Delay Differential Model for Tumor-Immune Dynamics with HIV Infection of CD4$^+$ T Cells

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Abstract

In this paper, we introduce a mathematical model to describe the interactions between a malignant tumor and the immune system with immunodeficiency. In order to improve the description of the phenomenon, we have taken into account the time delay due to the time needed by CD4$^+$ T-cells to be regenerated after eliminating cancer cells. The model consists of four populations: tumor cells, healthy effector cells (CD4$^+$ T cells), infected effector cells and free viral particles. We investigate the qualitative behavior of the model. The obtained results give a better understanding of cancer immunity and viral oncogenesis.

Keywords: ODEs, DDEs, tumor, HIV, immune response, Hopf bifurcation

1 Introduction

Human immunodeficiency virus (HIV) causes immunodeficiency by their destructive effect on CD4$^+$ T Lymphocytes, and this makes AIDS\(^1\) patients more vulnerable to different types of infections [5]. Basically the disease goes through four different stages: incubation period, acute infection, latency stage and AIDS. The last stage (AIDS) shows symptoms of various opportunistic infections and cancers such as Kaposi’s sarcoma, cervical cancer and cancers of the immune system known as lymphomas, therefore AIDS patients have various expectable and non-expectable clinical features [2, 3, 13]. Regarding lymphoma and Kaposi’s sarcoma, patients with HIV infection develop lymphoma about hundred times more often and Kaposi sarcoma about four hundred times more often than non-infected individuals [2, 3, 6].

Researchers in bio-mathematics focus on either the modeling of tumor dynamics and its treatments (see, e.g., [15, 16] and the references therein) or the HIV virus dynamics (see, e.g., [5, 10, 11, 12, 14] and the references therein). It is important to combine these two types of models to describe a such disease, since the occurrence of several types of cancers is related to the presence of the HIV virus.

This paper is organized in the following manner: In Section 2, we give a brief background of tumor-immune interaction with immunodeficiency, using ODE models. In Section 3, we introduce a delay differential model to describe cancer-immune system interactions, \textit{in vivo}, with HIV infection of CD4$^+$ T cells. The delay term is to describe the time needed by CD4$^+$ T lymphocyte to regenerate after eliminating one cancer cell. We study existence of three steady states of the model and their local stability in Section 4. Numerical simulations are provided in Section 5.

\(^{1}\)Acquired Immunodeficiency Syndrome (AIDS) is characterized by impairing the function of the immune system and by various clinical expressions. It was first recognized in 1981.
2 Background

In [7] the authors developed an (ODEs) model in order to understand the complex behavior of conjoint tumor-normal cell growth under the effects of a simple immune system, and both immune-deficiency and immuno-chemotherapeutic agents as well. They obtained that the deficiency has directly affected the behavior of tumor and normal cells as well as the immune system components. Among the possibilities, chemotherapeutic together with the immunotherapeutic agents demonstrated the best outcome in terms of reducing the size of the tumor in the absence of any deficiency. The presence of immune deficiency factors affect even the most successful therapeutic agents to be re-evaluated in order to obtain similar outcomes in terms of the reduction in size of the tumor cells in comparison to a properly functioning immune system in the absence of any deficiency.

Lou et al. [9] describes the HIV related cancer immune system interactions in tissue culture (in vitro). The new of this model is that it is the first model which takes into account the infected effector cells as a population in the model. They found conditions for Hopf bifurcation of the positive steady state, leading to periodic solutions, sequences of period doubling bifurcations and appearance of chaos. Further, chaos and periodic behavior alternate. These results are consistent with some clinical and experimental observations.

3 The DDE Model

To keep discussion and the model as simple as possible. Assume the four components: \( T(t) \), the tumor cells; \( E(t) \), healthy effector cells (CD4\(^+\)T cells); \( I(t) \), effector cells infected by the HIV viruses; and \( V(t) \), the free HIV viral particles. We consider the lag-time needed for CD4\(^+\)T lymphocyte to regenerate after eliminating one cancer cell. The interaction between the four variables model is then described by the model:

\[
\begin{align*}
\frac{dT}{dt} &= r_1 T(t) - k_1 E(t) T(t), \\
\frac{dE}{dt} &= r_2 T(t) + \alpha - \mu_1 E(t) - k_1 E(t) T(t) + (1-\epsilon)k_1(t-\tau)E(t-\tau) - k'_2 E(t) I(t) - k_3 E(t) V(t), \\
\frac{dI}{dt} &= k'_2 E(t) I(t) + k_3 E(t) V(t) - \mu_2 I(t), \\
\frac{dV}{dt} &= N\delta I(t) - cV(t).
\end{align*}
\]

