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Approximate SolutionOf A Cancer Immunotherapy Model By The Application Of Numerical Methods

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Abstract
The purpose of this paper is to explore an Ordinary Differential Equation (ODE) model of cancer immunotherapy. Initially, we provide an overview of cancer immunotherapy treatment method, as well as key mathematical concepts. Subsequently, we conduct a comprehensive analysis of the model proposed by De Pillis et al., which describes tumor growth in the absence of treatment.
Without treatment, (as we restricted our study here in this paper) tumor development (cancer cell growth) occurs rapidly, leading to a high rate of immune cell death, which is highly undesirable. However, when a drug is introduced, it stimulates the immune system to defend itself against cancer cells with the help of the drug. Finally, we perform numerical simulations to gain deeper insights into the theoretical findings.
However, numerical simulation are calculated by Matlab and compared with the results by numerical fourth order Runge-Kutta (RK4) and Nonstandard Finite Difference Scheme (NSFD).
Keywords: *SIR; immunotherapy, cancer, cancer cells, immune cells, treatment. NSFD; RK4.*

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I. INTRODUCTION

Immunotherapy is a treatment aimed at boosting the body's immune defenses against cancerous cells [9]. Immunotherapy now ranks as one of the leading cancer treatments after successfully curing Jimmy Carter. It has proven effective in treating skin cancer, lung cancer, and even brain cancer. Cancer can be prevented by avoiding obesity, smoking, and viruses [1,5,7].

Doctors aim to make patients' effector cells more effective at killing tumor cells. Immunotherapy is a treatment that utilizes a patient's immune system to combat diseases. Although immunotherapy is a promising field of study, many issues still need to be addressed before it becomes a viable option for everyone. Immunotherapy is still a subject of active research and is mathematically intriguing [3,10].

II. MODEL FORMULATION

In the early 2000s, De Pillis et al. developed a more advanced SIR model than that of Stepanova et al., which takes into account interactions between normal, tumor, and immune cells [14,15]. While there have been some extensions and validations of this model [15,13,17], they remain close to the original formulation by De Pillis et al [14,15,16]. Tumor growth is described by the following system of ordinary differential equations (ODEs) [7,9,14]:

III. THE MODEL

The differential equations governing the model are as follows [9,14]:

$$\begin{cases} \dfrac{dN}{dt} = r_2 N(t)\left(1 - b_2 N(t)\right) - k_4 C(t) N(t), \\ \dfrac{dC}{dt} = r_1 C(t)(1 - b_1 C(t))) - k_2 I(t) C(t) - k_3 C(t) N(t), \\ \dfrac{dI}{dt} = s + \dfrac{\rho\, I(t) C(t)}{\alpha + C(t)} - k_1 I(t)\, C(t) - d_1 I(t). \end{cases} \quad (1)$$

Where:
$N(t)$ is the population of normal cells.
$C(t)$ is the population of tumor cells.
$I(t)$ is the population of immune cells.
d_1 corresponds to cell mortality rates.

$r_1$is the growth rate of tumor cells) and$r_2$the growth rate of normal cells.
b_1 and b_2 are carrying capacities.
$k_1, k_2, k_3$and$k_4$are rates of destruction for the various cell types.

The presence of tumor cells stimulates the immune response, represented by the growth term for immune cells: $\frac{\rho I(t)C(t)}{\alpha+C(t)}$, where ρ and α are positive constants. The interactions between immune and tumor cells can result in either tumor cell death or the inactivation of immune cells, represented by competition terms associated with the parameters k_i.[9]
For their tumor growth model, De Pillis et al. proposed the parameter set listed in Table 1 [9,14].

Figures (1), (2), (3) and (4) illustrate the evolution of these populations: Normal cells, immune cells and tumor ones.

IV. NUMERICAL RESULTS AND ANALYSIS

Note: De Pillis et al. use cell count (cell) as the unit, so that one unit represents the carrying capacity of normal cells in the tumor region. In general he assumed that there are 3.10^4 cells per mm^3.[9,14].

