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STABILITY AND ZERO-HOPF BIFURCATION ANALYSIS OF A TUMOUR AND T-HELPER CELLS INTERACTION MODEL IN THE CASE OF HIV INFECTION

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Abstract. In this paper, we present a mathematical model governing the dynamics of tumour-immune cells interaction under HIV infection. The interactions between tumour cells, helper T-cells, infected helper T-cells and virus cells are explained by using delay differential equations including two different discrete time delays. In the model, these time lags describe the time needed by the helper T-cells to find (or recognize) tumour cells and virus, respectively. First, we analyze the dynamics of the model without delays. We prove the positivity of the solution, analyze the local and global stabilities of the steady states of the model. Second, we study the effects of two discrete time delays on the stability of the endemically infected equilibrium point. We determine the conditions on parameters at which the system undergoes a zero-Hopf bifurcation. Choosing one of the delay terms as a bifurcation parameter and fixing the other, we show that a zero-Hopf bifurcation arises as the bifurcation parameter passes through a critical value. Finally, we perform numerical simulations to support and extend our theoretical results. The results concluded help to better understand the links between the immune system and the tumour development in the case of HIV infection.

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1. INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that attacks and destroys the immune system, so that it causes the HIV infection [10] and the disease called AIDS (Acquired Immune Deficiency Syndrome [8, 24, 30]). AIDS is a condition in humans in which the progressive collapse of the immune system allows infections and cancers which threat human life. According to data published by the World Health Organization (WHO), it is presumed that more than 35 million people died due to AIDS since it was first discovered in 1981, and 37.9 million people were living with HIV at the end of 2018. There is no cure for AIDS but there are certain medicines that are used to slow down this disease.

The main target of HIV is the immune system, especially the $CD4^+$ T-cells, which are the most sufficient white blood cells, or lymphocytes. $CD4^+$ T lymphocytes play a central role in orchestrating the beginning and maintenance of the adaptive immune response [2,13]. These cells are more commonly referred to as helper T-cells which is the term we will use in this paper. The helper T-cells can be categorized as effector and non-effector helper T-cells. The effector helper T-cells are triggered by the tumour cell proliferation, and they have a death rate which is considerably small compare to the normal helper T-cells. These cells are mediated by the cytokines secreted by the differentiated cells. Therefore, they are specific to certain disease [2]. HIV causes the destruction of helper T-cells; as a result, it decreases the body's ability to fight the infection. The count of helper T-cell is normally around 1000 mm^{-3} in a human being. However, when it decreases to 200 mm^{-3} or below in an HIV infected individual, then that person is classified as having AIDS [15,26].

HIV infected individuals have a high risk of developing certain tumours. The connection between HIV/AIDS and certain tumours has not been understood completely, but it likely depends on a weakened immune system [4, 6, 33, 36]. When normal cells begin to change and grow uncontrollably, a mass called tumour forms. A tumour can be benign, also called non-cancerous, or malignant which is cancerous (see the reference [1] for more details). Malignancies that are found to have a high incidence of HIV-infected individuals are Kaposi's sarcoma (KS), Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), squamous cell carcinomas, plasmacytomas and leiomyosarcoma in children [36]. In the tumour cells of HIV infected patients, no viral sequence in the DNA was found; therefore, it seems that the virus doesn't include the tumour itself [20]. Furthermore, the immune surveillance hypothesis explains that the immune system patrols the body to recognize and destroy invading pathogens [6,7].

There is a variety of mathematical models that studied and analyzed the tumour growth [19, 27]. Also, in recent years, modeling, analysis and control of the HIV infection have attracted the attention of researchers in bio-mathematics (see, for example, [11, 25, 26] and references cited therein). However, the interaction between both the HIV-immune system and the tumour-immune system has not been fully understood, since several types of tumours are associated to the HIV occurrence. Therefore, it is important to investigate the dynamics of the immune system in this situation. A few of such studies can be found in [5, 12, 21, 22, 29].

The aim of this work is to better understand the interaction between tumour and immune system in an HIV infected individual. More precisely, we want to analyze how the existence of HIV infection affects the dynamics of the immune system and tumour cells. To do this, we use a system of delay differential equations where the time lag describes the time needed by helper T-cells to find (or it can be said 'recognize') tumour cells and virus. Inspired by the studies in [12, 29], we present a mathematical model involving four populations: tumour cells, uninfected effector

helper T-cells, infected helper T-cells and free virus. The models presented in this manuscript and also [12, 29] are improved from the model introduced in the papers by Lou et al. [21, 22]. In [22], Lou et al. presented a model of cell-to-cell spread of HIV together with tumour in tissue cultures (in vitro). They aimed at explaining some properties concerning tumour occurring during the HIV infection. The same model is studied with the delay in [21].

In [5], Bodnar et al. proposed a model to describe the HIV related tumour-immune system interactions in vitro. Moreover, in [12], Forys and Poleszczuk considered a similar model. However, they considered the issue of immune reaction against tumour and the second way for HIV to disseminate in vivo (circulating free viral particles to T-cells directly). In [29], Rihan and Rahman studied a model which describes the interaction between tumour cells, the general population of the helper T-cells, infected helper T-cells and virus where the time lag is considered to represent the time needed by the healthy effector cells to recognize the tumour cells and virus. Also, they consider that HIV disseminates in vivo by circulating free viral particles to T-cells directly.

The difference between the study in [29] and the present paper is that the model we examined here involves two different discrete delays, and its stability and bifurcation analysis is given for the full model, i.e., without reducing the dimension of the model proposed. In addition, the difference between the study in [12] and this work is that the helper T-cells that we consider are exactly the effector helper T-cells, not general ones. HIV attacks the helper T-cells but then each helper T-cell is target to the virus. Namely, we care more about the cells that are specific to tumour and what happened to them is more important for us.

In this paper, the existence, uniqueness and non-negativity of solutions, and also both local and global stabilities of steady states of the model without delay are first studied. And then, the existence of a zero-Hopf bifurcation for the model with delay is given. Apart from Section 1, the paper is organized in the following aspect: In Section 2, we introduce a mathematical model of HIV infection with tumour cells; the mathematical analysis of the ODE model is performed. The theoretical results about steady states and their stabilities are presented in Section 3. Later, the analysis is presented for the DDE model in Section 4. The existence of a zero-Hopf bifurcation is investigated in this section. Numerical simulations that support and extend the theoretical results are given in Section 5. Section 6 is devoted to conclusions and predictions of the models.

2. THE MODEL

We consider the following delay differential equation system describing the tumour-immune system interactions in the case of HIV:

$$\begin{aligned}
\frac{dT}{dt} &= r_1 T(t) - k_1 T(t) E(t-\tau_1), \\
\frac{dE}{dt} &= r_2 T(t) - \mu_1 E(t) - \theta k_1 T(t) E(t-\tau_1) - k_2 E(t-\tau_2) V(t), \\
\frac{dI}{dt} &= k_2 E(t-\tau_2) V(t) - cI(t), \\
\frac{dV}{dt} &= N\delta I(t) - \mu_2 V(t),
\end{aligned} \tag{2.1}$$

where $T(t), E(t), I(t), V(t)$ denote the concentration of tumour cells, healthy effector helper T-cells, helper T-cells infected by free HIVs and free HIV particles at time t, respectively, and all parameters are positive. The time lags τ_1 and τ_2 describe the time needed by the helper T-cells to recognize tumour cells and virus, respectively.

We assume that the tumour cells grow exponentially with a constant proliferation rate; we do not consider resource limitation. Such type of tumour growth is experimentally observed at the beginning of the tumour development [35]. Also, we assume the linear response of the immune system to tumour cell presence. In the model, we take this response as proportional to the multiplication of both tumour and immune system cell concentrations.

Healthy effector helper T-cells are reproduced as a result of the presence of tumour. The parameter r_2 indicates the antigenicity of tumour. Antigenicity can be thought of as a measure of how different the tumour cells are from normal cells [16]. Parameters μ_1, c and μ_2 are natural death rates of the healthy T-cells, the infected T-cells and the HIV particles, respectively, because cells have a finite life span. Also, the parameter θ represents the small percentage of T-cells that do not survive after killing the tumour cells (the inequality $\theta \leq 1$ is obvious because of the definition of this parameter).

HIV can spread out in vivo either by transmission of cell-free virus or directly from cell-to-cell via the formation of virological synapses as stated in [9, 17, 18]. In this model, similar to [11], we assume that the transition of the healthy T-cells into the infected ones is due to direct interaction with the virus. Accordingly, the infection rate is given by k_2 which increases the count of the infected helper T-cells.

Finally, according to [26], the virus is produced by the productively infected T-cells. Here, we have assumed that on average each productively infected helper T-cell produces N virus during its lifetime. Since the average lifetime of a productively infected cell is $\frac{1}{\delta}$, the average rate of virus production is $N\delta$. Therefore, $N\delta$ represents the source for free viruses. In this derivation, we have ignored the loss of virus due to the infection of a cell.

3. Analysis of the ODE model

In this section, we study the model without delay. By taking $\tau_1 = \tau_2 = 0$ in system (2.1) we obtain the following ODE model:

$$\begin{aligned}
\frac{dT}{dt} &= r_1 T(t) - k_1 T(t) E(t), \\
\frac{dE}{dt} &= r_2 T(t) - \mu_1 E(t) - \theta k_1 T(t) E(t) - k_2 E(t) V(t), \\
\frac{dI}{dt} &= k_2 E(t) V(t) - cI(t), \\
\frac{dV}{dt} &= N\delta I(t) - \mu_2 V(t),
\end{aligned} \tag{3.1}$$

where all parameters and variables are the same as described in the former section.

