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Qualitative analysis and numerical simulations of new model describing cancer☆

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ABSTRACT

Cancer is a major illness which still results in the loss of human lives regardless of the inroads we make in the scientific and medical world. For this reason, recently, the medical world has started to use protocol containing interleukine-10 (IL-10) and anti-PD-L1 inhibitor in order to further activate the fight of immune system cells against cancer cells. This is why it is vital to scrutinize this illness in mathematical terms by means of enhancing the immune system's reaction against cancer cells through anti-PD-L1 and IL-10. This study introduces the quadrivariant system where cancer cells, CD8+T cells, IL-10 and anti-PD-L1 variables are generated for the first time. After it is obtained that the solutions of this new system are positive, stability analysis of the equilibrium points of the system is made. The existence and uniqueness of the solutions of the system is given by fixed point theory, and the outcomes are put into practice through a number of explanatory diagrams. One of our aims in creating this model is to try to see the behavior of cancer cells by administering a dose of medicine and to analyze the process. As a result, it has been observed that immune system cells fight cancer cells effectively under the effect of single-dose IL-10 and anti-PD-L1.

1. Introduction

Tumors are characterized by cell clusters which lose command and consequently show abnormal growth. The emergent tumors are categorized under two groups, namely benign and malignant tumors; the malignant tumors, more widely known by the name cancer, have the notoriety of costing countless lives worldwide every year. With its function of preventing this type of hazardous formations and their spread within the body, immune system is also classified and construed under two different titles, which are innate immune system and adaptive immune system.

Innate immune system is the hereditary system of a human being, which is inherent in his/her body from birth till death. This type of immune system is defined by the human body combating organisms without generating any antibodies, with primary components: Epithelial barriers of the digestive system, skin and respiratory system which hinder the entrance of microbes, neutrophil, magrophage and natural killer cells [1].

On the other hand, adaptive immune system is a subsequently obtained system, where the human body combats the organisms by generating antibodies. Following an asymptomatic course in general, adaptive immune system becomes active in the presence of microbes, and responds by developing effective mechanisms that eliminate them, recording this

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incident in its memory. Adaptive immune system, which contains antibodies, can be denoted by the humoral system (B lymphocytes) and the cellular system consisting of cells (T lymphocyte). CD4+T (helper) cells and CD8+T (cytotoxic) cells constitute the main lymphocyte subgroups, CD8+T cells being the lymphocytes to carry out the task of annihilating cancer cells.

In unusual cases, immune system yields unsatisfactory results in terms of combat with unwelcome formations. This includes the connection signal of PD-L1, one of the fundamental interactions between cancer and immune system, to PD-1 [2–4]. As a result of the interaction between the PD-L1 proteins existing on the surface of cancer cells and the PD-1 that exists on the surface of T lymphocytes, the activation of lymphocytes is debilitated, bringing about a halt in the immune response [5]. It indicates that the activation of the PD-1/PD-L1 path is a mechanism which allows tumors to break away from the host's immune system [6]. Here, the purpose of immune checkpoint inhibitors, such as anti-PD-L1, is to enhance the effectiveness of T cell activation by blocking negative paths.

A protein-based cytokine playing a prominent role in regulating the systemic response in the event of cell growth, cell healing, inflammation, or injury, IL-10 increases cell CD8+T cells secretion [7]. While the use of IL-10 provides control over tumor growth and decrease in metastatic charge [8,9], and displays low-dose anti-inflammatory properties, it also brings forth the activation of the fatal CD8+T cells, especially in higher concentrations. IL-10 enhances the activation of antigen-stimulated CD8+T cell, enabling it to survive. Therefore, it is considered that IL-10 is an affirmative signal for antigen-stimulated CD8+T cells [10].

Widely known as the reinterpretation of real-world problems with mathematical equations, mathematical modeling has recently come to be one of the means utilized by scientists to predict the courses of diseases that give rise to serious problems. Owing to mathematical modeling, fast-paced research has become possible instead of long trial-and-error processes.

The ordinary differential equations (ODE) serves via mathematical models for enthusing real-world problems in the fields of biology, medicine, and economy, as well as many others like science and technology. The fact that differential equations are applicable to nearly all disciplines brings prominence to the relevant studies.

The purpose of this study is to utilize a mathematical model which has come to the forefront in different scientific fields such as physics, biology, engineering, and so on, to present a new nonlinear, inasmuch as the contribution of mathematical modeling has become undeniable when foretelling the changing properties throughout the course of cancer and some other diseases [11–31].

This paper is composed of five chapters. The original model will be given with the ordinary differential equations in Section 2. The third chapter includes positivity of the system solution and stability analysis of the system while the fourth chapter presents the qualitative analysis of the system with the help of the fixed point theory. Finally, the fifth chapter sets forth the figures involving the solutions of the system, and the comments about the figures.

2. The governing system

Developing treatment techniques that prevent tumor growth and cancer is vital for not only improving the quality of life and expanding the life-span, but also gaining various social and economical benefits. Since cancer, which is one of the diseases with the highest fatality rate in the modern age, impacts more than one system, it is also hard to cure. Therefore, it is crucial to study the disease by focusing on the distinct components of immune system in order to bring cancer under control more efficiently. In parallel with this, this study develops a new mathematical model by bringing components IL-10 and anti-PD-L1 into equation as it increases both the number and the efficiency of CD8+T cells (see Fig. 1).

