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Review Paper

Chemotherapy Model of Tumor ODEs and Their Numerical Solutions

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ABSTRACT
The purpose of this paper is to solve annonlinear Ordinary Differential Equation (ODE) system model of cancer chemotherapy. Initially, we provide an overview of cancer temporal model. Subsequently, we conduct a comprehensive analysis of suggested model withouttreatment. It is a lung cancer prediction model describes us the behavior of the proliferating cells and the role of the nutrients available in the tumor (Concentration) and the minimum (hypoxia) which can help the tumor cells to divide.
In this paper numerical simulations have been used, to gain deeper insights into the theoretical findings. However, approximate numerical solutions to the temporal model are represented by fourth order Runge-Kutta (RK4), Nonstandard Finite Difference Scheme (NSFD) and also Explicit Euler method.
Keywords: *Temporel, tumor cells, proliferating cells, Euler method, treatment. NSFD; RK4.*

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I. INTRODUCTION

The focus of this study is on non-vascularized lung metastases. Data from scans will be used to predict nodule volume and activity evolution [3]. This information is critical for medical decisions, especially for high-risk patients, to assess the necessity and risks of treatments like chemotherapy or surgery [14]. Prioritizing the removal of rapidly growing metastases is also important for other patients [16,4,5,6].

Non-vascularized tumors are composed of three types of cells [10,20]:

Proliferating Cells: They divide rapidly, use glucose for energy, and avoid the usual mechanisms that eliminate mutated cells.
Quiescent Cells: These were once proliferating cells but are now dormant due to nutrient scarcity. They can resume division when nutrients become available.
Necrotic Cells: Quiescent cells that perish due to a lack of nutrients.
Hypoxia denotes a shortage of oxygen, which can hinder cell division.

II. MODEL FORMULATION

This study introduces a time-dependent tumor growth model based on ordinary differential equations (ODEs) [18]. It builds upon earlier models, focusing on non-vascularized tumors [7]. The model tracks the evolution of tumor volume over time, considering two cell types: proliferating and quiescent cells. Nutrient availability within the tumor, represented by "C," affects cell division ("P") but doesn't account for spatial aspects [19]. It is assumed that that when "C" exceeds a certain threshold ("Chyp"), normal cell division occurs, and they employ a smoothed function to describe this behavior [10,20,8].

The model presents the following system of ordinary differential equations (ODEs) [20,10]:

$$\begin{cases} \dfrac{dV}{dt} = \gamma\, P\, V, \\ \dfrac{dP}{dt} = \gamma P(1-P) - (1-\gamma)P, \\ \dfrac{dC}{dt} = (1-C)\left(\dfrac{V}{V_0}\right)^{\frac{2}{3}} - \alpha\, P\, C, \\ \gamma = \dfrac{1 + tanh(10(C - C_{hyp}))}{2}. \end{cases} \quad (1)$$

In this system we denote the following [10]:

P: The proportion of proliferating cells within the tumor (P in the range [0, 1]).
Q: The proportion of quiescent cells within the tumor (Q in the range [0, 1]). Assuming the equivalence of quiescent and necrotic cells, we have 1 = P + Q.
V: The total volume of the tumor (the quantity of proliferating cells within the tumor is thus PV, and the quantity of quiescent cells is QV).

C is the quantity of nutrients available within the tumor. This represents a concentration, and it does not take into account diffusion and distribution issues. It is assumed that this concentration remains constant and is equal to 1 in healthy tissues.

Chyp represents the minimal concentration of nutrients required for a cell to divide. This concept is often associated with hypoxia, which refers to conditions of reduced oxygen availability.

Differential equations describe how these variables change over time, capturing tumor growth dynamics and nutrient availability [1].

Numerical methods, such as Euler and Runge-Kutta, can be applied to solve these differential equations and understand the temporal evolution of the variables [10,2].

Figures (1), (2), (3) and (4) illustrate the evolution of these populations: proliferating volume of tumor cells and the concentration (the quantity of nutrients available in the tumor).

NUMERICAL RESULTS AND ANALYSIS

The initial values and the parameters used to solve the system (1) are summarized in the table 1 [10].

Parameter	Description	Value
V_0	Total volume of the tumor	10
P_0	Proliferating cells	0.16
C_0	Nutrient Concentration	1
C_{hyp}	Threshold Concentration	0.7
α	Constant	1.5
γ	Related to difference between C and C_hyp	0.9976

Table 1: Parameters of TemporelModel [10,20].

To analyze and solve this system, you would typically use mathematical techniques such as numerical methods or computer simulations. The specific parameter values and initial conditions would need to be determined based on the characteristics of the disease you are modeling.

Solving this system of differential equations analytically can be challenging, especially for nonlinear systems like the one you've presented. Typically, such systems are solved numerically using software tools like MATLAB [9,17].

The initial values and the parameters used to solve the system are summarized in the following table. They were taken from[10].