One can write system (3.1) as a vector equation form as follows:

$$\frac{dX(t)}{dt} = F(t, X(t)), \tag{3.2}$$

where $X(t) = (T(t), E(t), I(t), V(t))^T$ and $F(t) = (f_1(t), f_2(t), f_3(t), f_4(t))^T$ in which

$$\begin{aligned}
f_1(t) &= r_1 T(t) - k_1 T(t) E(t), \\
f_2(t) &= r_2 T(t) - \mu_1 E(t) - \theta k_1 T(t) E(t) - k_2 E(t) V(t), \\
f_3(t) &= k_2 E(t) V(t) - cI(t), \\
f_4(t) &= N\delta I(t) - \mu_2 V(t).
\end{aligned}$$

3.1. *Positivity of solutions*

The following Lemma underlines that for positive initial data, the solution of system (3.1) uniquely exists and remains in $\mathbb{R}^4_+$. From biological point of view, it means that the model is reasonable in the sense that no population becomes negative. Therefore, there is no need analyzing of the trivial steady state of system (3.1).

Lemma 1. *The solution of system (3.1) with non-negative initial conditions T_0, E_0, I_0 and V_0 uniquely exists and remains in $\mathbb{R}^4_+$.*

Proof. Note that $F(t, X(t))$ in Eq. (3.2) is continuous and also Lipschitz with respect to $X(t)$ on any four-dimensional box D. Then system (3.1) has the unique solution on $[0, b)$ where b can be determined as $t \to b^-$ at which either the solution becomes unbounded or the solution approaches to the boundary of D. In addition, We assume that $T(t)$, $E(t)$, $I(t)$ and $V(t)$ initially have positive values. Recall that all constants in the system are positive. For positive initial conditions T_0, E_0, I_0 and V_0, from the first and the second equations of system (3.1) we have the following (where $A(t)$ is the integrating factor):

$$T(t) = T_0 e^{\int_0^t r_1 - k_1 E(s) ds} \geq 0, \qquad \forall t \geq 0.$$

$$E(t) = \frac{A(0)E_0 + r_2 \int_0^t A(s)T(s)ds}{A(t)} \geq 0, \qquad \forall t \geq 0.$$

From the third and the fourth equations of the system, we have

$$I(t) = I_0 e^{-ct} + k_2 e^{-ct} \int_0^t e^{cs} E(s)V(s)ds,$$
$$V(t) = V_0 e^{-\mu_2 t} + N\delta e^{-\mu_2 t} \int_0^t e^{\mu_2 s} I(s)ds.$$

Let us denote by t_* the first time for which one of the populations $I(t)$ and $V(t)$ become zero, or more precisely $\min\{I(t_*), V(t_*)\} = 0$. Without loss of generality, let $V(t_*) = 0$. So, $I(t_*) > 0$ for $t \in [0, t_*]$ since t_* is the first time for which one of the populations $I(t)$ and $V(t)$ become zero. Also $V(t) > 0$ for $t \in [0, t_*)$ since we assume that $T(t)$, $E(t)$, $I(t)$ and $V(t)$ initially have non-negative values. Therefore, $V(t)$ must be non-increasing on $[0, t_*]$, or more precisely

$$\left.\frac{dV}{dt}\right|_{t=t_*} \leqslant 0.$$

On the other hand, one can see that from the last equation of system (3.1)

$$\left.\frac{dV}{dt}\right|_{t=t_*} = N\delta I(t_*) - \mu_2 V(t_*) = N\delta I(t_*) > 0$$

since the equation $V(t_*) = 0$ holds. Consequently, this leads to a contradiction. Thus, there cannot be found a t_* such that $V(t_*) = 0$. So, for $\forall t > 0$, $V(t) > 0$ and $I(t) > 0$. This completes the proof. □

3.2. *Steady states*

In order to fully understand the dynamics of the model, first we must establish the values of steady states. The steady states of system (3.1) can be obtained by setting the equations $f_1(t)$, $f_2(t)$, $f_3(t)$, $f_4(t)$ simultaneously equal to zero. The following lemma explains the steady states of the model.

Lemma 2. *Let*

$$\Re_1 = r_2 - \theta r_1 \text{ and } \Re_0 = \sqrt{\frac{N\delta k_2 r_1}{c k_1 \mu_2}}.$$

If $\Re_1 > 0$, then system (3.1) has two non-negative steady states other than the trivial one:

(1) *If $\Re_0 \neq 1$, then one obtains the non-infected steady state $S_0 = \left(\frac{\mu_1 r_1}{k_1(r_2 - \theta r_1)}, \frac{r_1}{k_1}, 0, 0\right)$.*

(2) *If $\Re_0 = 1$, then one obtains the steady state $S^* = \left(\frac{\mu_1 r_1 + k_2 r_1 \vartheta}{k_1(r_2 - \theta r_1)}, \frac{r_1}{k_1}, \frac{r_1 k_2}{k_1 c}\vartheta, \vartheta\right)$, where $\vartheta \in \mathbb{R}^+ \cup \{0\}$.*

3.3. *Local stability analysis*

The fact that the stability properties depend on the eigenvalues of the system is well-known for linear ODEs. However, our model is nonlinear, and thus we must use linearization. We will investigate the local stability properties of the steady states by approximating the nonlinear system of differential equations with a linear system at the points S_0 and S^*. The local stability analysis of these steady states is given below.

Theorem 1. *For system (3.1), if $\Re_1 > 0$ and $\Re_0 < 1$, then the steady state S_0 is locally asymptotically stable. Furthermore, the steady state S^* is always L-stable.*

Proof. First, we linearize system (3.1) around its steady states and then find its Jacobian matrices as follows:

$$J_{S_0} = \begin{bmatrix} 0 & -\frac{\mu_1 r_1}{r_2-\theta r_1} & 0 & 0 \\ r_2-\theta r_1 & -\mu_1 - \frac{\theta\mu_1 r_1}{r_2-\theta r_1} & 0 & -\frac{r_1 k_2}{k_1} \\ 0 & 0 & -c & \frac{r_1 k_2}{k_1} \\ 0 & 0 & N\delta & -\mu_2 \end{bmatrix}, \tag{3.3}$$

and

$$J_{S^*} = \begin{bmatrix} 0 & -r_1\frac{\mu_1+k_2\vartheta}{r_2-\theta r_1} & 0 & 0 \\ r_2-\theta r_1 & -\mu_1-k_2\vartheta-\theta r_1\left(\frac{\mu_1+k_2\vartheta}{r_2-\theta r_1}\right) & 0 & -\frac{r_1 k_2}{k_1} \\ 0 & k_2\vartheta & -c & \frac{r_1 k_2}{k_1} \\ 0 & 0 & N\delta & -\mu_2 \end{bmatrix}. \tag{3.4}$$

If all eigenvalues of the Jacobian matrix have negative real parts, then the steady state is locally asymptotically stable. Characteristic equation of J_{S_0} is given by

$$P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4,$$

where

$$a_1 = \frac{1}{r_2-\theta r_1}\left((c+\mu_2)(r_2-\theta r_1)+\mu_1 r_2\right),$$

$$a_2 = \frac{1}{k_1(r_2-\theta r_1)}\left((c\mu_2 k_1 - N\delta k_2 r_1)(r_2-\theta r_1)+\mu_1 k_1 r_2(c+\mu_2)+\mu_1 k_1 r_1(r_2-\theta r_1)\right),$$

$$a_3 = \frac{\mu_1}{k_1(r_2-\theta r_1)}(k_1 r_1(c+\mu_2)(r_2-\theta r_1)+r_2(c\mu_2 k_1 - N\delta k_2 r_1)),$$

$$a_4 = \frac{\mu_1 r_1}{k_1}(c\mu_2 k_1 - N\delta k_2 r_1).$$

Also, one can calculate that

$$a_1a_2a_3 - a_3^2 - a_1^2a_4 = \frac{\mu_1 r_2(c+\mu_2)}{k_1^2(r_2-\theta r_1)^3}\cdot \begin{pmatrix} (r_2-\theta r_1)^2(c\mu_2k_1 - N\delta k_2 r_1 - \mu_1 k_1 r_1)^2 \\ +(c+\mu_2)(r_2-\theta r_1)(c\mu_2k_1 - N\delta k_2 r_1)\mu_1 k_1 r_2 \\ +(c+\mu_2)(r_2-\theta r_1)\mu_1^2k_1^2 r_1 r_2 + (c\mu_2k_1 - N\delta k_2 r_1)\mu_1^2 k_1 r_2^2 \\ +(c+\mu_2)^2(r_2-\theta r_1)^2\mu_1 k_1^2 r_1 \end{pmatrix}.$$

Here, we know all parameters are positive. If $\Re_0 < 1$, then we obtain $a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0$. So, because of the Routh-Hurwitz criteria all eigenvalues of the Jacobian matrix for S_0 have negative real parts. Thus, the steady state S_0 is locally asymptotically stable.