Hence, the first and original system that explores the interplay among CD8+T lymphocyte, cancer cells, IL-10 and anti-PD-L1 is as follows [32] :

$$\frac{dT}{dt} = a + bI_{10}CT\left(1 - \frac{T}{p}\right) - cT \tag{1}$$

$$\frac{dC}{dt} = dC\left(1 - \frac{C}{q}\right) - eCTI_{10} - zCTZ \tag{2}$$

$$\frac{dI_{10}}{dt} = -fI_{10} \tag{3}$$

$$\frac{dZ}{dt} = -\gamma Z \tag{4}$$

Here, T, C, I_{10}, Z symbolize CD8+T lymphocytes, cancer cells, IL-10 cytokine and anti-PD-L1, respectively.

While a represents the initial density of CD8+T cells, b stands for the reproduction rate of CD8+T cells under the influence of IL-10, c denotes the death ratio of CD8+T cells, p refers to the carrying capacity of CD8+T cells, d represents the tumor growth ratio, q stands for the carrying capacity of cancer cells, e denotes the death ratio of cancer cells under the influence of IL-10, and z refers to the death ratio of cancer cells under the influence of anti-PD-L1 within the framework of the system in time. f and γ represent the decay rates of IL-10 and anti-PD-L1, respectively.

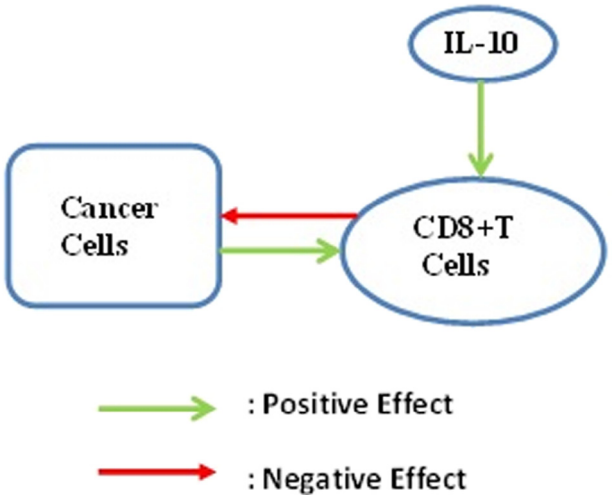

Fig. 1. Interaction between cancer cells and CD8+T lymphocytes with IL-10 interleukine and anti-PD-L1 inhibitor.

Assumptions of the System

- The parameters are assessed according to the alteration of the cells, cytokine, and inhibitor within a one-hour interval.
- The tumor cells, IL-10, and anti-PD-L1 are extrinsic and subsequently incorporated into the system.
- IL-10 and anti-PD-L1 given to the patient are administered within a protocol consisting of repeated doses at different times. The system which is proposed is examined in response to a single-dose of medication.
- Logistic modeling is employed as the cell growth model, leading to the attainment of certain parameters, along with the information that the response rate of the patients who are treated with an active dose of IL-10 is 21% while the patients who are treated with anti-PD-L1 is 25% on average [33], through the instrument of a computer.
- Modeling, where the bulk consists of a monoclonal tumor cells and is not a subtype cell displaying aggressive characteristics, is also implemented.
- There are no formations to restrain the growth of the bulk in its growing environment; in other words, it is not anatomically constricted.
- There exists veinings which nutrify tumor cells, and blood supply is sufficient.
- Immune system works under normal conditions and the patient is adults who do not have any chronic medical problems.
- The interaction between tumor cells and only CD8+T cells out of immune system cells under the influence of IL-10 and anti-PD-L1 is analyzed.

3. Analysis of the system

3.1. Positivity of the system's solution

From the Eq. (1), we can write as a form of inequality

$$-cT \leq \frac{dT}{dt},$$

Hence, obtained

$$T(t) = T_0 e^{-ct}.$$

The initial value of T cells is $T(0)$, which is an integral constant and indicates a positive amount with the limit t tends to infinity, resulting in $T(t) > 0$. As a result, $T(t)$ is always a positive number.

From the Eq. (2), it is written as a form of inequality

$$-eCTI_{10} - zCTZ \leq \frac{dC}{dt},$$

Hence, we obtain

$$C(t) = C_0 e^{-(eTI_{10}+zTZ)t}.$$

Table 1
The value of parameter for the (1)–(4) model as $c = cells$, $h = hour$.

Parameter	Value (Unit)	Reference
a	0.0001 ($c\,h^{-1}\,mm^{-3}$)	[34]
b	0.175 ($c^{-1}\,h^{-1}\,mm^{3}$)	estimated
c	0.005 (h^{-1})	[34]
p	1 ($c\,mm^{-3}$)	[34]
d	0.02 ($c\,h^{-1}mm^{-3}$)	[34]
q	1 ($c\,mm^{-3}$)	[34]
e	0.15 (h^{-1})	estimated
z	1 ($c^{-1}h^{-1}mm^{3}$)	estimated
f	0.01 (h^{-1})	estimated
γ	0.001925 (h^{-1})	estimated

The initial value of cancer cells is $C(0)$ indicates a positive amount with the limit t tends to infinity resulting in $C(t) > 0$. As a result, $C(t)$ is always a positive number.