APPLICATION OF ODE MATLAB METHOD

We have performed calculations using Ode 45 with$h$ =1. Here are the results:

t	V_0	P_0	C_0
	(1.0e+13 *)		
0	0.0000	0.1600	1.0000
1	0.0000	0.3399	0.7977
2	0.0000	0.5816	0.6744
3	0.0000	0.7890	0.6679
4	0.0000	0.9088	0.7489
5	0.0000	0.9628	0.8434
6	0.0000	0.9844	0.9126
7	0.0000	0.9927	0.9527
8	0.0000	0.9958	0.9749
9	0.0000	0.9969	0.9869
10	0.0000	0.9973	0.9935
11	0.0000	0.9975	0.9961
12	0.0000	0.9976	0.9985
13	0.0000	0.9976	0.9990
14	0.0000	0.9976	1.0001
15	0.0000	0.9976	0.9997
16	0.0000	0.9976	0.9991
17	0.0000	0.9976	0.9989
18	0.0000	0.9976	0.9996
19	0.0000	0.9976	0.9999
20	0.0001	0.9976	1.0003
21	0.0002	0.9976	0.9998
22	0.0005	0.9976	0.9998
23	0.0014	0.9976	1.0001
24	0.0038	0.9976	0.9998
25	0.0102	0.9976	0.9998
26	0.0277	0.9976	1.0000
27	0.0750	0.9976	1.0007
28	0.2028	0.9976	1.0000
29	0.5486	0.9976	0.9999
30	1.4841	0.9976	0.9994

