after t=600 seconds. This observation indicates that the diffusion process maintains a consistent behavior regardless of the specific fractional order α employed in the model. Comparing our fractional-order model with previous work underscores the smoother solutions and higher performance of our approach. This emphasizes the broader applicability and enhanced capabilities of the finite difference method in modeling topical drug diffusion. This approach has proven to be highly effective, providing a more accurate representation of drug diffusion with memory and non-local effects, which are characteristic of biological systems.

References

1) Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. *Biomaterials Research*. 2021;25(1):1–15. Available from: https://doi.org/10.1186/s40824-021-00226-6.
2) Caputo M, Cametti C. Diffusion through skin in the light of a fractional derivative approach: progress and challenges. *Journal of Pharmacokinetics and Pharmacodynamics*. 2021;48(1):3–19. Available from: https://doi.org/10.1007/s10928-020-09715-y.
3) Supe S, Takudage P. Methods for evaluating penetration of drug into the skin: A review. *Skin Research and Technology*. 2021;27(3):299–308. Available from: https://doi.org/10.1111/srt.12968.
4) Jonsdottir F, Snorradottir BS, Gunnarsson S, Georgsdottir E, Sigurdsson S. Transdermal Drug Delivery: Determining Permeation Parameters Using Tape Stripping and Numerical Modeling. *Pharmaceutics*. 2022;14(9):1–12. Available from: https://doi.org/10.3390/pharmaceutics14091880.
5) Benslimane A, Fatmi S, Taouzinet L, Hammiche D. Mathematical modeling of transdermal drug delivery using microneedle. *Materials Today: Proceedings*. 2022;53(Part 1):213–217. Available from: https://doi.org/10.1016/j.matpr.2022.01.028.
6) Mubarak S, Khanday MA, Lone A, Rasool N. An analytical approach to study the drug diffusion through transdermal drug delivery system. *Appl Math E - Notes*. 2021;21:198–208. Available from: https://www.emis.de/journals/AMEN/2021/AMEN-200831.pdf.
7) Čukić M, Galovic S. Mathematical modeling of anomalous diffusive behavior in transdermal drug-delivery including time-delayed flux concept. *Chaos, Solitons & Fractals*. 2023;172:1–12. Available from: https://doi.org/10.1016/j.chaos.2023.113584.
8) New Trends in Fractional Differential Equations with Real-World Applications in Physics. In: Singh J, Hristov JY, Hammouch Z, editors. Frontiers in Physics. Frontiers Media SA. 2020;p. 1–172. Available from: https://www.frontiersin.org/research-topics/12142/new-trends-in-fractional-differential-equations-with-real-world-applications-in-physics.
9) Diethelm K, Kiryakova V, Luchko Y, Machado JAT, Tarasov VE. Trends, directions for further research, and some open problems of fractional calculus. *Nonlinear Dynamics*. 2022;107(4):3245–3270. Available from: https://doi.org/10.1007/s11071-021-07158-9.
10) Kumar D, Baleanu D. Editorial: Fractional Calculus and Its Applications in Physics. *Frontiers in Physics*. 2019;7:1–2. Available from: https://doi.org/10.3389/fphy.2019.00081.

11) Joshi H, Jha BK. On a reaction–diffusion model for calcium dynamics in neurons with Mittag–Leffler memory. *The European Physical Journal Plus*. 2021;136(6). Available from: https://doi.org/10.1140/epjp/s13360-021-01610-w.
12) Sonawane J, Sontakke B, Takale K. Approximate Solution of Sub diffusion Bio heat Transfer Equation. *Baghdad Science Journal*. 2023;20((1 Special Issue)):394–399. Available from: https://doi.org/10.21123/bsj.2023.8410.
13) Kharde U, Takale K, Gaikwad S. Numerical solution of time fractional drug concentration equation in central nervous system. *Journal of Mathematical and Computational Science*. 2021;11(6):7317–7336. Available from: https://scik.org/index.php/jmcs/article/view/6470.
14) Rehman MAU, Ahmad J, Hassan A, Awrejcewicz J, Pawlowski W, Karamti H, et al. The Dynamics of a Fractional-Order Mathematical Model of Cancer Tumor Disease. *Symmetry*. 2022;14(8):1–28. Available from: https://doi.org/10.3390/sym14081694.
15) Mungkasi S. Modelling And Simulation of Topical Drug Diffusion in The Dermal Layer of Human Body. *Journal of Advanced Research in Fluid Mechanics and Thermal Sciences*. 2021;86(2):39–49. Available from: https://doi.org/10.37934/arfmts.86.2.3949.
16) Owolabi KM, Atangana A. Numerical Methods for Fractional Differentiation;vol. 54 of Springer Series in Computational Mathematics. 1st ed. Singapore. Springer. 2019. Available from: https://doi.org/10.1007/978-981-15-0098-5.
17) Kharde U, Takale K, Gaikwad S. Crank-Nicolson Method For Time Fractional Drug Concentration Crank-Nicolson Method For Time Fractional Drug Concentration Equation In Central Nervous System. *Advances and Applications in Mathematical Sciences*. 2022;22(2):407–433. Available from: https://www.mililink.com/upload/article/1115784474aams_vol_222_december_2022_a4_p407-433_uttam_kharde,_kalyanrao_takale_and_shrikrishna_gaikwad.pdf.
18) Ghode K, Takale K, Gaikwad S, Bondar K. Python: Powerful Tool For Solving Space-Time Fractional Traveling Wave Equation. *Advances and Applications in Mathematical Sciences*. 2022;22(2):503–526. Available from: https://www.mililink.com/upload/article/1168715543aams_vol_222_december_2022_a10_p503-526_krishna_ghode_et_al..pdf.