However, for the steady state S^* the characteristic equation has the form of

$$P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4,$$

where

$$\begin{aligned} a_1 &= c+\mu_1+\mu_2+k_2\vartheta+\theta r_1\frac{\mu_1+k_2\vartheta}{r_2-\theta r_1}, \\ a_2 &= \theta r_1(c+\mu_2)\frac{\mu_1+\vartheta k_2}{r_2-\theta r_1} + (\vartheta k_2+\mu_1)(c+\mu_2+r_1), \\ a_3 &= c\mu_1 r_1 + \mu_1\mu_2 r_1 + c\vartheta\mu_2 k_2 + c\vartheta k_2 r_1 + \vartheta\mu_2 k_2 r_1, \\ a_4 &= 0. \end{aligned}$$

Here, one of the eigenvalues is equal to zero. Applying the Routh-Hurwitz criteria to the reduced characteristic equation below:

$$P(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 + a_4$$

we get three remaining eigenvalues of the Jacobian matrix that have negative real parts. Therefore, the steady state S^* is Lyapunov stable (L-stable) (see the reference [3] for the definition of Lyapunov Stability). □

3.4. *Global stability analysis*

In this section, our aim is to investigate the long time behavior of the given system by analyzing global stability. Let's start this section with a remark. Next, we prove the global stability of the disease-free steady state.

Remark 1. The steady state S^* cannot be globally stable since it is L-stable. Some numerical simulations that support this observation will be given later.

Theorem 2. *For system (3.1), if* $\Re_1 > 0$ *and* $\Re_0 < 1$, *then the disease free steady state* S_0 *is globally asymptotically stable on* Γ *where*

$$\Gamma = \left\{ (T, E, I, V) \in \mathbb{R}_+^4 : T+E+I+V \le \frac{r_1}{k_1} \right\}.$$

Proof. First, system (3.1) can be thought as a compartmental model, i.e., the system can be written as follows:

$$\begin{aligned} \frac{dx}{dt} &= \mathcal{F}(x,y) - \mathcal{V}(x,y) \\ \frac{dy}{dt} &= g(x,y) \end{aligned} \tag{3.5}$$

with $g = (g_1, g_2)^T$ where $g_1 = r_1 T - k_1 TE$ and $g_2 = r_2 T - \mu_1 E - \theta k_1 TE - k_2 EV$. Here, $x = (I, V)^T$ and $y = (T, E)^T$ represent the populations in disease compartments and non-disease compartments, respectively. In addition, $\mathcal{F} = (\mathcal{F}_1, \mathcal{F}_2)^T$ and $\mathcal{V} = (\mathcal{V}_1, \mathcal{V}_2)^T$ where $\mathcal{F}_1 = k_2 EV$, $\mathcal{F}_2 = N\delta I$ represent the rates of new infections in the disease compartments, and $\mathcal{V}_1 = cI$, $\mathcal{V}_2 = \mu_2 V$ represent the transition terms in the disease compartments.

One can easily check that following assumptions are satisfied in order to ensure the model (3.5) is well posed:

(1) $\mathcal{F}_i(0,y) = 0$ and $\mathcal{V}_i(0,y) = 0$ for all $y \geq 0$ and $i = 1,2$.
(2) $\mathcal{F}_i(x,y) \geq 0$ for all non-negative x and y and $i = 1,2$.
(3) $\mathcal{V}_i(x,y) \leq 0$ whenever $x_i = 0$, $i = 1,2$.
(4) $\mathcal{V}_1(x,y) + \mathcal{V}_2(x,y) \geq 0$ for all non-negative x and y.
(5) The disease free system $\frac{dy}{dt} = g(0,y)$ has a unique equilibrium that is locally asymptotically stable. This equilibrium point is $y_0 = (T_0, E_0) = \left(\frac{\mu_1 r_1}{k_1(r_2 - \theta r_1)}, \frac{r_1}{k_1} \right)$.

Therefore, the linearized equations for the disease compartments can be written as follows:

$$\frac{dx}{dt} = (F - V)x,$$

where F and V are 2×2 matrices with entries

$$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(0,y_0) = \begin{bmatrix} 0 & \frac{k_2 r_1}{k_1} \\ N\delta & 0 \end{bmatrix} \text{ and } V = \frac{\partial \mathcal{V}_i}{\partial x_j}(0,y_0) = \begin{bmatrix} c & 0 \\ 0 & \mu_2 \end{bmatrix}.$$

Hence, the next generation matrix is

$$K = FV^{-1} = \begin{bmatrix} 0 & \frac{k_2 r_1}{k_1} \\ N\delta & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{c} & 0 \\ 0 & \frac{1}{\mu_2} \end{bmatrix} = \begin{bmatrix} 0 & \frac{k_2 r_1}{\mu_2 k_1} \\ \frac{N\delta}{c} & 0 \end{bmatrix} = \begin{bmatrix} 0 & \frac{k_2 E_0}{\mu_2} \\ \frac{N\delta}{c} & 0 \end{bmatrix},$$

and the reproduction number $\mathcal{R}_0$ can be defined as the spectral radius of K (see the references [14], [31], [34]), that can be calculated as

$$\mathcal{R}_0 = \sqrt{\frac{N\delta k_2 r_1}{c\mu_2 k_1}} = \sqrt{\frac{N\delta k_2 E_0}{c\mu_2}}.$$

One can easily show that the biologically feasible region

$$\Gamma = \left\{ (T, E, I, V) \in \mathbb{R}^4 : T + E + I + V \leq \frac{r_1}{k_1} \right\}$$

is positively invariant. On the other hand, set

$$f(x,y) = \begin{bmatrix} k_2 V (E_0 - E) \\ 0 \end{bmatrix}.$$

Then for the disease compartments can be written as

$$\frac{dx}{dt} = (F - V)x - f(x,y).$$

So, the Lyapunov function on Γ can be constructed as in [14] and [31]. $Q = W^T V^{-1} x$ is a Lyapunov function where W^T be the left eigenvector of $V^{-1}F$. A straightforward calculation gives

$$Q = W^T V^{-1} x = \begin{bmatrix} 1 & \frac{k_2 r_1 \sqrt{c\mu_2 k_1}}{k_1 c \sqrt{N\delta k_2 r_1}} \end{bmatrix} \begin{bmatrix} \frac{1}{c} & 0 \\ 0 & \frac{1}{\mu_2} \end{bmatrix} \begin{bmatrix} I \\ V \end{bmatrix} = \frac{1}{c} I + \frac{k_2 r_1 \sqrt{c\mu_2 k_1}}{k_1 c\mu_2 \sqrt{N\delta k_2 r_1}} V.$$

One can now easily verify that Q is a Lyapunov function on Γ provided $\mathcal{R}_0 < 1$ as follows:

$$\begin{aligned} \frac{dQ}{dt} &= \frac{1}{c}(k_2 EV - cI) + \frac{k_2 r_1 \sqrt{c\mu_2}}{k_1 c\mu_2 \sqrt{N\delta k_2 E_0}} (N\delta I - \mu_2 V) \\ &= V \left(\frac{k_2 E}{c} - \frac{k_2 r_1 \sqrt{c\mu_2}}{k_1 c \sqrt{N\delta k_2 E_0}} \right) + I \left(\frac{N\delta k_2 r_1 \sqrt{c\mu_2}}{k_1 c\mu_2 \sqrt{N\delta k_2 E_0}} - 1 \right) \\ &= V \left(\frac{k_2 E}{c} - \frac{k_2 r_1 \sqrt{c\mu_2}}{k_1 c \sqrt{N\delta k_2 E_0}} \right) + I \left(\frac{\sqrt{N\delta k_2 r_1}}{\sqrt{k_1 c\mu_2}} - 1 \right) < 0. \end{aligned} \tag{3.6}$$

Hence Q is a Lyapunov function on Γ, and the largest compact invariant set in $\left\{ (T, E, I, V) \in \Gamma : \frac{dQ}{dt} = 0 \right\}$ is $\{S_0\}$. Thus, by LaSalle's invariance principle, every solution of system (3.1) with initial conditions in Γ approaches S_0 as $t \to \infty$ whenever $\mathcal{R}_0 < 1$. Therefore, the disease-free equilibrium point S_0 is globally asymptotically stable on Γ for $\mathcal{R}_0 < 1$. □

4. Analysis of the DDE model

In this section, we study the local stability of the equilibria and the existence of zero-Hopf bifurcation in system (2.1) by dividing it into the following cases due to the delay:

(1) $\tau_1 = \tau_2 = \tau$,
(2) $\tau_1 > 0$ and $\tau_2 = 0$,
(3) $\tau_1 > 0$, and $\tau_2 > 0$ but $\tau_1 \neq \tau_2$.

Note that the case without delay ($\tau_1 = \tau_2 = 0$) is already analyzed in the former section. Also, note that the steady states of system (2.1) is the same as those of system (3.1). Therefore, Lemma 2 still holds for system (2.1). We now want to analyze the system for the endemic equilibrium point S^* which exists under the condition $\Re_0 = 1$.