From the Eq. (3), we can be expressed as a form of inequality

$$0 \leq \frac{dI_{10}}{dt},$$

Then, obtained $I_{10} > 0$. From the Eq. (4),

$$\frac{dZ}{dt} = -\gamma Z,$$

we write as a form of inequality $0 \leq \frac{dZ}{dt}$ and get $Z > 0$.

So, $T(t)$, $C(t)$, $I_{10}(t)$ and $Z(t)$ are always a positive number.

3.2. Stability analysis of the equilibria

The stability analysis will be given for the system (1)–(4). Firstly, we have to equate the left hand side of the equations to 0 to be able to write independently of time.

$$\begin{aligned}
&a + bI_{10}CT\left(1 - \frac{T}{p}\right) - cT = 0,\\
&dC\left(1 - \frac{C}{q}\right) - eCTI_{10} - zCTZ = 0,\\
&-fI_{10} = 0,\\
&-\gamma Z = 0,
\end{aligned}$$

We obtain $I_{10} = 0$, $Z = 0$, $T = \frac{q}{c}$ and following

$$dC\left(1 - \frac{C}{q}\right) = 0.$$

Hence, get $C = 0$, $C = q$.

Let P_1, P_2 are the stability points of the system (1)–(4) and the Jacobian matrix of this system is computed.

$$J(P) = \begin{pmatrix}
bI_{10}C - 2bI_{10}C\frac{T}{p} - c & -eCI_{10} - zCZ & 0 & 0\\
bI_{10}T\left(1 - \frac{T}{p}\right) & d - 2d\frac{C}{q} - eTI_{10} - zTZ & 0 & 0\\
bCT\left(1 - \frac{T}{p}\right) & -eCT & -f & 0\\
0 & -eCT & 0 & -\gamma
\end{pmatrix}.$$

Hence, $J(P_1)$ is

$$\lambda_1^{(1)} = -c, \lambda_2^{(1)} = d, \lambda_3^{(1)} = -f, \lambda_4^{(1)} = -\gamma$$

and $J(P_2)$ is

$$\lambda_1^{(2)} = -c, \lambda_2^{(2)} = -d, \lambda_3^{(2)} = -f, \lambda_4^{(2)} = -\gamma.$$

With the parameters in Table 1, it appears that the 2nd components (d and $-d$) of the eigenvalue vectors that the stability of the system depends on the growth rate of the tumor.It is seen that the first of these values is positive and the second is negative. So, it is said that P_1 is unstable and P_2 is stable. In other words, P_2 is asymptotic stable since

$\left|arg\left(\lambda_j^{(2)}\right)\right| > \frac{\pi}{2}$ for the eigenvalues obtained from the solution of the characteristic equation of $det\left(J(P_2) - \lambda_j^{(2)} I\right) = 0$, for $j \in \{1, 2, 3, 4\}$.

The tumor concentration at the two equilibria makes a big difference according to Table 1. Biologically speaking, when $C = 0$, there is an equilibrium point without the tumor. In this case, the immune system is effective in fighting the tumor and no treatment is needed. The other equilibrium point that obtained $C = q$, has a tumor concentration close to the carrying capacity of the tumor itself and treatment is needed.

4. Qualitative analysis of the solutions of the system

In differential calculus, it is crucial to prove the presence of a problem. Since this work examines a nonlinear system, it is possible that there exists no technique to produce precise solutions of the system. Nevertheless, not only the solution system's existence, but also the uniqueness of the results are revealed in this section by use of the fixed theory.

A continuation of the system (5) is acquired by implementing the fractional integral onto Eqs. (1)–(4) as given below:

$$\begin{aligned}
T(t) - T(0) &= \int_0^t \left[a + bI_{10}(\lambda)\left(CT(\lambda)\,1 - \frac{T(\lambda)}{p}\right) - cT(\lambda)\right] d\lambda,\\
C(t) - C(0) &= \int_0^t \left[dC(\lambda)\left(1 - \frac{C(\lambda)}{q}\right) - eC(\lambda)\,T(\lambda)\,I_{10}(\lambda) - zC(\lambda)\,T(\lambda)\,Z(\lambda)\right] d\lambda,\\
I_{10}(t) - I_{10}(0) &= \int_0^t \left[-fI_{10}(\lambda)\right] d\lambda,\\
Z(t) - Z(0) &= \int_0^t \left[-\gamma Z(\lambda)\right] d\lambda.
\end{aligned} \tag{5}$$

The following kernels can be defined:

$$\begin{aligned}
M_1(t, T) &= a + bI_{10}(t)\,C(t)\,T(t)\left(1 - \frac{T(t)}{p}\right) - cT(t),\\
M_2(t, C) &= dC(t)\left(1 - \frac{C(t)}{q}\right) - eC(t)\,T(t)\,I(t)_{10} - zC(t)\,T(t)\,Z(t),\\
M_3(t, I_{10}) &= -fI_{10}(t),\\
M_4(t, Z) &= -\gamma Z(t).
\end{aligned} \tag{6}$$