Parameter	Value	Unit
N_0	0.23	mm
C_0	0.13	mm
I_0	0.1	mm
b_1	1	1/cell
b_2	1	1/cell
k_1	1	1/(cell.day)
k_2	0.5	1/(cell.day)
k_3	1	1/(cell.day)
k_4	1	1/(cell.day)
r_1	1.5	1/day
r_2	1	1/day
d_1	0.2	1/day
s	0.33	cell/day
α	0.3	cell
β	0.01	1/day

Table 1: Parameters of the De Pillis et al. Model [9,14].

When the system of nonlinear ordinary differential equations (ODEs) is initialized with the following dimensions: N_0 = 0.23 mm, C_0= 0.13 mm, and I_0 = 0.1 mm, beyond 30 days, the system converges to a stable state where the normal cells reach a normalized population of N_1 = 0.44 cell from day no. 60. Specifically, the normal cells initially grow rapidly in the first few days and attained $N_{\{max\}} = 0.52$ cell. As a result, the population of immune cells is strongly stimulated and reaches a maximum value of *Imax* = 0.49 cell. The concurrent presence of the tumor and the cell mortality rate d_1 leads to a decrease to I_1 = 0.44 cell. Thus, the tumor can tend toward an equilibrium value of C_1 = 0.54 cell after increasing rapidly from the beginning.

This set of differential equations describes how the populations of susceptible, infectious, and recovered individuals change over time in response to interactions and transitions between these compartments. The model considers births, deaths, disease transmission, recovery, and natural mortality rates [9,11].

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 [4,12].

The initial values and the parameters used to solve the system are summarized in the following table. They were taken from[9,14].

V. APPLICATION OF ODE MATLAB METHOD

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

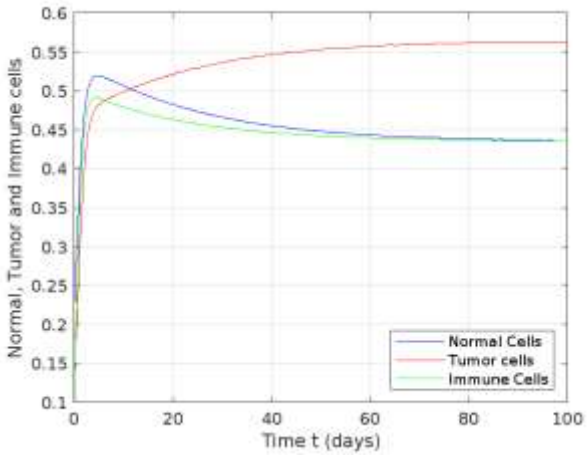

Figure 1: The evolution of the population of normal cells, immune cells, and tumor cells.

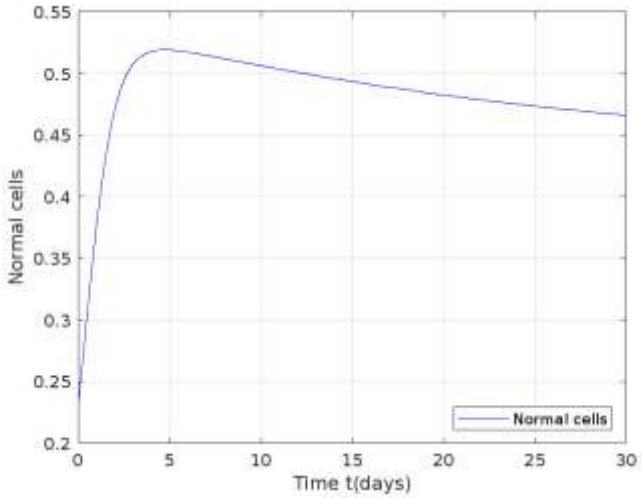

Figure 2: The evolution of the population of normal cells of the considered model using Matlab