4.1. *Bifurcation analysis of system (2.1) when* $\tau_1 = \tau_2 = \tau$

Under the condition $\Re_0 = 1$, the corresponding linearized system at S^* as follows:

$$\begin{aligned}
\frac{dT}{dt} &= a_{13}E(t-\tau),\\
\frac{dE}{dt} &= a_{21}T(t) + a_{22}E(t) + a_{23}E(t-\tau) + a_{25}V(t),\\
\frac{dI}{dt} &= a_{33}E(t-\tau) + a_{34}I(t) + a_{35}V(t),\\
\frac{dV}{dt} &= a_{44}I(t) + a_{45}V(t),
\end{aligned} \tag{4.1}$$

where

$$\begin{aligned}
a_{13} &= -\frac{r_1(\mu_1 + k_1\vartheta)}{r_2 - \theta r_1}, & a_{21} &= r_2 - \theta r_1,\\
a_{22} &= -\mu_1, & a_{23} &= -\frac{r_2 k_2 \vartheta - \theta r_1 \mu_1}{r_2 - \theta r_1},\\
a_{25} &= -\frac{k_2 r_1}{k_1}, & a_{33} &= k_2\vartheta,\\
a_{34} &= -c, & a_{35} &= \frac{k_2 r_1}{k_1},\\
a_{43} &= N\delta, & a_{45} &= -\mu_2.
\end{aligned}$$

Therefore, for this case corresponding characteristic equation of system (4.1) becomes:

$$P(\lambda,\tau) \equiv \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + e^{-\lambda\tau}(b_1\lambda^3 + b_2\lambda^2 + b_3\lambda) = 0, \tag{4.2}$$

where

$$\begin{aligned}
a_1 &= c + \mu_1 + \mu_2,\\
a_2 &= \mu_1(c + \mu_2),\\
b_1 &= \frac{k_2\vartheta r_2 + \mu_1\theta r_1}{r_2 - \theta r_1},\\
b_2 &= \left(\frac{k_2\vartheta r_2 + \mu_1\theta r_1}{r_2 - \theta r_1}\right)(c + \mu_2) + r_1(\mu_1 + k_2\vartheta),\\
b_3 &= r_1(\mu_1 k_2\vartheta)(c + \mu_2) + c\mu_2 k_2\vartheta.
\end{aligned}$$

$P(\lambda,\tau)$ in Eq. (4.2) is a transcendental polynomial and has infinitely many roots. First, it is easy to see that one of its roots is zero. This is a simple root since a_2 and b_3 are positive because of the positivity of the parameters of the model. Notice that when $\tau = 0$ in Eq. (4.2), one obtains the characteristic equation of the ODE system in which the distribution of its eigenvalues is already studied in the former section.

In this section, our aim is to investigate the existence of the zero-Hopf bifurcation. In other words, we will determine the conditions on the parameters for the occurrence of a zero-Hopf bifurcation. To do this, we first need to show the existence of a pair of purely imaginary roots for Eq. (4.2).

Let us denote $\lambda = \eta(\tau) + iw(\tau)$. We look for a pair of purely imaginary roots such that $\lambda(\tau^*) = i\omega(\tau^*) = i\omega_0$, $\omega_0 > 0$ (without loss of generality). Notice that if such an $\omega(\tau^*) = \omega_0$ does not exist, then the steady state S^* stays stable forever because of the continuity. It is clear that $\lambda = i\omega$, $\omega > 0$, is a root of Eq. (4.2) if

$$(i\omega)^3 + a_1(i\omega)^2 + a_2(i\omega) + e^{-(i\omega)\tau}(b_1(i\omega)^3 + b_2(i\omega) + b_3) = 0.$$

Separating the real and imaginary parts, we obtain the following equations:

$$\begin{aligned} -a_1\omega^2 - b_1 cos(\omega\tau)\omega^2 + b_3 cos(\omega\tau) + b_2 sin(\omega\tau)\omega &= 0, \\ -\omega^3 + a_2\omega + b_2 cos(\omega\tau)\omega + b_1 sin(\omega\tau)\omega^2 - b_3 sin(\omega\tau) &= 0. \end{aligned} \tag{4.3}$$

Squaring first both sides of these equations and then adding them up, one reaches to the following equation:

$$\omega^6 + ({a_1}^2 - 2a_2 - {b_1}^2)\omega^4 + ({a_2}^2 + 2b_1b_3 - {b_2}^2)\omega^2 - {b_3}^2 = 0. \tag{4.4}$$

Now, let us take $\omega^2 = z$, then we can rewrite Eq. (4.4) as follows:

$$z^3 + ({a_1}^2 - 2a_2 - {b_1}^2)z^2 + ({a_2}^2 + 2b_1b_3 - {b_2}^2)z - {b_3}^2 = 0. \tag{4.5}$$

It is obvious that $-{b_3}^2 < 0$. Also, by the Vieta's Theorem [23], it is known that the expression ${b_3}^2$ is equal to the product of the roots. Therefore, the product of the roots of Eq. (4.5) is positive. Then, it is clear that at least one of them is positive since Eq. (4.5) has at most three roots. As a result of this, it is assured that there is at least one positive root ω_0 of Eq. (4.4), too. Thus, the characteristic equation (4.2) has a pair of purely imaginary roots $\pm i\omega_0$ at τ^*. Now, if we solve $sin(\omega\tau)$ and $cos(\omega\tau)$ from Eq. (4.3) simultaneously, we obtain the following equations:

$$\begin{aligned} sin(\omega\tau) &= \frac{b_2a_1\omega^3 - (b_3 - b_1\omega^2)(\omega^3 - a_2\omega)}{{b_2}^2\omega^2 + (b_1\omega^2 - b_3)^2}, \\ cos(\omega\tau) &= \frac{a_1\omega^2(b_3 - {b_1}^2) + b_2\omega^2(\omega^2 - a_2)}{{b_2}^2\omega^2 + (b_1\omega^2 - b_3)^2}. \end{aligned} \tag{4.6}$$

Finally, utilizing these equations we solve τ_n for $n = 0, 1, 2, \ldots$ as follows:

$$\tau_n = \frac{1}{\omega_0}\arccos\left(\frac{a_1{\omega_0}^2(b_3 - b_1{\omega_0}^2) + b_2{\omega_0}^2({\omega_0}^2 - a_2)}{{b_2}^2{\omega_0}^2 + (b_1{\omega_0}^2 - b_3)^2}\right) + \frac{2\pi n}{\omega_0}. \tag{4.7}$$

Let us denote $\tau^* = \min\{\tau_n : n = 0,1,2,..\} > 0$ such that $i\omega_0 = i\omega(\tau^*)$ is a root of Eq. (4.2). Now, differentiating both sides of Eq. (4.2) with respect to τ, and then utilizing Eq. (4.2), we derive the following equation:

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1} &= -\frac{(3\lambda^2+2a_1\lambda+a_2)-\tau e^{-\lambda\tau}(b_1\lambda^2+b_2\lambda+b_3)+e^{-\lambda\tau}(2b_1\lambda+b_2)}{-\lambda e^{-\lambda\tau}(b_1\lambda^2+b_2\lambda+b_3)}\\ &= \frac{(3\lambda^2+2a_1\lambda+a_2)e^{\lambda\tau}}{\lambda(b_1\lambda^2+b_2\lambda+b_3)} - \frac{2b_1\lambda+b_2}{\lambda(b_1\lambda^2+b_2\lambda+b_3)} - \frac{\tau}{\lambda}\\ &= -\frac{3\lambda^2+2a_1\lambda+a_2}{\lambda^4+a_1\lambda^3+a_2\lambda^2} - \frac{2b_1\lambda+b_2}{b_1\lambda^3+b_2\lambda^2+b_3\lambda} - \frac{\tau}{\lambda}.\end{aligned} \tag{4.8}$$

Thus, its reel part has the form of

$$Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau^*} = \frac{\omega_0^2\left(3\omega_0^4+(2a_1^2-4a_2)\omega_0^2+a_2^2\right)}{(\omega_0^4-a_2\omega_0^2)^2+(a_1\omega_0^3)^2} - \frac{-2b_1^2\omega_0^4+(2b_1b_3-b_2^2)\omega_0^2}{(b_2\omega_0^2)^2+(b_3\omega_0-b_1\omega_0^3)^2} > 0$$

since $2a_1^2-4a_2>0$ and $2b_1b_3-b_2^2<0$. Hence, the transversality condition holds.

Combining all derivations above, we have concluded the following Theorem.

Theorem 3. *Assume that $\Re_1 > 0$ and $\Re_0 = 1$ hold. Let us denote $\tau^* = \min\{\tau_n : n = 0,1,2,..\} > 0$ such that $\omega(\tau^*) = \omega_0$. Then Eq. (4.2) has a simple root zero, and also its all other roots have negative real parts for $\tau \in [0,\tau^*)$. Therefore, S^* is stable for $\tau \in [0,\tau^*)$. Moreover, system (2.1) undergoes a zero-Hopf bifurcation at S^* when τ passes through τ^*.*

4.2. *Bifurcation analysis of system (2.1) when $\tau_1 > 0$ and $\tau_2 = 0$*

Under the condition $\Re_0 = 1$, the corresponding characteristic equation of system (2.1) is:

$$P(\lambda,\tau_1) \equiv \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + e^{-\lambda\tau_1}(b_1\lambda^3 + b_2\lambda^2 + b_3\lambda) = 0, \tag{4.9}$$

where

$$\begin{aligned}a_1 &= c+\mu_1+\mu_2+k_2\vartheta,\\ a_2 &= (\mu_1+k_2\vartheta)(c+\mu_2),\\ a_3 &= k_2\vartheta c\mu_2,\\ b_1 &= \frac{\theta r_1(\mu_1+k_2\vartheta)}{r_2-\theta r_1},\\ b_2 &= \frac{\theta r_1}{r_2-\theta r_1}(c+\mu_2)(\mu_1+k_2\vartheta) + r_1(\mu_1+k_2\vartheta),\\ b_3 &= r_1(\mu_1+k_2\vartheta)(c+\mu_2).\end{aligned}$$

$P(\lambda,\tau_1)$ in Eq. (4.9) is a transcendental polynomial and has infinitely many roots. First, it is easy to see that one of its roots is zero. This is a simple root since a_3 and b_3 are positive because of the positivity of the parameters of the model.