Theorem 1. *If inequality (7) holds the kernel M_1 satisfies Lipschitz condition and contraction.*

$$0 \le b\sigma_3\sigma_2 + 2\frac{b}{q}\sigma_3\sigma_2\sigma_1 - c < 1 \tag{7}$$

Proof. Let T and T_1 be functions, obtained by

$$\begin{aligned}
\|M_1(t, T) - M_1(t, T_1)\| &= \left\|bI_{10}(t)\,C(t)\left[T(t)\left(1 - \frac{T(t)}{p}\right) - T_1(t)\left(1 - \frac{T_1(\lambda)}{p}\right)\right] - c\left(T(t) - T_1(t)\right)\right\|,\\
&= \left\|bI_{10}(t)\,C(t)\left(T(t) - T_1(t)\right) + \frac{b}{p}I_{10}(t)\,C(t)\left(T^2(t) - {T_1}^2(t)\right)\right.\\
&\quad \left. - c\left(T(t) - T_1(t)\right)\right\|,\\
&\le \left(b\,\|I_{10}(t)\|\,\|C(t)\| + \frac{b}{p}\,\|I_{10}(t)\|\,\|C(t)\|\,\|T(t) + T_1(t)\| - c\right)\|(T(t) - T_1(t))\|,\\
&\le \left(b\sigma_3\sigma_2 + 2\frac{b}{q}\sigma_3\sigma_2\sigma_1 - c\right)\|T(t) - T_1(t)\|.
\end{aligned}$$

Taking $\varsigma_1 = b\sigma_3\sigma_2 + 2\frac{b}{q}\sigma_3\sigma_2\sigma_1 - c$ where $\|T(t)\| \le \sigma_1$, $\|C(t)\| \le \sigma_2$, $\|I_{10}(t)\| \le \sigma_3$, $\|Z(t)\| \le \sigma_4$ are bounded functions, we get

$$\|M_1(t, T) - M_1(t, T_1)\| \le \varsigma_1\,\|T(t) - T_1(t)\|. \tag{8}$$

Hence, the Lipschitz condition is satisfied for the kernel M_1 and since $b\sigma_3\sigma_2 + 2\frac{b}{q}\sigma_3\sigma_2\sigma_1 - c < 1$, M_1 is also a contraction.

Similarly, it can be shown that the kernels M_2, M_3, M_4 and satisfy the Lipschitz condition as follows:

$$\|M_2(t,C) - M_2(t,C_1)\| \leq \varsigma_2 \|C(t) - C_1(t)\|,$$

$$\left\|M_3(t,I_{10}) - M_3\left(t,I_{10_1}\right)\right\| \leq \varsigma_3 \left\|I_{10}(t) - I_{10_1}(t)\right\|,$$

$$\|M_4(t,Z) - M_4(t,Z_1)\| \leq \varsigma_4 \|Z(t) - Z_1(t)\|.$$

Using the aforesaid kernels, Eq. (5) becomes

$$\begin{aligned}
T(t) &= T(0) + \int_0^t M_1(\lambda, T)\, d\lambda,\\
C(t) &= C(0) + \int_0^t M_2(\lambda, C)\, d\lambda,\\
I_{10}(t) &= I_{10}(0) + \int_0^t M_3(\lambda, I_{10})\, d\lambda,\\
Z(t) &= Z(0) + \int_0^t M_4(\lambda, Z)\, d\lambda.
\end{aligned} \tag{9}$$

The following recursive formula is given:

$$\begin{aligned}
T_n(t) &= \int_0^t M_1(\lambda, T_{n-1})\, d\lambda,\\
C_n(t) &= \int_0^t M_2(\lambda, C_{n-1})\, d\lambda,\\
I_{10n}(t) &= \int_0^t M_3\left(\lambda, I_{10n-1}\right) d\lambda,\\
Z_n(t) &= \int_0^t M_4(\lambda, Z_{n-1})\, d\lambda,
\end{aligned} \tag{10}$$

where the initial conditions are

$$\begin{aligned}
T_0(t) &= T(0),\\
C_0(t) &= C(0),\\
I_{10_0}(t) &= I_{10}(0),\\
Z_0(t) &= Z(0).
\end{aligned} \tag{11}$$

The differences between successive terms are given as below:

$$\Upsilon_n(t) = T_n(t) - T_{n-1}(t) = \int_0^t \left[M_1(\lambda, T_{n-1}) - M_1(\lambda, T_{n-2})\right] d\lambda,$$

$$\Phi_n(t) = C_n(t) - C_{n-1}(t) = \int_0^t \left[M_2(\lambda, C_{n-1}) - M_2(\lambda, C_{n-2})\right] d\lambda,$$

$$\Omega_n(t) = I_{10n}(t) - I_{10n-1}(t) = \int_0^t \left[M_3\left(\lambda, I_{10n-1}\right) - M_3\left(\lambda, I_{10n-2}\right)\right] d\lambda,$$

$$\Theta_n(t) = Z_n(t) - Z_{n-1}(t) = \int_0^t \left[M_4(\lambda, Z_{n-1}) - M_4(\lambda, Z_{n-2})\right] d\lambda. \tag{12}$$