Table 2: Values for V, P and C with Ode 45 for h=1

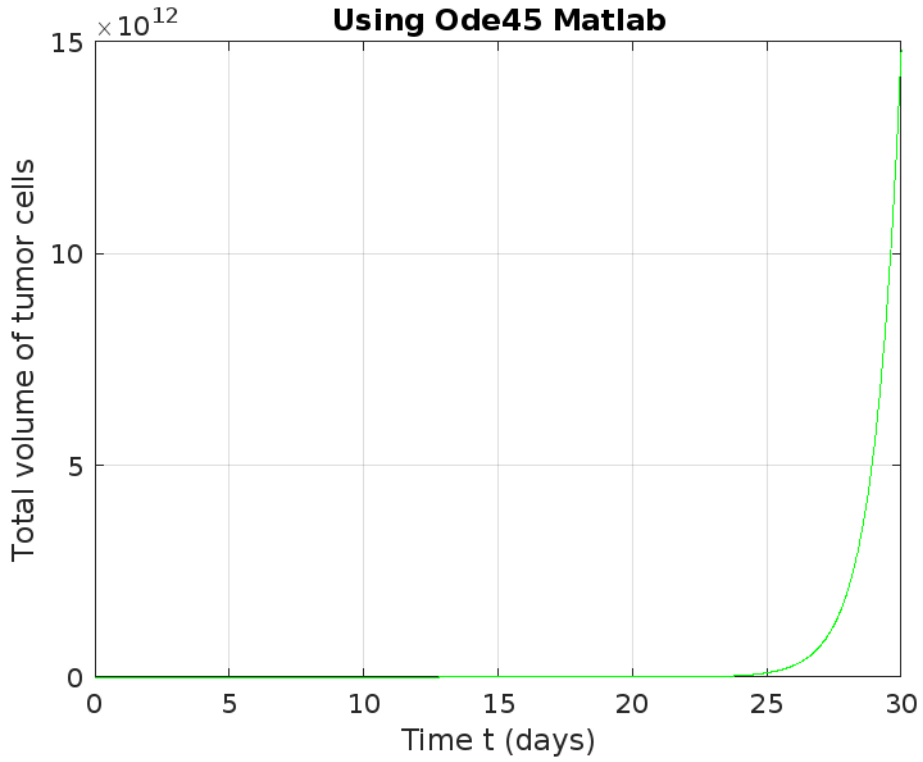

Figure 1: Total volume of tumor cells using ode45

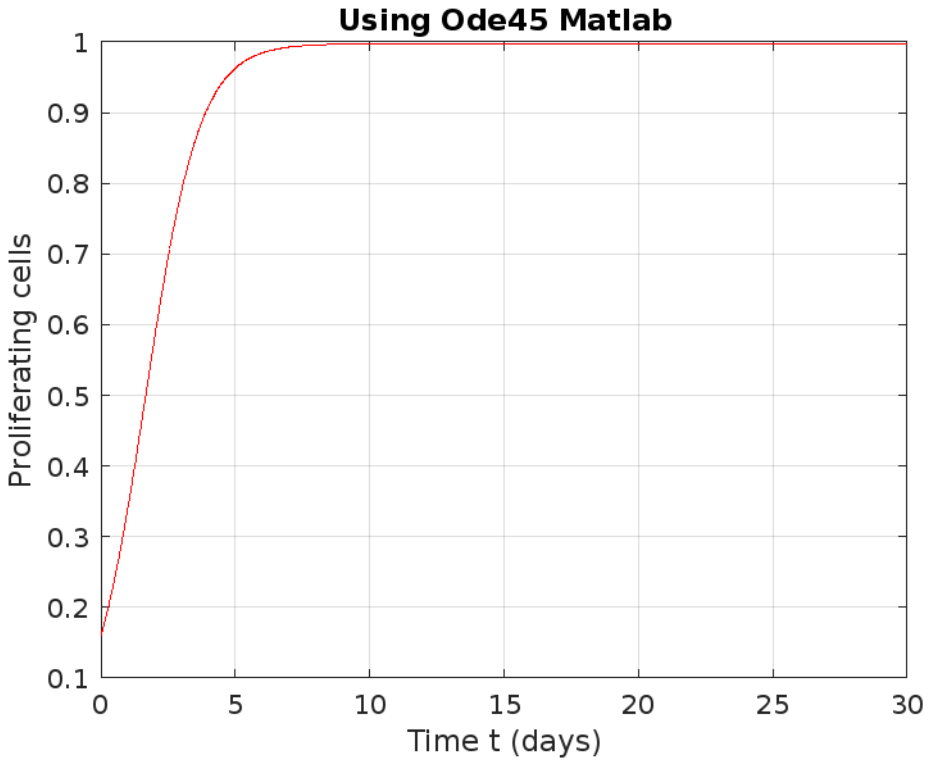

Figure 2: The evolution of the population of proliferating cellsusing Matlab

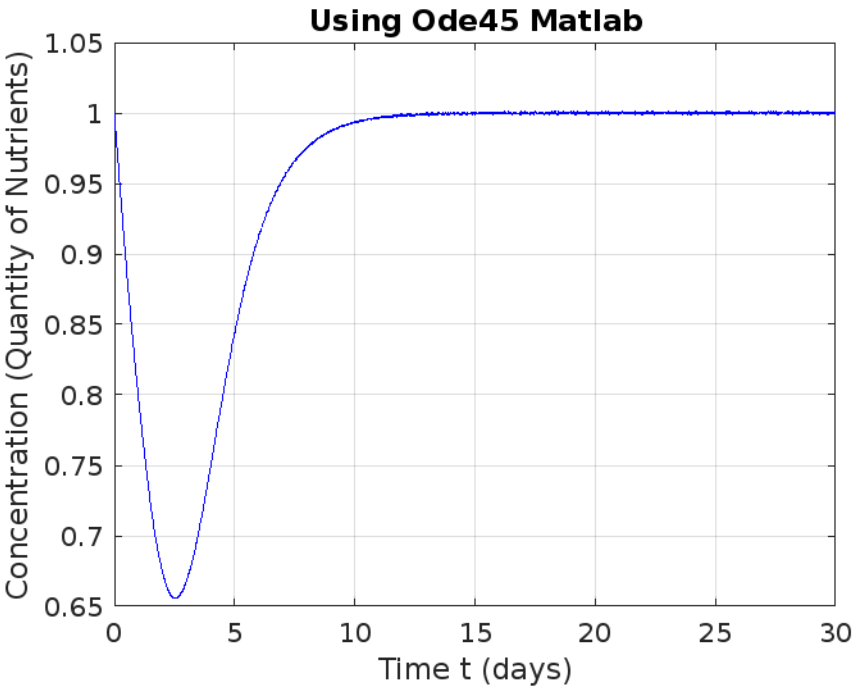

Figure 3: The concentration of the nutrient using Matlab

The method you choose should align with your problem's unique traits, such as nonlinearities, boundary conditions, geometry, and the desired accuracy level. Careful analysis of your problem and an evaluation of various methods is crucial in selecting the most appropriate one. Furthermore, you can often implement these methods efficiently using computer software and numerical libraries [10].

RUNGE KUTTA 4TH ORDER (RK4)

The Fourth-Order Runge-Kutta method, or RK4, is a numerical approach for solving ordinary differential equations (ODEs). Known for its accuracy and reliability, RK4 is widely used, especially for solving initial value problems. In such problems, an ODE and an initial condition that defines the function's value at a specific point are provided [11].

The 4th-order Runge-Kutta method is a numerical technique used to solve ordinary differential equations of the form:

$$\begin{cases} \frac{dy}{dx} = f(x,y), \\ y(0) = y_0. \end{cases} \quad (2)$$

The 4th-order Runge-Kutta method is based on the following elements:

$$y_{i+1} = y_i + (a_1K_1 + a_2K_2 + a_3K_3 + a_4K_4)h,$$

where knowing the value of $y = y_i \text{at} x_i$, we can find the value of $y = y_{i+1}\ at\ x_{i+1}$, and $h = x_{i+1} - x_i$. Equation (1) is approximated using the first five terms of the Taylor series [13]:

$$y_{i+1} = y_i + \frac{dy}{dx}|_{x_i,y_i}(x_{i+1} - x_i) + \frac{1}{2!}\frac{d^2y}{dx^2}|_{x_i,y_i}(x_{i+1} - x_i)^2 + \frac{1}{3!}\frac{d^3y}{dx^3}|_{x_i,y_i}(x_{i+1} - x_i)^3 \frac{1}{4!}\frac{d^4y}{dx^4}|_{x_i,y_i}(x_{i+1} - x_i)^4. \quad (3)$$

Given that $\frac{dy}{dx} = f(x,y)$ and $x_{i+1} - x_i = h$:

$$y_{i+1} = y_i + hf(x_i,y_i) + \frac{h^2}{2!}f'(x_i,y_i)| + \frac{h^3}{3!}f''(x_i,y_i) + \frac{h^4}{4!}f'''(x_i,y_i). \quad (4)$$

One of the most popular solutions used is:

$$y_{i+1} = y_i + \frac{1}{6}(K_1 + 2K_2 + 2K_3 + K_4)h,$$

such that:

$$\begin{aligned} K_1 &= f(x_i, y_i), \\ K_2 &= f\left(x_i + \frac{1}{2}h, y_i + \frac{1}{2}K_1 h\right), \\ K_3 &= f\left(x_i + \frac{1}{2}h, y_i + \frac{1}{2}K_2 h\right), \\ K_4 &= f(x_i + h, y_i + K_3 h). \end{aligned}$$

APPLICATION OF THE FOURTH ORDER RUNGE KUTTA METHOD

We have performed calculations using RK4 with h =1. Here are the results:

t	***V***	***P***	***C***
	1.0e+13 *		1.0e+301 *
0	0.0000	0.1600	0.0000
1	0.0000	0.3395	0.0000
2	0.0000	0.5811	0.0000
3	0.0000	0.7884	0.0000
4	0.0000	0.9079	0.0000
5	0.0000	0.9620	0.0000
6	0.0000	0.9839	0.0000
7	0.0000	0.9924	0.0000
8	0.0000	0.9956	0.0000
9	0.0000	0.9969	0.0000
10	0.0000	0.9973	0.0000
11	0.0000	0.9975	0.0000
12	0.0000	0.9976	0.0000
13	0.0000	0.9976	0.0000
14	0.0000	0.9976	0.0000
15	0.0000	0.9976	0.0000
16	0.0000	0.9976	0.0000
17	0.0000	0.9976	0.0000
18	0.0000	0.9976	0.0000
19	0.0000	0.9976	0.0000
20	0.0001	0.9976	0.0000
21	0.0002	0.9976	0.0000
22	0.0005	0.9976	0.0000
23	0.0013	0.9976	0.0000
24	0.0035	0.9976	0.0000
25	0.0095	0.9976	0.0000
26	0.0255	0.9976	7.0532
27	0.0688	0.9976	NaN
28	0.1853	0.9976	NaN
29	0.4996	0.9976	NaN
30	1.3466	0.9976	NaN

Table 3: Values for V, P and C with RK4 for h=1.