In this section, we will determine the conditions on the parameters for the occurrence of a zero-Hopf bifurcation. To do this, we first need to show the existence of a pair of purely imaginary roots for Eq. (4.9).

Let us denote $\lambda = \eta(\tau_1) + iw(\tau_1)$. We look for a pair of purely imaginary roots such that $\lambda(\tau_1^*) = i\omega(\tau_1^*) = i\omega_1$, $\omega_1 > 0$ (without loss of generality). It is clear that $\lambda = i\omega$, $\omega > 0$, is a root of Eq. (4.9) if

$$(i\omega)^3 + a_1(i\omega)^2 + a_2(i\omega) + a_3 + e^{-(i\omega)\tau_1}(b_1(i\omega)^2 + b_2(i\omega) + b_3) = 0$$

Separating the real and imaginary parts, we obtain the following equations:

$$\begin{array}{ll} -a_1\omega^2 + a_3 & = b_1\omega^2 cos(\omega\tau_1) - b_3 cos(\omega\tau_1) - b_2\omega sin(\omega\tau_1), \\ \omega^3 - a_2\omega & = b_2\omega cos(\omega\tau_1) + b_1\omega^2 sin(\omega\tau_1) - b_3 sin(\omega\tau_1). \end{array} \tag{4.10}$$

Squaring first both sides of these equations and then adding them up, one reaches to the following equation:

$$\omega^6 + ({a_1}^2 - 2a_2 - {b_1}^2)\omega^4 + ({a_2}^2 - 2a_1a_3 + 2b_1b_3 - {b_2}^2)\omega^2 + {a_3}^2 - {b_3}^2 = 0 \tag{4.11}$$

Now, let us take $\omega^2 = z$, then we can rewrite Eq. (4.11) as follows:

$$z^3 + ({a_1}^2 - 2a_2 - {b_1}^2)z^2 + ({a_2}^2 - 2a_1a_3 + 2b_1b_3 - {b_2}^2)z + {a_3}^2 - {b_3}^2 = 0. \tag{4.12}$$

It is known that the expression ${b_3}^2 - {a_3}^2$ is equal to the product of the roots by the Vieta's Theorem [23]. Therefore, the product of the roots of Eq. (4.12) must be positive. Then, at least one of them must be positive since Eq. (4.12) has at most three roots. Let us define the following:

$$\Re_2 = {b_3}^2 - {a_3}^2 = r_1(\mu_1 + k_2\vartheta)(c + \mu_2) - k_2\vartheta c\mu_2$$

then, assume that $\Re_2 > 0$. This guarantees that there is at least one positive root of Eq. (4.12). Following that, there exist at least one positive root o (4.11), too. Thus, the characteristic equation (4.9) has a pair of purely imaginary roots $\pm i\omega_1$ at τ_1^*. Now, if we solve $sin(\omega\tau)$ and $cos(\omega\tau)$ from Eq. (4.10) simultaneously, we obtain the following equations:

$$\begin{array}{ll} cos(\omega\tau) & = \dfrac{b_2\omega^2(\omega^2 - a_2) + (b_1\omega^2 - b_3)(a_3 - a_1\omega^2)}{{b_2}^2\omega^2 + (b_1\omega^2 - b_3)^2}, \\ sin(\omega\tau) & = \dfrac{(a_2\omega - \omega^3)(b_3 - b_1\omega^2) - b_2\omega(a_3 - a_1\omega^2)}{{b_2}^2\omega^2 + (b_1\omega^2 - b_3)^2}. \end{array} \tag{4.13}$$

Finally, utilizing these equations we solve τ_1^n for $n = 0, 1, 2, \ldots$ as follows:

$$\tau_1^n = \frac{1}{\omega}\arccos\left(\frac{b_2\omega^2(\omega^2 - a_2) + (b_1\omega^2 - b_3)(a_3 - a_1\omega^2)}{{b_2}^2\omega^2 + (b_1\omega^2 - b_3)^2}\right) + \frac{2\pi n}{\omega} \tag{4.14}$$

Let us denote $\tau_1^* = \min\{\tau_1^n : n = 0,1,2,..\} > 0$ such that $i\omega_1 = i\omega(\tau_1^*)$ is a root of Eq. (4.9). Now, differentiating both sides of Eq. (4.9) with respect to τ_1, one can show that the transversality condition holds.

Theorem 4. *Assume that $\Re_1 > 0$, $\Re_2 > 0$ and $\Re_0 = 1$ hold. Let us denote $\tau_1^* = \min\{\tau_1^n : n = 0,1,2,..\} > 0$ such that $\omega(\tau_1^*) = \omega_1$. Then Eq. (4.9) has a simple root zero, and also its all other roots have negative real parts for $\tau_1 \in [0,\tau_1^*)$. Therefore, S^* is stable for $\tau_1 \in [0,\tau_1^*)$. Moreover, system (2.1) undergoes a zero-Hopf bifurcation at S^* when τ_1 passes through τ_1^*.*

4.3. *Bifurcation analysis of system (2.1) when $\tau_1 > 0$, $\tau_2 > 0$ but $\tau_1 \neq \tau_2$*

Under the condition $\Re_0 = 1$, the corresponding characteristic equation of linearized system at S^* as follows:

$$P(\lambda,\tau_1,\tau_2) \equiv \lambda\left(P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2}\right) = 0, \tag{4.15}$$

where

$$\begin{aligned} P_0(\lambda) &= \lambda^3 + a_1\lambda^2 + a_2\lambda, \\ P_1(\lambda) &= b_1\lambda^2 + b_2\lambda + b_3, \\ P_2(\lambda) &= c_1\lambda^2 + c_2\lambda + c_3. \end{aligned}$$

The coefficients can be found in the following

$$\begin{aligned} a_1 &= c + \mu_1 + \mu_2, \\ a_2 &= \mu_1(c + \mu_2), \\ b_1 &= \frac{\theta r_1(\mu_1 + k_2\vartheta)}{r_2 - \theta r_1}, \\ b_2 &= \frac{\theta r_1}{r_2 - \theta r_1}(c + \mu_2)(\mu_1 + k_2\vartheta) + r_1(\mu_1 + k_2\vartheta), \\ b_3 &= r_1(\mu_1 + k_2\vartheta)(c + \mu_2), \\ c_1 &= k_2\vartheta, \\ c_2 &= k_2\vartheta(c + \mu_2), \\ c_3 &= k_2\vartheta c\mu_2. \end{aligned}$$

$P(\lambda,\tau_1,\tau_2)$ in Eq. (4.15) is a transcendental polynomial and has infinitely many roots. Again, it is easy to see that one of its roots is zero. This is a simple root since b_3 and c_3 are positive because of the positivity of the parameters of the model.

In this section, we investigate the existence of the zero-Hopf bifurcation with τ_1 in its interval of stability, regarding τ_2 as a parameter. So, we consider the system under the previous case.

Let us denote $\lambda = \eta(\tau_2) + iw(\tau_2)$. We look for a pair of purely imaginary roots such that $\lambda(\tau_2^*) = i\omega(\tau_2^*) = i\omega_2$, $\omega_2 > 0$. Choosing τ_2 as a parameter, we obtain that

$\lambda = i\omega$, $\omega > 0$, is a root of Eq. (4.15) if

$$P(i\omega, \tau_1, \tau_2) \equiv i\omega \left(P_0(i\omega) + P_1(i\omega)e^{-i\omega\tau_1} + P_2(i\omega)e^{-i\omega\tau_2}\right) = 0$$

$P_i(i\omega)$ are given in the following:

$$\begin{aligned} P_0(i\omega) &= -a_1\omega^2 + i(-\omega^3 + a_2\omega), \\ P_1(i\omega) &= (b_3 - b_1\omega^2) + i(b_2\omega), \\ P_2(i\omega) &= (c_3 - c_1\omega^2) + i(c_2\omega). \end{aligned}$$

Since $\mid e^{-i\omega\tau_1} \mid = 1$ we have the following equations:

$$\begin{aligned} \mid P_0(i\omega) + P_2(i\omega)e^{-i\omega\tau_2} \mid &= \mid P_1(i\omega)e^{-i\omega\tau_1} \mid \\ &= \mid P_1(i\omega) \mid\mid e^{-i\omega\tau_1} \mid \\ &= \mid P_1(i\omega) \mid \end{aligned}$$

which equals to

$$\begin{aligned} \mid P_0(i\omega) + P_2(i\omega)e^{-i\omega\tau_2} \mid^2 &= \mid P_1(i\omega) \mid^2 \\ (P_0(i\omega) + P_2(i\omega)e^{-i\omega\tau_2})(\bar{P}_0(i\omega) + \bar{P}_2(i\omega)e^{i\omega\tau_2}) &= \mid P_1(i\omega) \mid^2 . \end{aligned}$$