It is quite obvious that

$$T_n(t) = \sum_{k=0}^{n} \Upsilon_k,$$

$$C_n(t) = \sum_{k=0}^{n} \Phi_k,$$

$$I_{10n}(t) = \sum_{k=0}^{n} \Omega_k,$$

$$Z_n(t) = \sum_{k=0}^{n} \Theta_k, \tag{13}$$

When the norm is applied to both sides of the equation Eq. (12), get

$$\begin{aligned} \|\Upsilon_n(t)\| &= \|T_n(t) - T_{n-1}(t)\| \\ &= \left\| \int_0^t \left[M_1(\lambda, T_{n-1}) - M_1(\lambda, T_{n-2})\right] d\lambda \right\| \end{aligned} \tag{14}$$

Eq. (14) becomes,

$$\begin{aligned} \|\Upsilon_n(t)\| &= \|T_n(t) - T_{n-1}(t)\| \\ &\leq \left\| \int_0^t \left[M_1(\lambda, T_{n-1}) - M_1(\lambda, T_{n-2})\right] d\lambda \right\| \end{aligned} \tag{15}$$

Since the kernel M_1 satisfies Lipschitz condition, the following equation is found.

$$\begin{aligned} \|\Upsilon_n(t)\| &= \|T_n(t) - T_{n-1}(t)\| \\ &\leq \varsigma_1 \int_0^t \|T_{n-1} - T_{n-2}\| \, d\lambda. \end{aligned} \tag{16}$$

Hence, obtained

$$\|\Upsilon_n(t)\| \leq \varsigma_1 \int_0^t \|\Upsilon_{n-1}(\lambda)\| \, d\lambda. \tag{17}$$

Similarly, we get

$$\|\Phi_n(t)\| \leq \varsigma_2 \int_0^t \|\Phi_{n-1}(\lambda)\| \, d\lambda,$$

$$\|\Omega_n(t)\| \leq \varsigma_3 \int_0^t \|\Omega_{n-1}(\lambda)\| \, d\lambda,$$

$$\|\Theta_n(t)\| \leq \varsigma_4 \int_0^t \|\Theta_{n-1}(\lambda)\| \, d\lambda. \tag{18}$$

Theorem 2. *The cancer-immune model (1)–(4) has a solutions if we can obtain t_0 such that*

$$t_0\varsigma_1 < 1 \tag{19}$$

Proof. We know that $T(t)$, $C(t)$, $I_{10}(t)$, $Z(t)$ are bounded and the kernels satisfy Lipschitz condition. With Eqs. (17), (18) and using recursive method, get

$$\begin{aligned}
&\|\Upsilon_n(t)\| \le \|T_n(0)\|(t\varsigma_1)^n,\\
&\|\Phi_n(t)\| \le \|C_n(0)\|(t\varsigma_2)^n,\\
&\|\Omega_n(t)\| \le \|I_{10n}(0)\|(t\varsigma_3)^n,\\
&\|\Theta_n(t)\| \le \|Z_n(0)\|(t\varsigma_4)^n.
\end{aligned} \tag{20}$$

So, Eq. (13) exists. Now, we will prove the above functions are solution of Eqs. (1)–(4). Let

$$\begin{aligned}
&T(t) - T(0) = T_n(t) - \mathcal{G}_n(t),\\
&C(t) - C(0) = C_n(t) - \mathcal{J}_n(t),\\
&I_{10}(t) - I_{10}(0) = I_{10n}(t) - \mathcal{N}_n(t),\\
&Z(t) - Z(0) = Z_n(t) - \mathcal{V}_n(t),
\end{aligned} \tag{21}$$

Then, get

$$\begin{aligned}
\|\mathcal{G}_n(t)\| &= \left\| \int_0^t [M_1(\lambda, T) - M_1(\lambda, T_{n-1})]\, d\lambda \right\|\\
&\le \int_0^t \|M_1(\lambda, T) - M_1(\lambda, T_{n-1})\, d\lambda\|\\
&\le t\varsigma_1 \|T - T_{n-1}\|.
\end{aligned} \tag{22}$$

By repeating the recursive, it becomes

$$\|\mathcal{G}_n(t)\| \le (t)^{n+1}\varsigma_1^{n+1}\sigma_1. \tag{23}$$

At the point t_0, we have

$$\|\mathcal{G}_n(t)\| \le (t_0)^{n+1}\varsigma_1^{n+1}\sigma_1. \tag{24}$$

By taking limit in the Eq. (24) for n tends to infinity, get

$$\|\mathcal{G}_n(t)\| \to 0.$$

Similarly, we have

$$\|\mathcal{J}_n(t)\| \to 0,\ \|\mathcal{N}_n(t)\| \to 0,\ \|\mathcal{V}_n(t)\| \to 0, \|\mathcal{W}_n(t)\| \to 0.$$

Finally, proof of existence is satisfied.