Eq (1a) includes a linear term in order to model the proliferation rate of tumor cells while the second term represents interactions with the immune system which is taken to be proportional to the product of both \( E(t) \) and \( T(t) \) concentrations. Eq (1b) describes the rate of change for the healthy CD4\(^+\)T cells population consists of recruitment term due to the presence of the tumor, where \( r_2 \) models the antigenicity of the tumor. Normal rate of the flow of effector cells towards the cancer cells area is assigned in parameter \( \alpha \). The third term represents the natural death of the effector cells at a rate of \( \mu_1 \). The parameter \( k'_2 \), describes the rate at which infected CD4\(^+\)T cells infect a healthy T-cell. The fourth and fifth terms in the equation for effector cells dynamics describe the process of effector cells regeneration after the injection of lytic granules into the target cells. The term \( k_3 E(t) V(t) \) models the rate at which free virus infects effector cells. Eq (1c) gives the rate of change for the concentration of effector cells infected by free viral infection where \( \mu_2 \) reflects the death rate of the infected effector cells. Eq (1d) describes the change of rate...
for the free viruses cause the immunodeficiency, where the first term introduce the production source of viruses and the last term expresses the natural death of viruses at rate of \( c \).

By the assumption that \( \frac{dV}{dt} = 0 \) in the whole process, thus the system (1) becomes

\[
\frac{dT}{dt} = r_1 T(t) - k_1 E(t) T(t), \quad (2a)
\]
\[
\frac{dE}{dt} = r_2 T(t) + \alpha - \mu_1 E(t) - k_1 E(t) T(t) + (1 - \epsilon) k_1 E(t - \tau) T(t - \tau) - k_2 E(t) I(t), \quad (2b)
\]
\[
\frac{dI}{dt} = k_2 E(t) I(t) - \mu_2 I(t), \quad (2c)
\]

where \( k_2 = k_2^* + k_3 \frac{N \delta}{c} \) The ranges of parameters values are defined in Table 1; See [9, 8, 6, 5, 1, 8, 14].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( r_1 )</th>
<th>( k_1 )</th>
<th>( r_2 )</th>
<th>( \frac{\alpha}{\mu_1} )</th>
<th>( k_2^* )</th>
<th>( k_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range values</td>
<td>0.05~0.5</td>
<td>( 10^{-5} \sim 10^{-3} )</td>
<td>0~0.05</td>
<td>800~1200</td>
<td>( 10^{-5} \sim 5 \times 10^{-4} )</td>
<td>( 2.4 \times 10^{-5} )</td>
</tr>
<tr>
<td>Parameter</td>
<td>( \mu_2 )</td>
<td>( \delta )</td>
<td>( c )</td>
<td>( \mu_1 )</td>
<td>( \epsilon )</td>
<td>( N )</td>
</tr>
<tr>
<td>Range values</td>
<td>0.3</td>
<td>0.3~0.7</td>
<td>2.1~3.8</td>
<td>0.03</td>
<td>0.1</td>
<td>100~2000</td>
</tr>
</tbody>
</table>

Table: The ranges of parameters values.

4 The Stability of the Steady States

In order to study the steady states of the system and their stability, set Eqs of the system (2) simultaneously equal to zero. Therefore system (2) could have three equilibria; healthy state; \( S_1 \equiv (T_1, E_1, I_1) = (0, \frac{\alpha}{r_1}, 0) \), HIV infection steady state without cancer; \( S_2 \equiv (T_2, E_2, I_2) = \left( 0, \frac{\mu_2}{k_2}, \frac{\alpha k_2 - \mu_1 \mu_2}{\mu_2 k_2} \right) \) and the steady state of cancer-immune system interaction \( S_3 \equiv (T_3, E_3, I_3) = \left( \frac{\mu_1 r_1 - \alpha k_1}{k_1(r_2 - \sigma_1)}, \frac{r_1}{k_1}, 0 \right) \). There is no positive steady state describing the coexistence of the tumor and HIV viruses.

For \( \tau = 0 \), the local stability of the steady states \( S_i = (T_i, E_i, I_i) \) for \( i = \{1, 2, 3\} \), are obtained from the Jacobian matrix:

\[
J = \begin{pmatrix}
r_1 - k_1 E_i & -k_1 T_i & 0 \\
r_2 - \epsilon k_1 E_i - \mu_1 - \epsilon k_1 T_i & -k_2 I_i - k_1 E_i & 0 \\
0 & k_2 I_i & k_2 E_i \mu_2
\end{pmatrix}.
\]

It is easily seen that the roots of the characteristic equation for the steady state \( S_1 \) are \( \lambda_1 = r_1 - \frac{\alpha k_1}{r_1} \), \( \lambda_2 = -\mu_1 \) and \( \lambda_3 = \frac{\alpha k_2}{\mu_2} - \mu_2 \). For steady state \( S_2 \), the characteristic equation has the form

\[
P(\lambda) = \left( r_1 - \frac{\mu_2 k_1}{k_2} \right) - \lambda \left( \lambda^2 + \lambda \frac{\alpha k_2}{\mu_2} + \alpha k_2 - \mu_1 \mu_2 \right) = 0.
\]