These tables show the values of V, P and C at different time points (t) for the given parameter values and step sizes. The Fourth-Order Runge-Kutta method was used to approximate the solutions for the temporal model.

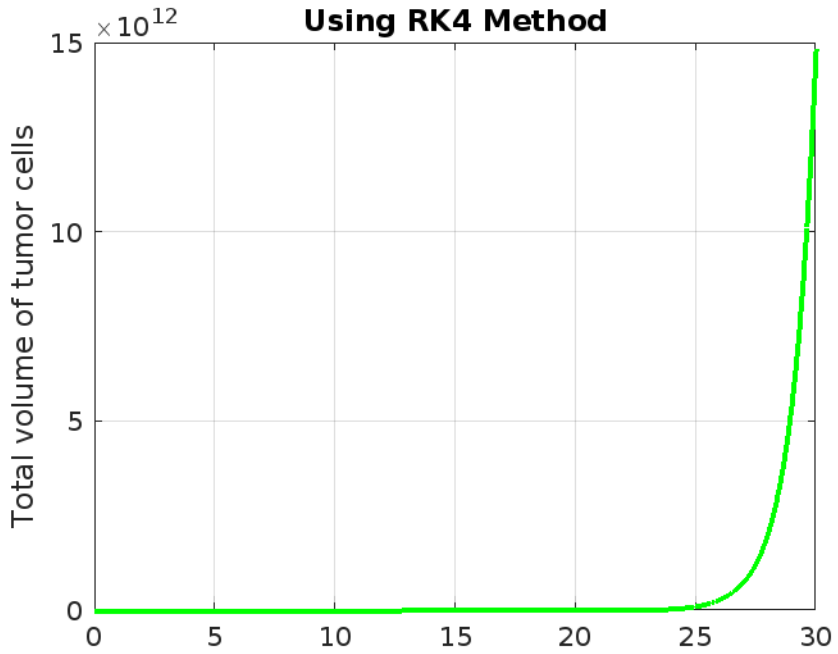

Figure 4: Approximate Solution Using RK4 for tumor V and $h = 1$

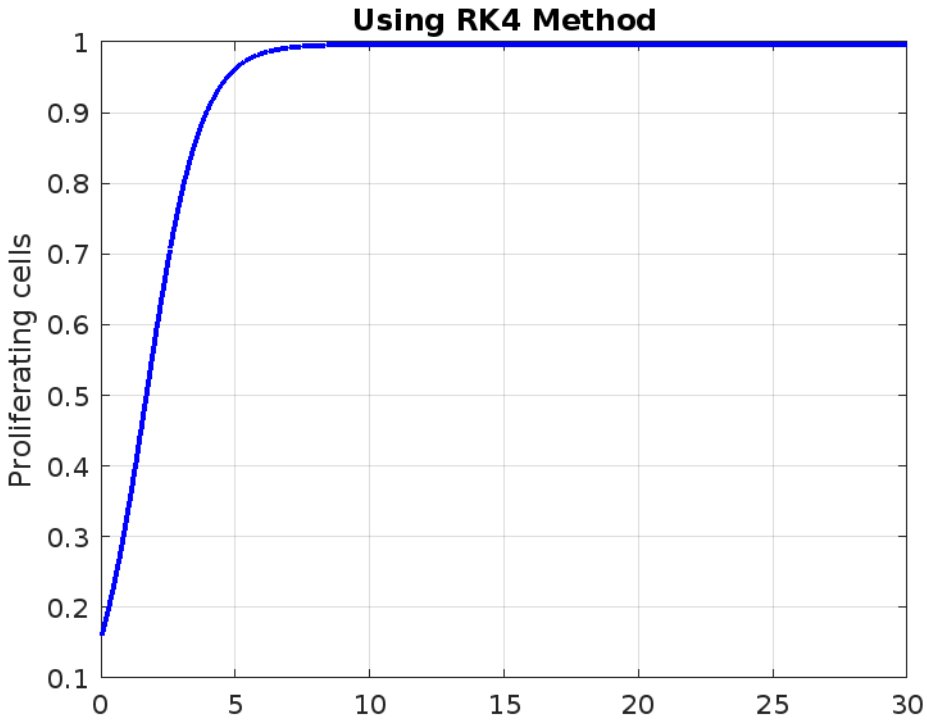

Figure 5: Approximate Solution Using RK4 for P and $h = 1$

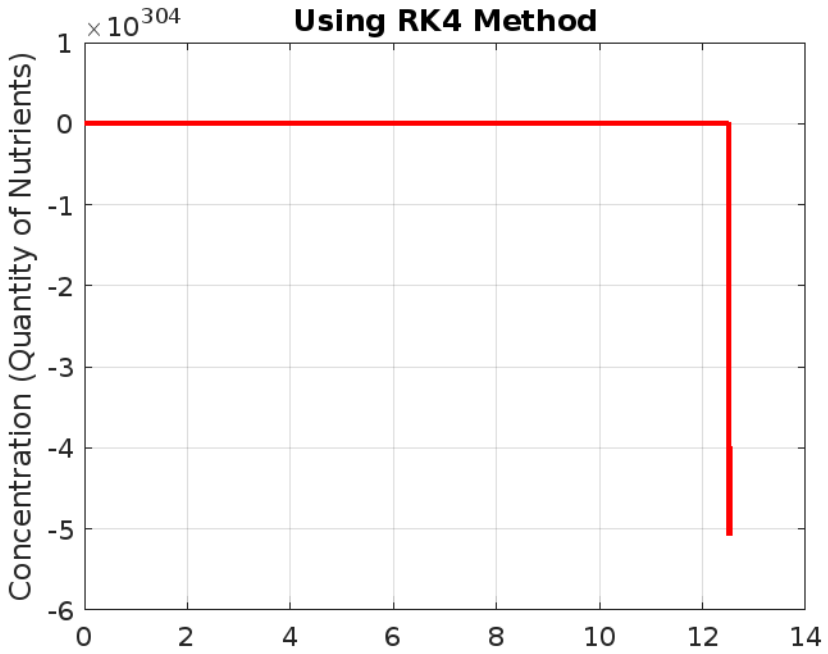

Figure 6: Approximate Solution Using RK4 for C and h = 1

NONSTANDARD FINITE DIFFERENCE METHOD (NSFD)

The Nonstandard Finite Difference (NSFD) method is a numerical approach employed for solving differential equations, notably partial differential equations (PDEs). It falls within the category of finite difference methods, which discretize spatial and/or temporal domains to approximate solutions to differential equations. What distinguishes NSFD is its utilization of nonstandard discretization schemes, offering advantages in specific scenarios [15].

The nonstandard finite difference method (NSFD) is applied to a small system of three nonlinear equations of the form:

$$\frac{dU}{dt} = AU + G(U),$$

where*A* is a constant matrix, *U* is a vector, and *G(U)* contains nonlinear terms, provided that there is a repeated eigenvalue of A. NSFD stands out because it allows for the addition or removal of nonlinearity within calculations, eliminating the need for interruptions and separate linear methods. Mickens introduced a set of modeling rules to facilitate the integration of crucial physical properties from differential equations into NSFD numerical schemes.[15,12].

	ED	**Mikens**
ED1	$\frac{du}{dt} = -\lambda\, u$	$\frac{u_{k+1} - u_k}{h} = -\lambda\, u_k$
ED2	$\frac{du}{dt} = -u^2$	$\frac{u_{k+1} - u_k}{h} = -u_k u_{k+1}$
ED3	$\frac{du}{dt} = -u^3$	$\frac{u_{k+1} - u_k}{h} = -\frac{2u_{k+1}^2\, u_k^2}{u_{k+1} + u_k}$

Table 4: NSFD Mickens

These equations depict different orders of time derivatives using the NSFD method. They incorporate terms at successive time intervals and constants like λ and h.

When applying the NSFD method to system (1), we derive the following difference equations:

$$\frac{V_{j+1} - V_j}{h} = \gamma \mathrm{P_j}\, \mathrm{V_j},$$

$$\frac{P_{j+1} - P_j}{h} = \gamma P_j(1 - P_j) - (1 - \gamma)P_j,$$

$$\frac{C_{j+1} - Cj}{h} = (1 - C_j)\left(\frac{v_j}{v_0}\right)^{\frac{2}{3}} - \alpha P_j V_j.$$

The obtained results represent the values of compartments N, C, and I at various time points (t) when employing the nonstandard finite difference method with the given parameters.

t	***V***	***P***	***C***
	1.0e+09 *		1.0e+73 *
0	0.0000	0.1600	0.0000
1	0.0000	0.2937	0.0000
2	0.0000	0.4999	0.0000
3	0.0000	0.7481	0.0000
4	0.0000	0.9343	0.0000
5	0.0000	0.9933	0.0000
6	0.0000	0.9976	0.0000
7	0.0000	0.9976	-0.0000
8	0.0000	0.9976	0.0000
9	0.0000	0.9976	-0.0000
10	0.0000	0.9976	0.0000
11	0.0000	0.9976	-0.0000
12	0.0000	0.9976	0.0000
13	0.0000	0.9976	-0.0000
14	0.0000	0.9976	0.0000
15	0.0001	0.9976	-0.0000
16	0.0002	0.9976	0.0000
17	0.0003	0.9976	-0.0000
18	0.0006	0.9976	0.0000
19	0.0012	0.9976	-0.0000
20	0.0024	0.9976	0.0000
21	0.0048	0.9976	-0.0000
22	0.0095	0.9976	0.0000
23	0.0190	0.9976	-0.0000
24	0.0379	0.9976	0.0000
25	0.0756	0.9976	-0.0000
26	0.1509	0.9976	0.0000
27	0.3010	0.9976	-0.0000
28	0.6005	0.9976	0.0000
29	1.1982	0.9976	-0.0000
30	2.3906	0.9976	6.2689

Table 5: NSFD method with a time step h=1.