Another substantial issue is to show the uniqueness of the system of solutions of Eqs. (1)–(4). Let $T_1(t)$, $C_1(t)$, $I_{10_1}(t)$ and $Z_1(t)$ be another solutions of the system (1)–(4). Then, we get

$$T(t) - T_1(t) = \int_0^t [M_1(\lambda, T) - M_1(\lambda, T_1)]\, d\lambda \tag{25}$$

and

$$\|T(t) - T_1(t)\| \le \int_0^t \|M_1(\lambda, T) - M_1(\lambda, T_1)\|\, d\lambda \tag{26}$$

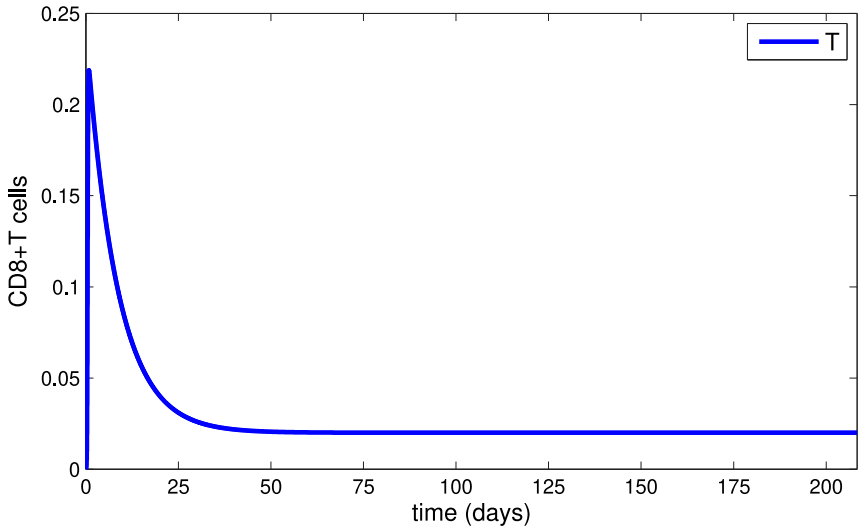

Fig. 2. CD8+T cells (T) in ordinary differential system (1)–(4).

Since the kernel satisfies Lipschitz condition, we get

$$\|T(t) - T_1(t)\| \leq t\varsigma_1 \|T(t) - T_1(t)\| \tag{27}$$

and then

$$\|T(t) - T_1(t)\| (t\varsigma_1) \leq 0. \tag{28}$$

Theorem 3. *If the below inequality holds*

$$(1 - t\varsigma_1) > 0, \tag{29}$$

the system (1)–(4) has a unique system of solutions.

Proof. If the condition (29) satisfies, we get

$$\|T(t) - T_1(t)\| (1 - t\varsigma_1) \leq 0 \tag{30}$$

so

$$\|T(t) - T_1(t)\| = 0.$$

We get

$$T(t) = T_1(t). \tag{31}$$

In the same manner, we have

$$C(t) = C_1(t),$$

$$I_{10}(t) = I_{101}(t),$$

$$Z(t) = Z_1(t),$$

5. Numerical simulations and discussion

We first demonstrate the numerical inquiry concerning the tumor-immune system incorporating ODE by using Euler's method, and assess a good number of values so that we can carry out a conclusive research. It is observed that the number of T lymphocyte cells show an increase in the beginning, but they start decreasing afterwards due to the decline in the tumor load. Moreover, taking advantage of the decrease in the T lymphocyte cells, the cancer cells show a growth up to their original proportions after approximately 200 days, as is seen in Fig. 3. Shortly, by the aid of Figs. 2–3 derived from the solution of system (1)–(4), we arrive at the conclusion that it is after 175 days when cancer cells show regrowth

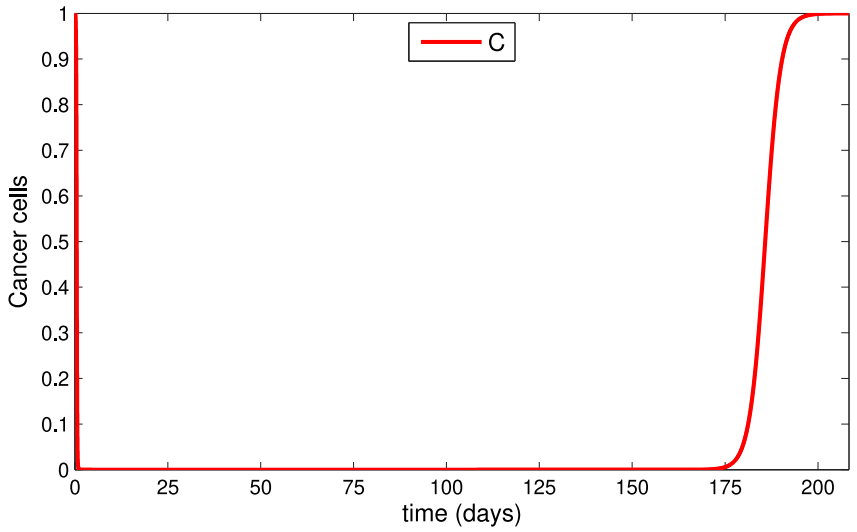

Fig. 3. Cancer cells (C) in ordinary differential system (1)–(4).