After some simplifications, the last equation becomes

$$\begin{aligned} &\mid P_0(i\omega) \mid^2 + \mid P_2(i\omega) \mid^2 + 2Re(P_0(i\omega)\bar{P}_2(i\omega))cos(\omega\tau_2) \\ &- 2Im(P_0(i\omega)\bar{P}_2(i\omega))sin(\omega\tau_2) = \mid P_1(i\omega) \mid^2 . \end{aligned} \tag{4.16}$$

Note that for $\omega > 0$, $P_0(i\omega) = -a_1\omega^2 + i(-\omega^3 + a_2\omega) \neq 0$ and $P_2(i\omega) = (c_3 - c_1\omega^2) + i(c_2\omega) \neq 0$. So the folllowing inequality holds.

$$[Re(P_0(i\omega)\bar{P}_2(i\omega))]^2 + [Im(P_0(i\omega)\bar{P}_2(i\omega))]^2 = \mid P_0(i\omega)\bar{P}_2(i\omega) \mid^2 > 0.$$

Finally, the Eqn. (4.16) can be written as

$$\begin{aligned} &\frac{\mid P_1(i\omega) \mid^2 - \mid P_0(i\omega) \mid^2 - \mid P_2(i\omega) \mid^2}{2 \mid P_0(i\omega)\bar{P}_2(i\omega) \mid} = \frac{Re(P_0(i\omega)\bar{P}_2(i\omega))}{\mid P_0(i\omega)\bar{P}_2(i\omega) \mid} cos(\omega\tau_2) \\ &- \frac{Im(P_0(i\omega)\bar{P}_2(i\omega))}{\mid P_0(i\omega)\bar{P}_2(i\omega) \mid} sin(\omega\tau_2). \end{aligned}$$

On the other hand, one can show that there is a continous $\phi(\omega)$ function such that:

$$cos(\phi(\omega)) = \frac{Re(P_0(i\omega)\bar{P}_2(i\omega))}{\mid P_0(i\omega)\bar{P}_2(i\omega) \mid} \text{ and } sin(\phi(\omega)) = \frac{Im(P_0(i\omega)\bar{P}_2(i\omega))}{\mid P_0(i\omega)\bar{P}_2(i\omega) \mid}$$

holds. Therefore, we have the following:

$$\left| \frac{\mid P_1(i\omega) \mid^2 - \mid P_0(i\omega) \mid^2 - \mid P_2(i\omega) \mid^2}{2 \mid P_0(i\omega)\bar{P}_2(i\omega) \mid} \right| = \mid cos(\phi(\omega) + \omega\tau_2) \mid \leq 1$$

and so,

$$\left| \mid P_1(i\omega) \mid^2 - \mid P_0(i\omega) \mid^2 - \mid P_2(i\omega) \mid^2 \right| \leq 2 \mid P_0(i\omega)\bar{P}_2(i\omega) \mid .$$

Finally, if we define

$$\Omega = \left\{\omega > 0 : || P_1(i\omega) |^2 - | P_0(i\omega) |^2 - | P_2(i\omega) |^2| \leq 2 | P_0(i\omega)\bar{P}_2(i\omega) |\right\}$$

then we have the following lemma:

Lemma 3. *Let* $\Re_2 = r_1(\mu_1 + k_2 v)(c + \mu_2) - k_2 v c \mu_2$. *If* $\Re_2 > 0$ *then the set* Ω *is not empty.*

The above lemma means that for $n = 0, 1, 2, ...$ and $\omega \in \Omega$ the characteristic equation has purely imaginary roots when

$$\tau_2^n = \frac{\psi(\omega_2) - \phi(\omega_2) + 2\pi n}{\omega_2} \tag{4.17}$$

where

$$cos(\psi(\omega_2)) = \frac{| P_1(i\omega) |^2 - | P_0(i\omega) |^2 - | P_2(i\omega) |^2}{2 | P_0(i\omega)\bar{P}_2(i\omega) |}.$$

On the other hand, we can write the characteristic equation as the form of

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau_2} = 0$$

where

$$P(\lambda) = P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1},$$
$$Q(\lambda) = P_2(\lambda).$$

So, let's define

$$F(\omega) = | P(i\omega) |^2 - | Q(i\omega) |^2 .$$

After some calculations, one can get the following inequality

$$\begin{aligned} w_2 F'(w_2) &= A w_2^6 + B w_2^5 + C w_2^4 + D w_2^3 + E w_2^2 + F w_2 + G \\ &= w_2^4(A w_2^2 + C) + w_2^3(B w_2^2 + D) + w_2(E w_2 + F) + G \end{aligned}$$

where the coefficients are

$$\begin{aligned} A &= (2 - 2b_1 \sin\omega_2 T_1) \\ B &= (T_1 (2a_1 b_1 + 2b_2) \sin\omega_2 T_1 - 2b_1 \sin\omega_2 T_1) \\ C &= (T_1 2b_3 \cos\omega_2 T_1 - T_1 2a_1 b_2 \cos\omega_2 T_1 + T_1 2a_2 b_1 \cos\omega_2 T_1) \\ D &= (-T_1 2a_2 b_2 \sin\omega_2 T_1 + T_1 2a_1 b_3 \sin\omega_2 T_1) \\ E &= \big(-T_1 2a_2 b_3 \cos\omega_2 T_1 - 2a_2^2 - 4a_2 b_2 \cos\omega_2 T_1 - 2b_2^2 - 2c_2^2 + 4b_1 b_3 \\ &\quad -4a_1 b_3 \cos\omega_2 T_1 - 4c_1 c_3) \\ F &= (6a_2 b_3 \sin\omega_2 T_1) \\ G &= 4(c_3^2 - b_3^2) \end{aligned}$$

Under the following conditions

H1): $m_1 = \dfrac{-C}{A}$. $m_1 \geq 0$ and $A \neq 0$ and $\omega_2 < \sqrt{m_1}$,

H2): $m_2 = \dfrac{-D}{B}$. $m_2 \geq 0$ and $B \neq 0$ and $\omega_2 < \sqrt{m_2}$,

H3): $m_3 = \dfrac{-F}{E}$. $E \neq 0$ and $\omega_2 < m_3$,

it is clear that $F'(w_2) < 0$ holds. This inequality also means that the transversality condition holds. Hence, we have the following result.

Theorem 5. *Assume that the conditions (H1),(H2) and (H3) defined above are satisfied and also* $\Re_0 = 1$, $\Re_1 > 0$ *and* $\Re_2 > 0$ *hold. Let us denote* $\tau_2^* = \min\{\tau_2^n : n = 0,1,2,..\} > 0$ *such that* $\omega(\tau_2^*) = \omega_2$. *Then,*

(1) *Eq. (4.15) has a simple root zero, and also its all other roots have negative real parts for* $\tau_1 \in [0,\tau_1^*)$ *and* $\tau_2 \in [0,\tau_2^*)$ *such that* $i\omega = i\omega(\tau_2^*)$, $\tau_2^* > 0$. *Therefore,* S^* *is stable for* $\tau_1 \in [0,\tau_1^*)$ *and* $\tau_2 \in [0,\tau_2^*)$.

(2) *For* $\tau_1 \in [0,\tau_1^*)$, *system (2.1) undergoes a zero-Hopf bifurcation at* S^* *when* τ_2 *passes through* τ_2^*.

5. Numerical simulations

In this section, we perform numerical simulations that support the analytic results proved in former sections. For each simulation, we use either the ODE package (ode45) or the DDE package (dde23) in MATLAB. To illustrate the theoretical results, we study numerically the dynamics of system (2.1) with the parameter values which are chosen from Table 1 below. Choosing parameter values characteristic of the in vivo situation is difficult; many of the parameters in our model have not been measured, or, if measurements have been attempted, they may not be as accurate as we need for quantitative predictions [25]. Thefore we choose these parameters for the reason that either they are used in other models describing a similar phenomenon or they are based on experimental data in the corresponding references.

5.1. *Numerical simulations when* $\tau_1 = \tau_2 = 0$

First, we use the following parameter values for simulations: $r_1 = 0.3$, $k_1 = 0.001$, $r_2 = 0.05$, $\mu_1 = 0.03$, $\theta = 0.1$, $k_2 = 2.4 \times 10^{-5}$, $c = 0.3$, $N = 275$, $\delta = 0.3$ and $\mu_2 = 2.1$. With respect to these parameters, the corresponding basic reproduction number and the disease-free steady state are $\Re_0 = 0.942857$ and $S_0 = (T_0, E_0, I_0, V_0) = (450, 300, 0, 0)$, respectively. Figure 1 illustrates the numerical solutions of the ODE model (3.1) for different initial values. It shows that as stated in Theorem 1 and Theorem 2, the disease-free steady state is globally asymptotically stable. These figures underline the ability of the immune system to eliminate the infection and to prevent more tumour cell growth. So, the immune system eradicates virus perfectly but has low persistence of the tumour.