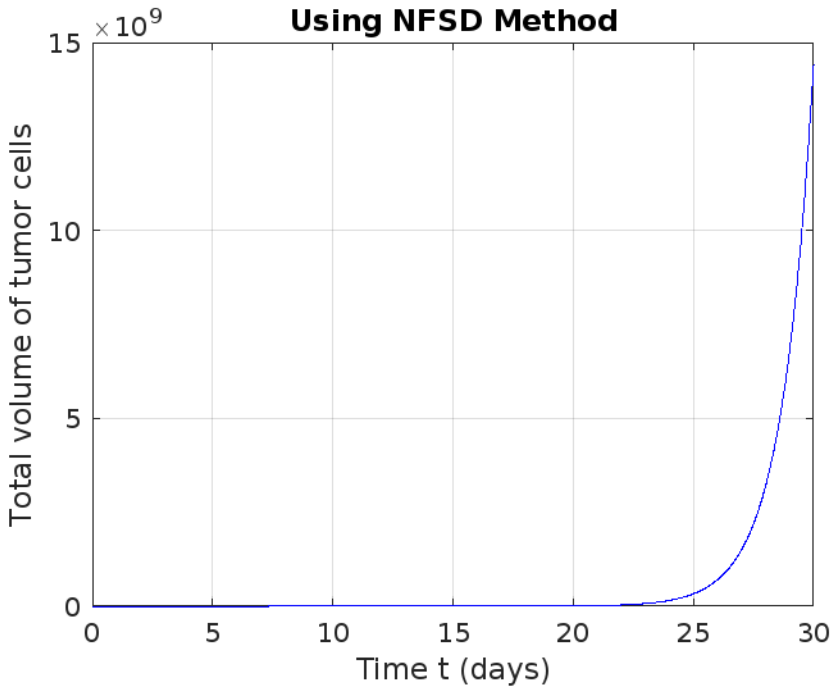

Figure 7: Approximate Solution Using NSFD for V and $h = 1$

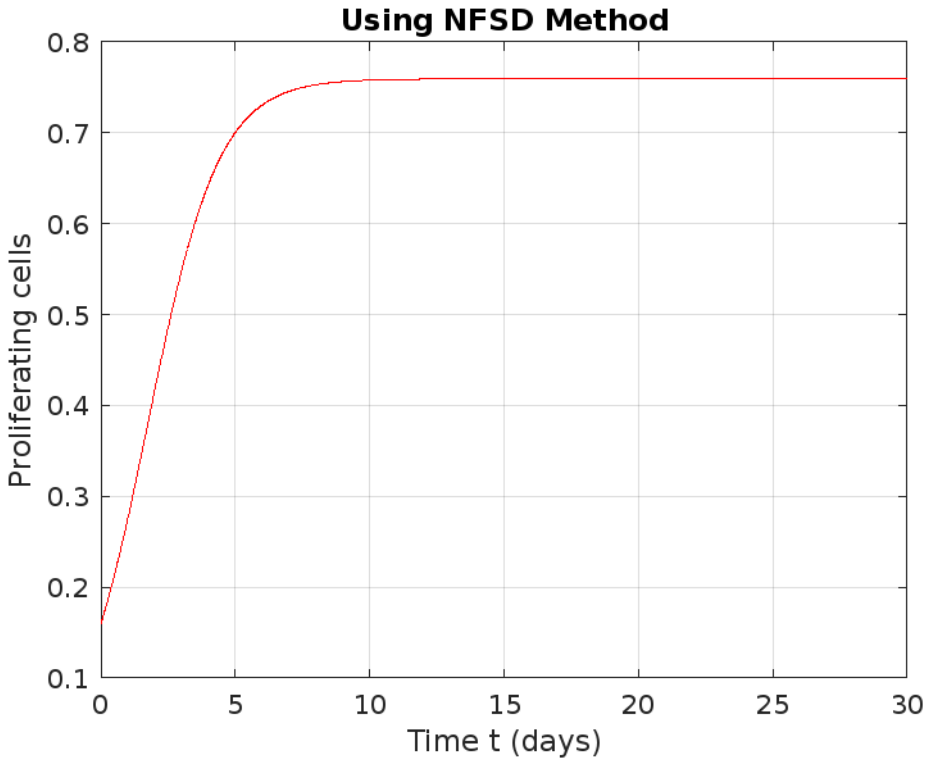

Figure 8: Approximate Solution Using NSFD for P cells and $h = 1$

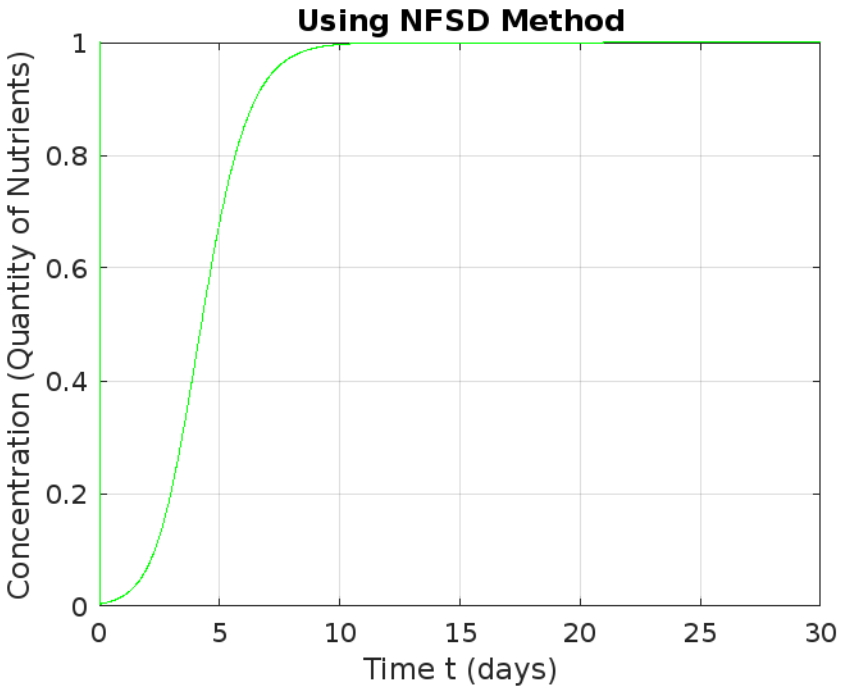

Figure 9: Approximate Solution Using NSFD for C and $h = 1$

EXPLICIT EULER METHOD

The Explicit Euler Method, also known as the Forward Euler Method, is a numerical technique used for approximating the solution of ordinary differential equations (ODEs) or differential equations. It's a straightforward and widely used method, especially for initial value problems [2,10,21].