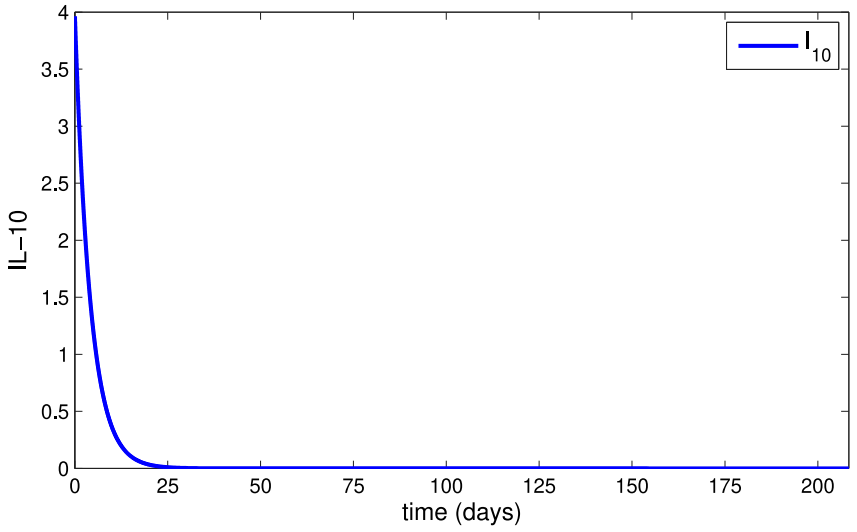

Fig. 4. IL-10 (I_{10}) in ordinary differential system (1)–(4).

up until the beginning phase. As for the administered single-dose IL-10 cytokine and anti-PD-L1 inhibitor, they display decline to a certain point due to their half-lives after being submitted to the system as seen in Figs. 4–5.

Fig. 6 includes the concentration figures of CD8+T cells and cancer cells as per the death rate of CD8+T cells. Following from Fig. 6(a), it is observed in Fig. 6(b) that the changes in the death rate of lymphocytes shorten the duration when cancer cells regrow.

Fig. 7 offers the concentration figures of IL-10 and cancer cells according to the IL-10 reduction ratio. Following from Fig. 7(a), how the minor changes in the IL-10 concentration affect the duration of cancer cell regrowth subsequent to their diminishment are shown in Fig. 7(b). It is seen that the duration during which cancer cells regrow becomes shorter.

Fig. 8 presents the concentration figures of anti-PD-L1 and cancer cells according to the anti-PD-L1 reduction ratio. Following from Fig. 8(a), it is seen in Fig. 8(b) that the changes in the anti-PD-L1 concentration shortens the duration in which cancer cells regrow.

6. Concluding remarks and future works

This work puts forth a new system investigating the interplay among lymphocyte cells, cancer cells, IL-10, and anti-PD-L1. After calculating the stability points of the propounded system, the existence of the system's solutions is given. And

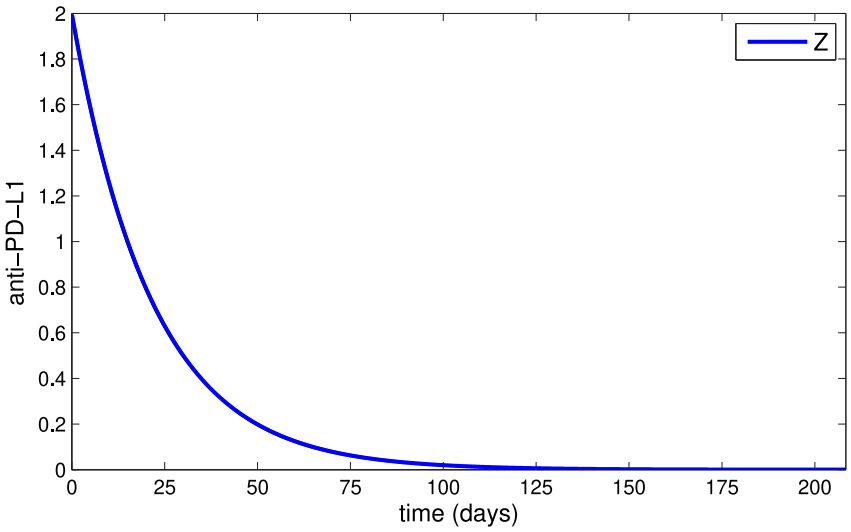

Fig. 5. anti-PD-L1 (Z) in ordinary differential system (1)–(4).

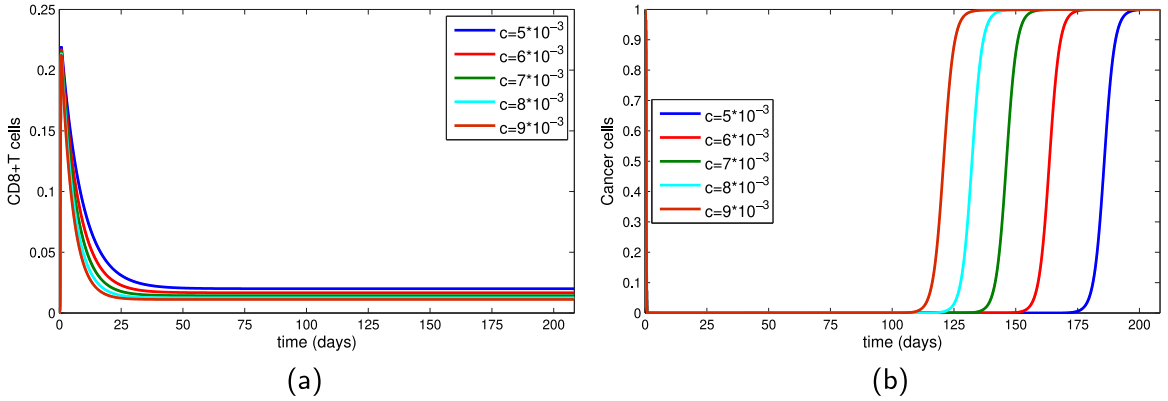

Fig. 6. Change in cancer cells due to increased death rate of CD8+T lymphocytes (c).