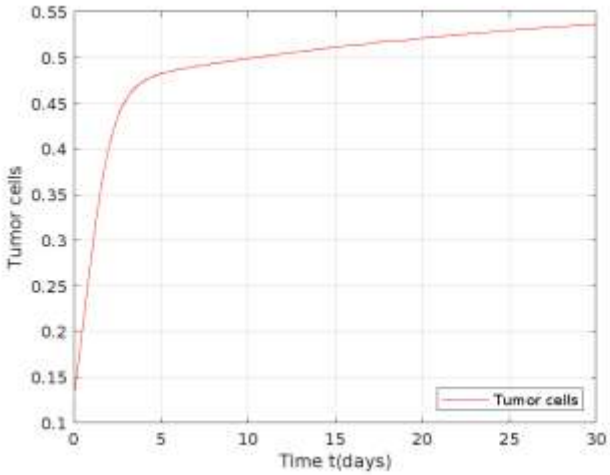

Figure 3: The evolution of the population of tumor cells of the considered model using Matlab

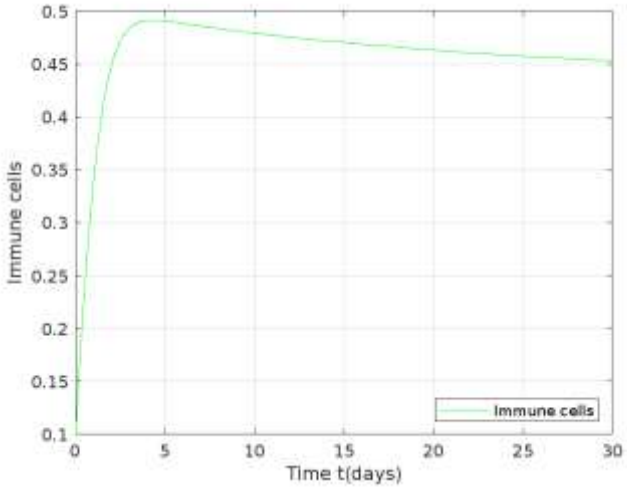

Figure 4: The evolution of the population of immune cells of the considered model using Matlab

The choice of method depends on the specific characteristics of your problem, including the nature of the nonlinearities, boundary conditions, geometry, and desired level of accuracy. It's essential to carefully analyze your problem and consider the strengths and weaknesses of different methods before selecting the most suitable one for your application. Additionally, computer software and numerical libraries are often available to implement these methods efficiently [19].

VI. RUNGE KUTTA 4TH ORDER (RK4)

The Fourth-Order Runge-Kutta method, often abbreviated as RK4, is a numerical technique used for solving ordinary differential equations (ODEs). It's a popular and widely used method because of its accuracy and reliability. RK4 is particularly effective for solving initial value problems, where you have an ODE and an initial condition specifying the value of the function at a particular point [6].

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 [8]:

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

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:

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

VII. APPLICATION OF THE FOURTH ORDER RUNGE KUTTA METHOD

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

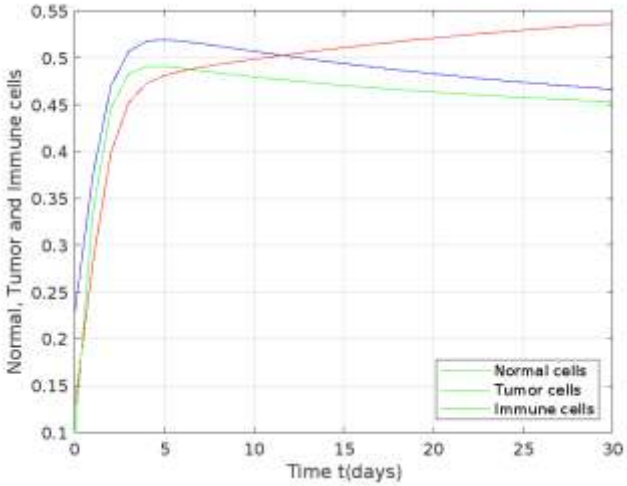

Figure 8: Approximate Solution Using RK4 for all cells (N, C and I) and h = 1

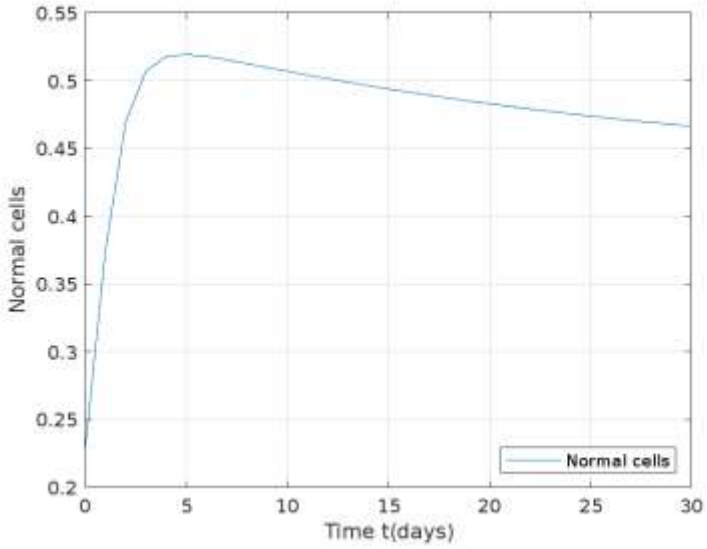

Figure 9: Approximate Solution Using RK4 for normal cells (N) and h = 1

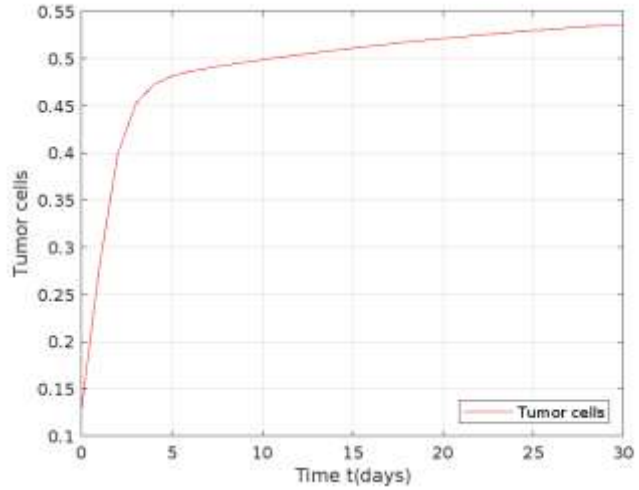

Figure 10: Approximate Solution Using RK4 for tumor cells (C) and *h* = 1

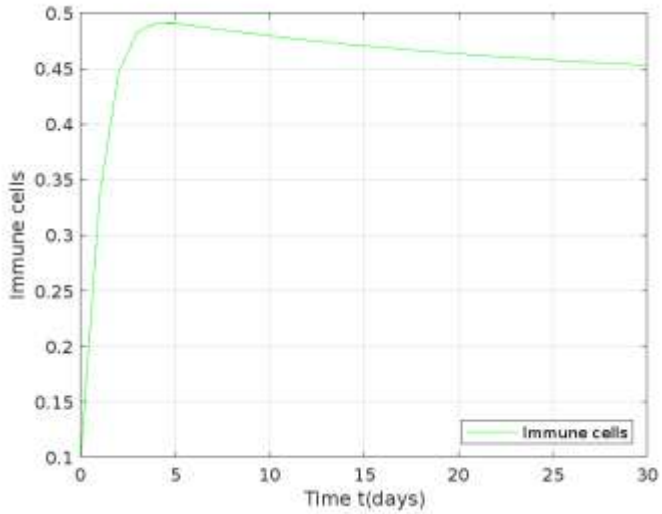

Figure 11: Approximate Solution Using RK4 for immune cells (I) and *h* = 1

VIII. NONSTANDARD FINITE DIFFERENCE METHOD (NSFD)

The Nonstandard Finite Difference (NSFD) method is a numerical technique used for solving differential equations, particularly partial differential equations (PDEs). It belongs to the class of finite difference methods, which are used to approximate solutions to differential equations by discretizing the spatial and/or temporal domains. What sets NSFD apart from standard finite difference methods is its use of nonstandard discretization schemes, which can provide advantages in certain situations [10].