TABLE 1. The range of parameter values with corresponding references

Parameters	Range Values	Unit	References
r_1	$0.05-0.5$	day^{-1}	[28]
k_1	$10^{-3}-10^{-5}$	$\text{mm}^3\text{day}^{-1}$	[25]
r_2	$0-0.05$	day^{-1}	[25]
μ_1	0.03	$\text{mm}^3\text{day}^{-1}$	[11]
θ	0.1	day^{-1}	[29]
k_2	2.4×10^{-5}	$\text{mm}^3\text{day}^{-1}$	[32]
c	0.3	day^{-1}	[29]
N	$100-2000$		[11]
δ	$0.3-0.7$	day^{-1}	[26]
μ_2	$2.1-3.8$	day^{-1}	[29]

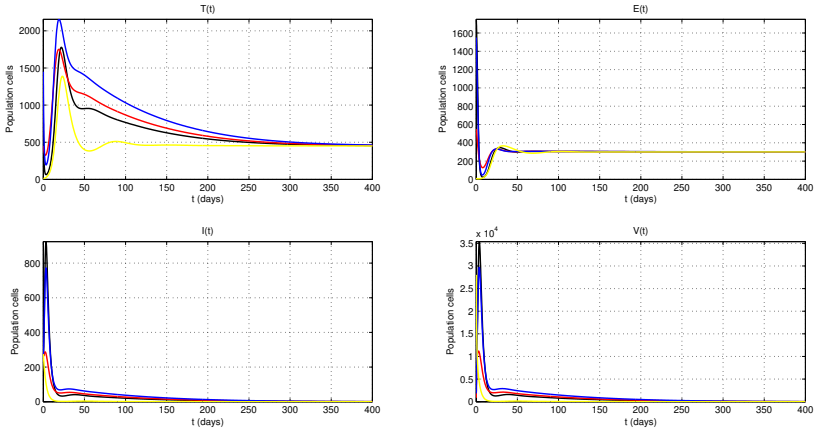

FIGURE 1. The numerical solutions of the ODE model (2.1) with different initial values. Each color represents a different solution with different initial values.

Second, Figure 3 presents the behaviour of solutions of system (3.1) for the parameter values: $r_1 = 0.1$, $k_1 = 0.0002$, $r_2 = 0.04$, $\mu_1 = 0.03$, $\theta = 0.1$, $k_2 = 2.4\times10^{-5}$, $c = 0.3$ $N = 275$, $\delta = 0.3$ and $\mu_2 = 2.1$. The corresponding basic reproduction number is equal to $\Re_0 = 1.571429$, and the disease free steady state is $S_0 = (T_0, E_0, I_0, V_0) = (500, 500, 0, 0)$ for this case. The uncontrolled growth of the tumour cells can be seen in Figure 3. The weakness caused by HIV may advance to uncontrolled tumour growth and spread in this case.

Third, we now solve the system with the parameter values that are $r_1 = 0.1$, $k_1 = 0.0003$, $r_2 = 0.03$, $\mu_1 = 0.03$, $\theta = 0.1$, $k_2 = 2.4\times10^{-5}$, $c = 0.3$, $N = 275$, $\delta =$

0.3 and $\mu_2 = 2.2$. The corresponding basic reproduction number for this case is equal to $\Re_0 = 1$, so the endemic steady state is $S^* = (540, 333.333, 2.66, 100)$. The coexistence of the tumour cells, the infected cells, and the virus can be seen from Figure 2 which illustrates the local stability of the disease-free steady state proven in Theorem 1. This means that the underlying HIV related tumour develops in the HIV infected individual because of the existence of virus; the tumour can escape from the surveillance of the immune system. As it can be seen from the simulations in Figure 2, the steady state could not be globally stable which was underlined by the remark in the former section.

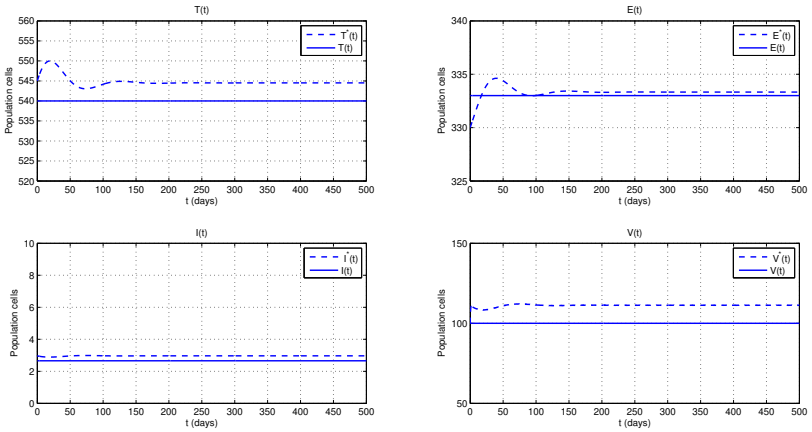

FIGURE 2. The numerical solutions of system (2.1) with initial values $(T_0, E_0, I_0, V_0) = (250, 750, 275, 250)$. The trajectories of the system are close enough to the steady state of the system, which is denoted by the solid line, however, not approach to it.

5.2. *Numerical simulations when* $\tau_1 = \tau_2 = \tau$

We numerically solve the DDE model (2.1) with the parameter values: $r_1 = 0.3$, $k_1 = 0.0032$, $r_2 = 0.05$, $\mu_1 = 0.03$, $\theta = 0.1$, $k_2 = 2.4 \times 10^{-5}$, $c = 0.3$, $N = 400$, $\delta = 0.7$, and $\mu_2 = 2.1$. Figures 4, 5 and 6 present the numerical solutions of the DDE system (2.1) when $\tau = 1.95$, $\tau = 1.962$ and $\tau = 1.97$, respectively. These figures show that τ plays a crucial role in the oscillations of the solutions around steady state. Clearly, delay causes the appearance of oscillations, and affects the stability of steady state.

Also, Figures 5 and 7 show the periodic solutions arising as the bifurcation parameter τ passes through the critical value $\tau^* \approx 1.962$. Here, one observes the occurrence of limit cycles due to the zero-Hopf bifurcation at $\tau = 1.95$. Figure 6 displays that the system becomes unstable for the value of τ which is grater than τ^*.

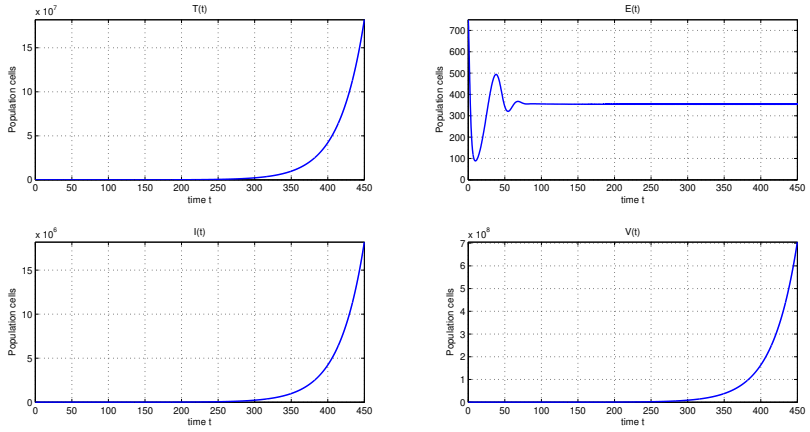

FIGURE 3. The numerical solutions of system (2.1) with initial values $(T_0, E_0, I_0, V_0) = (250, 750, 275, 250)$. Note that the trajectories of the system move away.

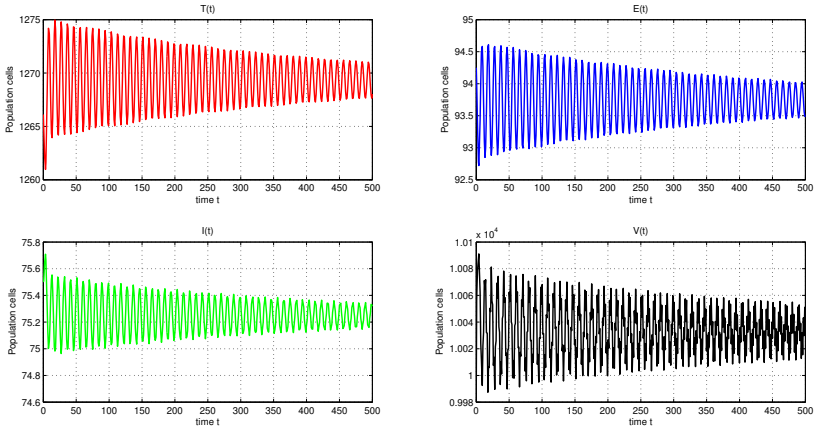

FIGURE 4. The numerical solutions of the DDE model (2.1) for $\tau = 1.95 < \tau^* \approx 1.962$. Simulations present stability.