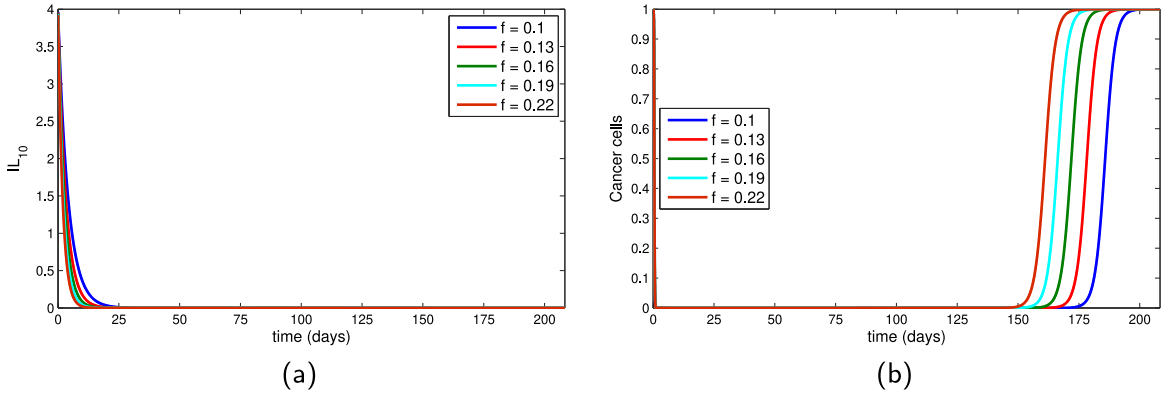

Fig. 7. Change in cancer cells due to increased disruption rate of IL-10 (f).

subsequently, diagrams of the system's numerical solutions are presented along with the comments about the figures. In addition to the figures are drawn with the values and starting points in Table 1, the figures are obtained due to the increase in the death rate of T lymphocyte cells, IL-10 and anti-PD-L1 disruption rate are examined.

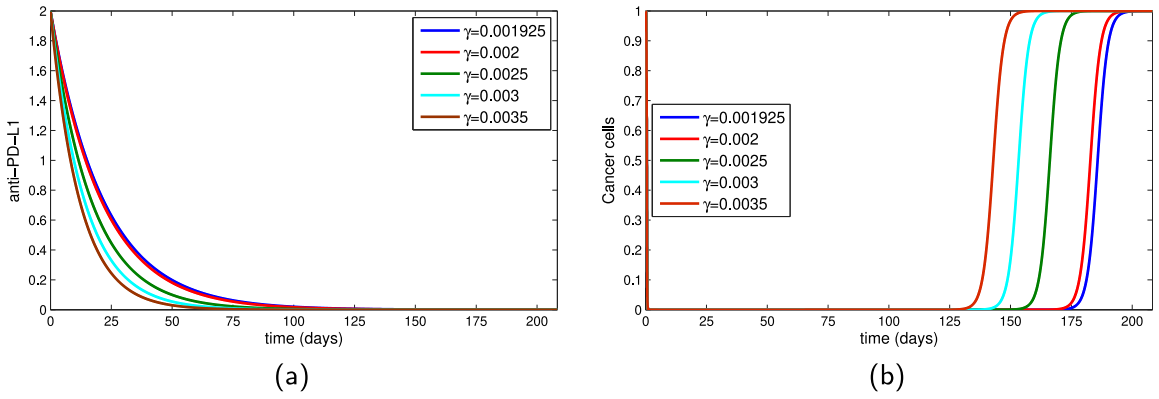

Fig. 8. Change in cancer cells due to increased disruption rate of anti-PD-L1 (γ).

It is known that patients with weaker immune systems are more prone to the risk of developing cancer. Analyzed accordingly, it can be seen in Figs. 6–8 that the probability of recurrence is higher and duration of recurrence is shorter during the periods when the concentration of immune system components decreases.

With this original system (1)–(4), which is created especially to reveal the relationship between IL-10, anti-PD-L1 and cancer cells, it is seen that IL-10 and anti-PD-L1 have an important role in inactivating cancer cells and the system eliminates cancer cells while under the effect of these two drugs, which are administered as a single-dose. Drug's effectiveness is accepted when a certain protocol is applied with repeated dose applications and treatments.

In future work, this new system, will be examined with the fractional derivative in the sense of Caputo, and it will be tried to see the effect of memory and heredity. In addition, this new system created can be improved by adding different variables.

CRediT authorship contribution statement

Esmehan Uçar: Conceptualization, Methodology, Software, Writing-review, and Editing.. **Necati Özdemir:** Conceptualization, Methodology, Writing-review, and Editing, Supervision.. **Eren Altun:** Conceptualization, Methodology,Data curation, Review original draft.

Data availability

No data was used for the research described in the article.

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