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 is unique in that the effect of nonlinearity can be added or removed without the need to interrupt calculations and use a separate linear method.

Mickens developed a set of modeling rules to guide the incorporation of essential physical properties of differential equations into NSFD numerical schemes.

Mickens has developed a set of modeling rules to guide the incorporation of essential physical properties of differential equations into NSFD (Non-Standard finite difference schemes).[10,13]

	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 represent different orders of derivatives with respect to time (t) using the NSFD approach. They involve various terms at consecutive time steps and constants such as λ and h .

In the application of the NSFD method to the system (1), the following difference equations are obtained:

$$\frac{N_{j+1} - N_j}{h} = \mathrm{r_2 N_j}\left(1 - \mathrm{b_2 N_j}\right) - \mathrm{k_4 C_j} N_j,$$

$$\frac{\mathrm{C_{j+1}} - C_j}{h} = (\mathrm{r_1 C_j}(1 - \mathrm{b_1 C_j}) - \mathrm{k_2 I_j C_j} - \mathrm{k_3 C_j N_j},$$

$$\frac{\mathrm{I_{j+1}} - Ij}{h} = \mathrm{s} + \frac{\rho I_j C_j}{\alpha + C_j} - \mathrm{k_1 I_j C_j} - \mathrm{d_1 I_j}.$$

In the application of the nonstandard finite difference method to the system (1), calculations were performed using Matlab for the following case:

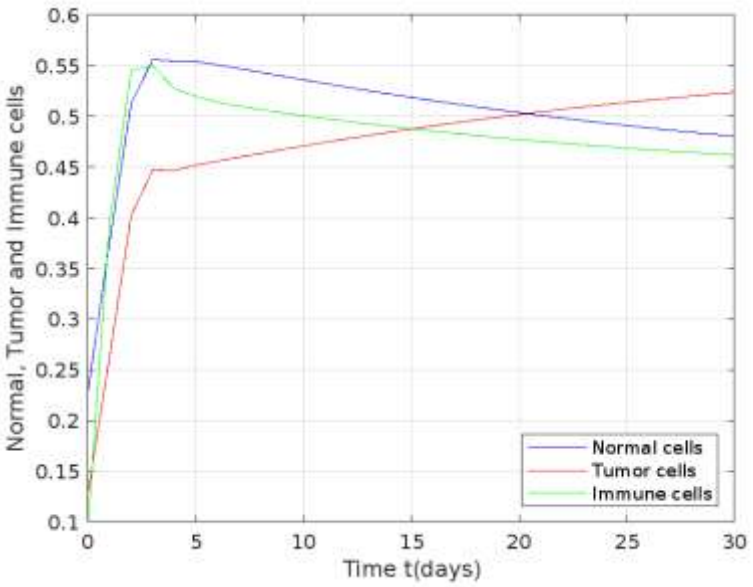

Figure 10: Approximate Solution Using NSFD for all cells and h = 1

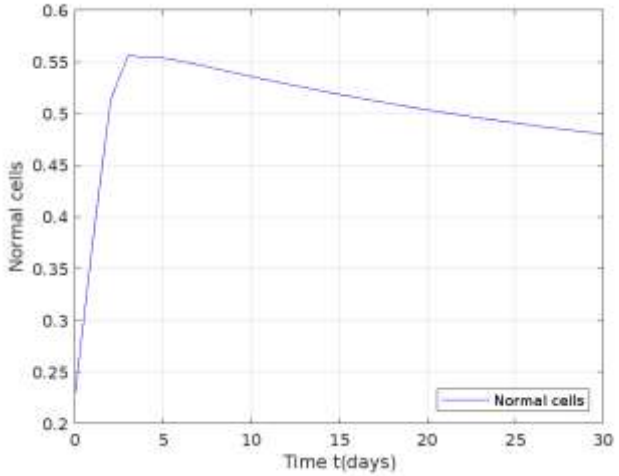

Figure 11: Approximate Solution Using NSFD for normal cells and *h* = 1

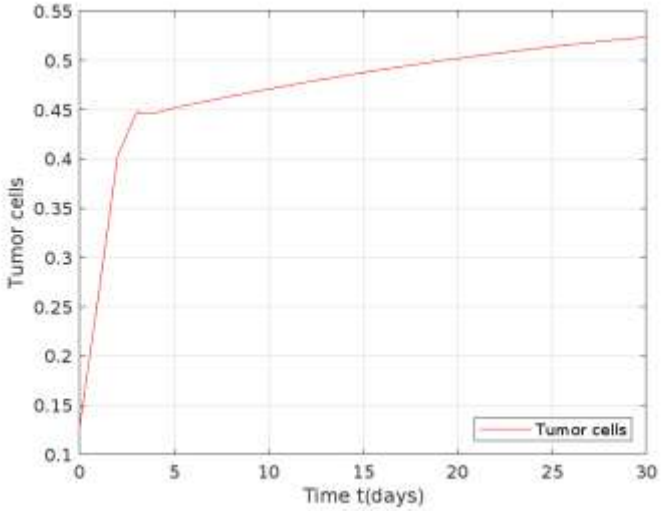

Figure 12: Approximate Solution Using NSFD for tumor cells and *h* = 1

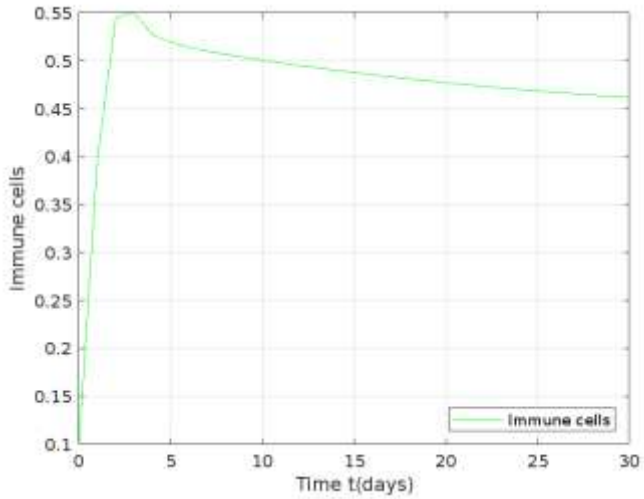

Figure 13: Approximate Solution Using NSFD for immune cells and *h* = 1

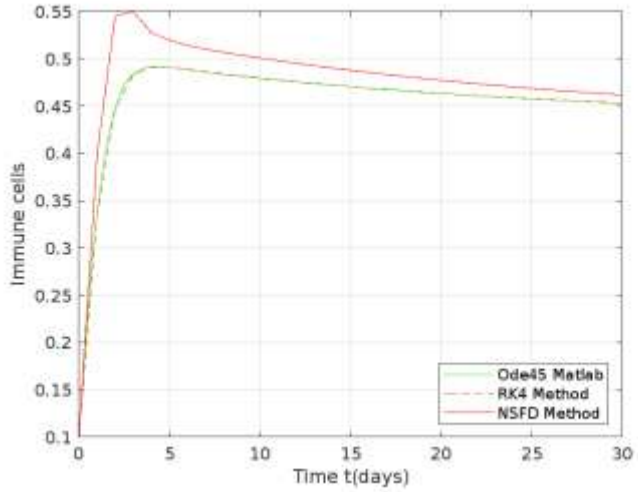

Figure 14: Approximate Solution Using Matlab, RK4 and NSFD for immune cells and $h = 1$