5.3. *Numerical simulations when* $\tau_1 > 0, \tau_2 > 0, \tau_1 \neq \tau_2$

We numerically solve the DDE model (2.1) with the parameter values: $r_1 = 0.3$, $k_1 = 0.0032$, $r_2 = 0.05$, $\mu_1 = 0.03$, $\theta = 0.1$, $k_2 = 2.4 \times 10^{-5}$, $c = 0.3$, $N = 400$, $\delta = 0.7$, and $\mu_2 = 2.1$. Figures 8 presents the numerical solutions of the DDE system

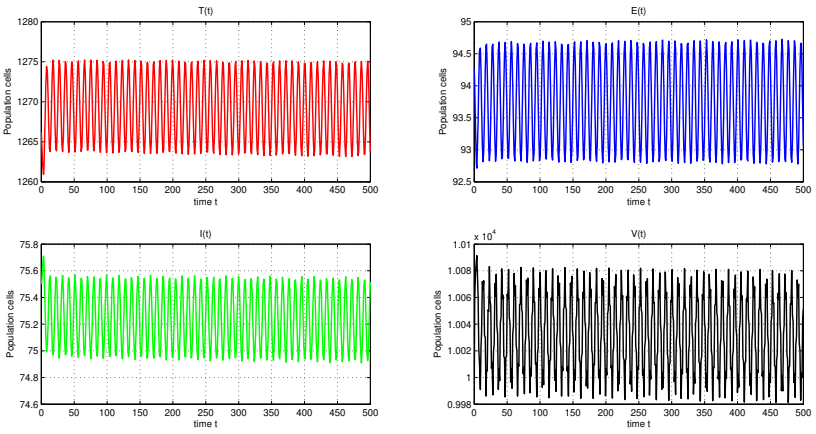

FIGURE 5. The numerical solutions of the DDE model (2.1) for $\tau = \tau^* \approx 1.962$. They present the cyclic behaviour.

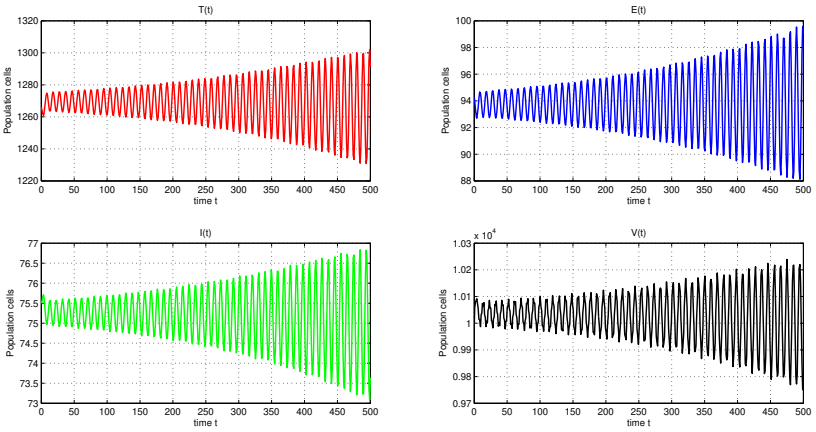

FIGURE 6. The numerical solutions of the DDE model (2.1) for $\tau = 1.97 > \tau^* \approx 1.962$. Simulations show unstability.

(2.1) when $\tau_1 = 1.8 < \tau_1^*$ and $\tau_2 = 2.3415$. These figures show that τ_2 plays a crucial role in the oscillations of the solutions around steady state. Clearly, delay causes the appearance of oscillations, and affects the stability of steady state.

Also, Figures 8 and 9 show the periodic solutions arising as the bifurcation parameter τ passes through the critical value $\tau_2^* \approx 2.3415$. Here, one observes the occurrence of limit cycles due to the zero-Hopf bifurcation at $\tau_2 = 2.3415$.

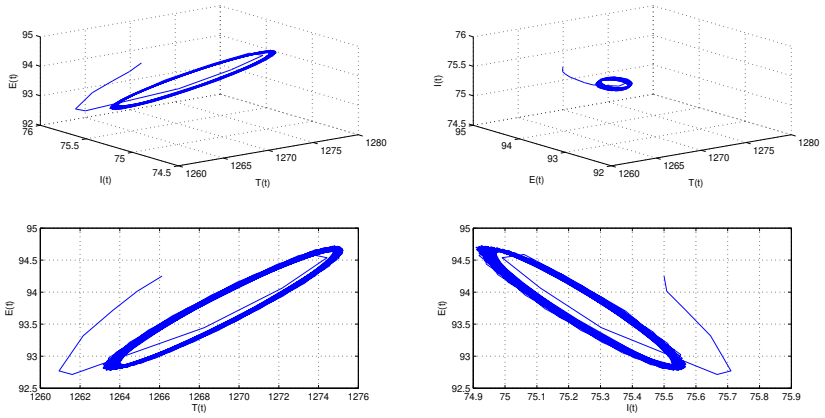

FIGURE 7. The numerical solutions of the DDE model (2.1) for $\tau = \tau^* \approx 1.962$.

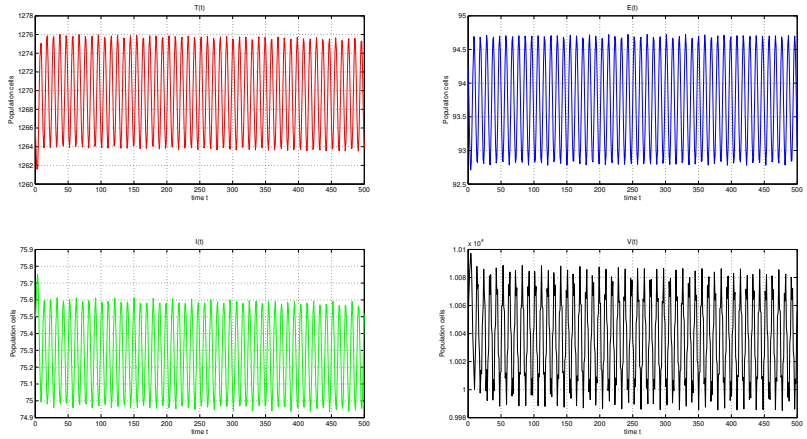

FIGURE 8. The numerical solutions of the DDE model (2.1) for $\tau_1 = 1.8 < \tau_1^*$ and $\tau_2 \approx \tau_2^* = 2.3415$. They present the cyclic behaviour.

6. DISCUSSION

HIV infected individuals suffer several types tumours during their infection, which creates a burden on the treatment. For this reason, it is very crucial to understand the relationship between HIV infection and certain tumours. In this paper, we have shown how HIV affects the immune system's ability to fight tumours. Since HIV is

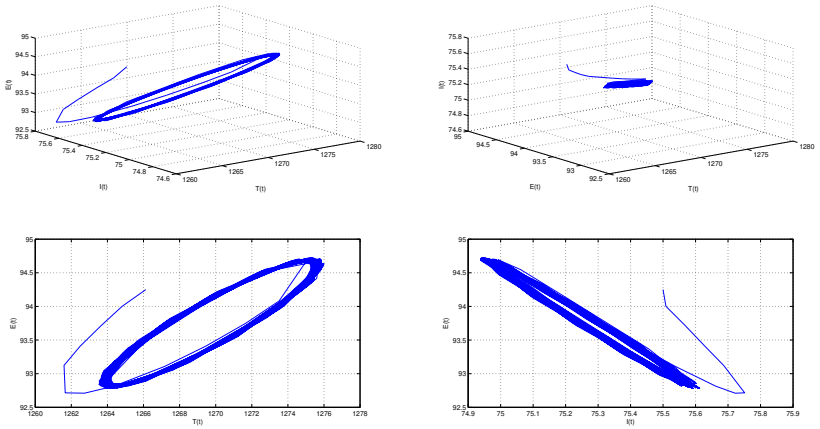

FIGURE 9. The numerical solutions of the DDE model (2.1) for $\tau_1 = 1.8 < \tau_1^*$ and $\tau_2 \approx \tau_2^* = 2.3415$.

present in vivo, the surveillance of the immune system is very weak. Accordingly, the growth of tumour is uncontrolled.

The model we introduced involves four components: tumour cells, uninfected helper T-cells, infected helper T-cells and free virus. Under the condition $\Re_1 > 0$, system (2.1) has two non-negative steady states. This condition means that the ratio of the rate of growth of the T-helper cells (triggered by tumour cells) with respect to the rate of growth of tumour cells is larger than the percentage of the helper cell loss due to killing tumour cells. First, the existence and positiveness of the solutions of the model without delay are studied. By utilizing the Routh-Hurwitz criteria, we have determined the conditions on the parameters for the stability of steady states of the model. When the condition $\Re_0 < 1$, we have proved that the non-infected steady state is both locally and globally asymptotically stable. This means that the ability of the immune system to eliminate the virus is strong enough but also there is low persistence of tumour. Also, we obtained that uncontrolled tumour growth and spread can be possible because of the exhaustion of the immune system response caused by infection. On the other hand, the infected steady state is L-stable. This biologically means that tumour can escape from surveillance of the immune system.

Second, the zero-Hopf bifurcation of the delay differential equation (DDE) model is studied. We study the effects of two discrete time delays on the stability of the endemically infected equilibrium point. We determine the conditions on parameters at which the system undergoes a zero-Hopf bifurcation. The time lags in the DDE model describe the time needed by the helper T-cells to find (or recognize) tumour cells and virus. Choosing one of the delay terms as a bifurcation parameter and fixing

the other, we have shown that a zero-Hopf bifurcation occurs as the bifurcation parameter passes through a critical value. In other words, the stability of the steady state S^* changes from stable to unstable, and periodic solutions with increasing periods arise. For the larger values of the bifurcation parameter, solutions become unstable. The performed numerical simulations support and extend our analytical results.

The results concluded underline that as the immune system gets weaker, it becomes difficult to keep up of the T-helper cells which leads to the compute exhaustion of tumour cells.

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