The quadratic equation has two real negative roots or two imaginary roots with negative real parts since for the existence of the steady state \( S_2 \) we have \( \alpha k_2 > \mu_1 \mu_2 \). Therefore \( S_2 \) is stable if \( \lambda_1 = r_1 - \frac{\mu_2 k_1}{k_2} < 0 \). Similarly \( S_3 \) is stable if \( \lambda_3 = \frac{r_1 k_2}{k_1} - \mu_2 < 0 \). From the above discussion we arrive at the following proposition:

**Proposition 1** Assume \( \tau = 0 \) in the system (2). If \( r_1 > \frac{\alpha k_1}{r_1} \), then \( S_1 \) is unstable (a saddle point). Moreover
(i) If \( \epsilon < \frac{r_2}{r_1} \) then \( S_3 \) exists; if additionally \( r_1 < \frac{\mu_2 k_1}{k_2} \), then it is locally asymptotically stable.

(ii) If \( \alpha > \frac{\mu_1 \mu_2}{k_2} \), then \( S_2 \) exists; if additionally \( r_1 < \frac{\mu_2 k_1}{k_2} \), then this state is stable.

For \( \tau > 0 \): It is easily seen that the eigenvalues of \( S_1 \) do not depend on the delay, therefore the stability behavior of \( S_1 \) is the same \( \forall \tau \geq 0 \). However for \( S_3 \) the linearized form of system (2) at \( S_3 \) is

\[
J = \begin{pmatrix}
0 & 0 & -k_1 \bar{T}_3 \\
0 & -\mu_1 - k_1 \bar{T}_3 + (1 - \epsilon) k_1 \bar{T}_3 e^{-\lambda \tau} & 0 \\
1 - r_1 & k_2 \bar{E}_3 - \mu_2 & 0
\end{pmatrix}.
\]

Thus, the characteristic equation for \( S_3 \) is

\[
W(\lambda, \tau) = (k_2 \bar{E}_3 - \mu_2 - \lambda) W_2(\lambda, \tau) = 0
\]

with

\[
W_2(\lambda) = P_\ast(\lambda) + Q_\ast(\lambda)e^{-\lambda \tau},
\]

and

\[
P_\ast(\lambda) = \lambda^2 + (\mu_1 + k_1 \bar{T}_3) \lambda + (r_2 - r_1) k_1 \bar{T}_3, \quad Q_\ast(\lambda) = k_1 \bar{T}_3 (1 - \epsilon)(-\lambda + r_1).
\]

Therefore it is not difficult to arrive at the following Proposition and Theorem [4]:

**Proposition 2** If \( r_2 < \epsilon k_1 \) and

(i) \( \mu_2 < k_2 \bar{E} \) then if \((\bar{T}, \bar{E})\) is stable or a steady state in the two-variable system, then \( S_3 \) is stable as a steady state of system (2);

(ii) \( \mu_2 > k_2 \bar{E} \), then \( S_3 \) is unstable.

**Theorem 1** Assume that the steady state \( S_3 \) of system (2) exists, that is the state \((\bar{T}, \bar{E})\) for the two variable system of tumor cells and healthy effector cells when there is no virus infection also exists.

(i) If \( r_2 - r_1 (2 - \epsilon) > 0 \), then \((\bar{T}, \bar{E})\) is stable for any positive delay \( \tau > 0 \).

(ii) If \( r_2 - r_1 (2 - \epsilon) < 0 \), then there exists the threshold delay \( \tau_{th} > 0 \), such that \((\bar{T}, \bar{E})\) is stable for \( \tau < \tau_{th} \), loss stability at \( \tau = \tau_{th} \) in which Hopf bifurcation occurs.

5 Numerical Simulations

We use the MATLAB package DDE23 to solve the resulting system of DDEs. From the graphs of Figure 1, we note in the absence of HIV and for different values of time-lag \( \tau \), that the model successfully reproduces the immune surveillance phenomenon and the time-lag term causes appearance of oscillation behaviour around the steady states. However, in the presence of HIV infection, the numerical simulations shown in Figure (2) the stability of the steady states when \( \tau = 0 \).

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References


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Figure 1: Solutions for model (2), when $r_1 = 0.1, k_1 = 10^{-3}, r_2 = 0.02, \mu_1 = 0.03, \epsilon = 0.1, k_3 = 2.4 \times 10^{-5}, k'_2 = 1 \times 10^{-5}, \mu_2 = 0.3, N = 165, d = 0.3, c = 3.8$. This shows the behavior of tumor cells and healthy CD4$^+$T cells for different values of the time-lag $\tau$.

Figure 2: Solutions for model (2), (Top) when $\tau = 0$, $r_1 = 0.1, k_1 = 10^{-3}, r_2 = 0.02, \mu_1 = 0.03, \epsilon = 0.1, k_3 = 2.4 \times 10^{-5}, k'_2 = 1 \times 10^{-5}, \mu_2 = 0.3, N = 165, d = 0.3, c = 3.8$; and (bottom) with the same values of the pacemakers except $r_2 = 0.005$. 