Here's how the Explicit Euler Method works:

You start with an initial value for your function at a specific point in the domain.

Then, you divide the domain into small time steps or intervals, denoted by "h."

At each time step, you update the function's value by taking the current value and adding the product of the derivative of the function with respect to time (the rate of change) and the time step "h."

Mathematically, for a function y(t) with its derivative dy/dt, the Explicit Euler Method can be expressed as follows:

$$y(t+h) = y(t) + h\,\frac{dy}{dt}.$$

This method essentially estimates the next value of the function based on its current value and the rate of change (derivative) at that point. It's called "explicit" because the update formula directly computes the new value based on known information at the current step.

The Explicit Euler Method is relatively simple to implement, but its accuracy depends on the choice of the time step "h." Smaller time steps generally lead to more accurate results but may require more computational effort. It's a useful method for getting an initial approximation of a solution, but for some differential equations, especially those with stiff behavior or rapid changes, more sophisticated numerical methods may be necessary to achieve accurate results[21].

Iterative Calculation: Starting from the initial condition, you iteratively compute the function's values at each time step using the following formula:

$$y(t_{i+1}) = y(t_i) + h\,f\big(t_i, y(t_i)\big).$$

Here:

$y(t_i)$ is the known value of the function at time t_i.
$y(t_{i+1})$ is the estimated value of the function at the next time step $t_{i+1} = t_i + h$.
h is the fixed time step.
$f(t_i, y(t_i))$ represents the derivative of y at time t_i, which is given by the differential equation $\frac{dy}{dx} = f(t, y)$.

APPLICATION OF THE EXPLICIT EULER METHOD
We have performed calculations using Euler Explicit method with h =1. Here are the results:

t	***V***	***P***	***C***
	1.0e+09 *		1.0e+73 *
0	0.0000	0.1600	0.0000
1	0.0000	0.2937	0.0000
2	0.0000	0.4999	0.0000
3	0.0000	0.7481	0.0000
4	0.0000	0.9343	0.0000
5	0.0000	0.9933	0.0000
6	0.0000	0.9976	0.0000
7	0.0000	0.9976	-0.0000
8	0.0000	0.9976	0.0000
9	0.0000	0.9976	-0.0000
10	0.0000	0.9976	0.0000
11	0.0000	0.9976	-0.0000
12	0.0000	0.9976	0.0000
13	0.0000	0.9976	-0.0000
14	0.0000	0.9976	0.0000
15	0.0001	0.9976	-0.0000
16	0.0002	0.9976	0.0000
17	0.0003	0.9976	-0.0000
18	0.0006	0.9976	0.0000
19	0.0012	0.9976	-0.0000
20	0.0024	0.9976	0.0000
21	0.0048	0.9976	-0.0000
22	0.0095	0.9976	0.0000
23	0.0190	0.9976	-0.0000
24	0.0379	0.9976	0.0000
25	0.0756	0.9976	-0.0000
26	0.1509	0.9976	0.0000
27	0.3010	0.9976	-0.0000
28	0.6005	0.9976	0.0000
29	1.1982	0.9976	-0.0000
30	2.3906	0.9976	6.2689

Table 6: NSFD method with a time step h=1.