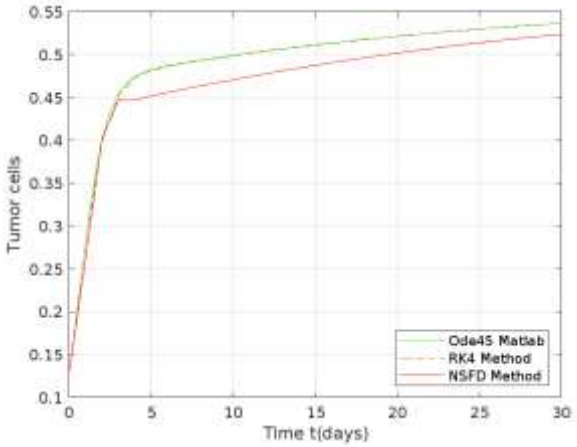

Figure 15: Approximate Solution Using Matlab, RK4 and NSFD for tumor cells and $h = 1$

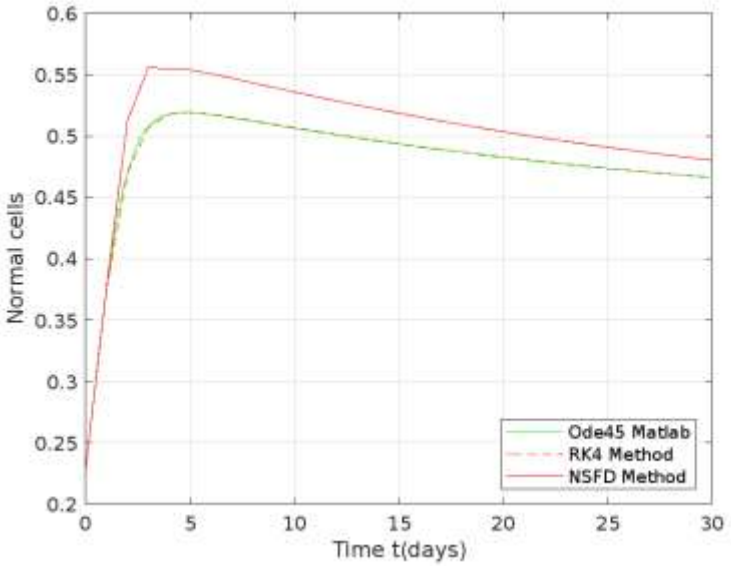

Figure 16: Approximate Solution Using Matlab, RK4 and NSFD for normal cells and $h = 1$

IX. Discussion

The analysis of the drug-free system (1) provides an overview of the system's behavior in the presence of the actively administered drug . In particular, we are interested in the behavior of the drug system after the drug is no longer actively administered.

Figures (14), (15), and (16) "NFSD" represent the solutions for N, C, and I obtained through numerical methods. As observed, Normal, Tumor and Immune cells increased during the first days. However, after that period, the normal and immunity rates slowed down, while the tumor rate was faster. It showed also that the system became stable after 60 days..

From these simulations, it is evident that immunity will increase faster with treatment and drugs and this will play a significant role in controlling the spread of tumor. Figure 14, 14 and 16 show that the applied numerical methods coincident beyond the first 5 days and convergent after that until the day no 60 the normal and immune cells coincident again while the tumor cells diverges away from both of them.

X. CONCLUSION

This paper is part of the broader study of a model of ordinary differential equations for cancer immunotherapy. Mathematical models of immune-tumor interactions provide an analytical framework for addressing specific questions about tumor immune dynamics.

The model we have investigated in this paper is the De Pillis et al. cancer immunotherapy model. Analyzing the untreated system provides an insight into the behavior of the system with treatment.

In other words, mathematical models can help us answer questions that directly impact human health. This significantly affects the health of each individual because mathematical modeling will be the key to personalized medicine [10].

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