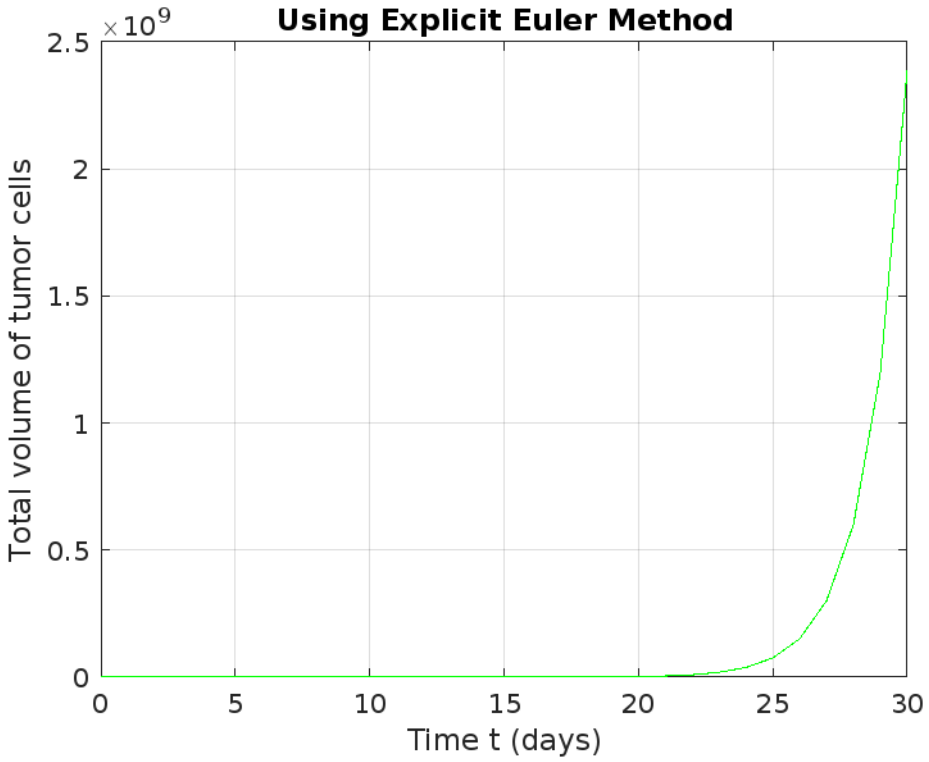

Figure 10: Approximate Solution Using Explicit Euler for V and $h = 1$

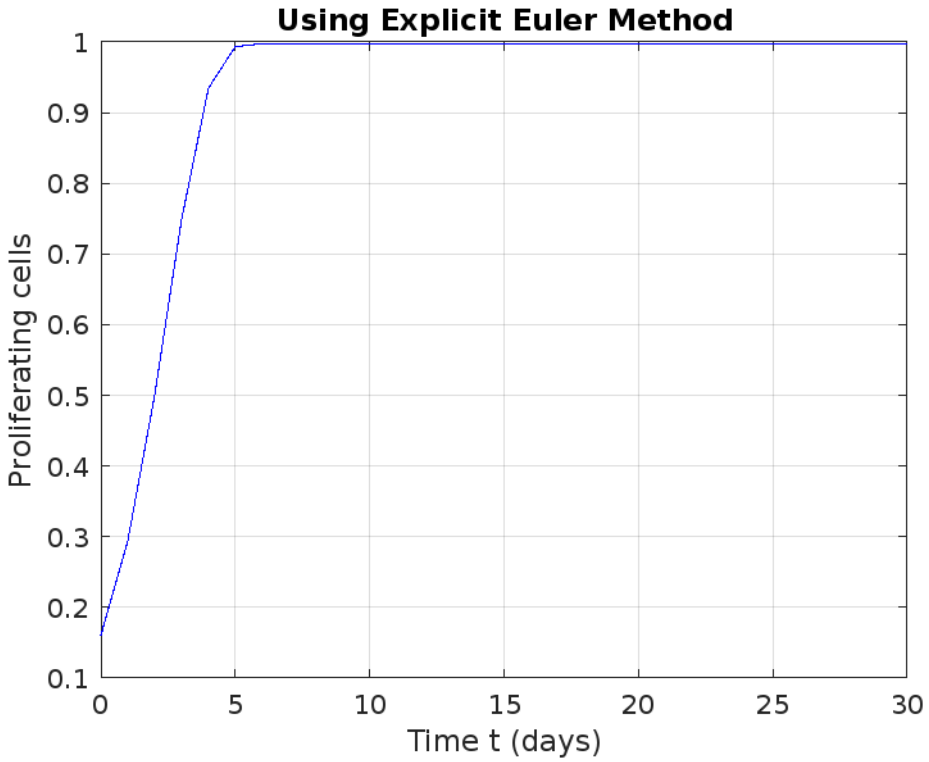

Figure 11: Approximate Solution Using Explicit Euler P and $h = 1$

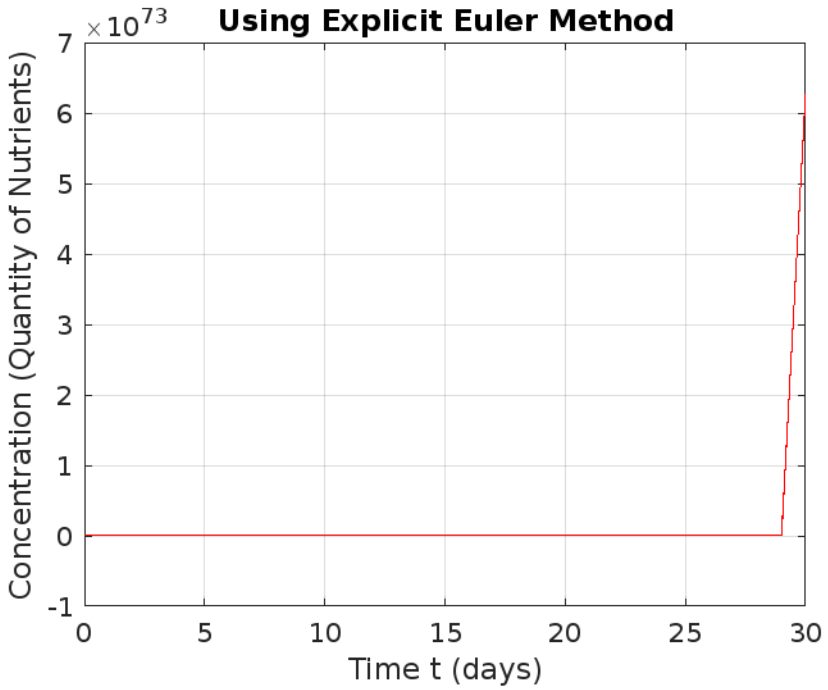

Figure 12: Approximate Solution for C Using Explicit Euler and $h = 1$

III. DISCUSSION

The analysis of system (1) without the presence of an actively administered drug provides an overview of the system's behavior, especially after the drug treatment has ceased.

For the proliferating cells for example as shown in Figures (2) with Matlab, (5) with RK4 (9) with NFSD; the cells are increasing for the first 7 days , and for the first 5 days in Figure (16) with Euler. After that became constant P=1.
While the volume of the tumor V is constant approaching from zero for all 4 methods during the first 25 days and then starts to increase exponentially rapidly.
The concentration C is small and this affect the growth of the proliferating cells P as shown in Figures (3), (6), (9) and (12).

IV. CONCLUSION

In this study, we focused on the Temporal Chemotherapy model. Our analysis of the untreated system sheds light on how the system behaves when treatment is not applied. In essence, these mathematical models enable us to find answers to questions directly related to human health. This has a significant impact on individual well-being because mathematical modeling plays a pivotal role in the development of personalized medicine [10].

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