COMPLICATED DYNAMICS OF TUMOR-IMMUNE SYSTEM INTERACTION MODEL WITH DISTRIBUTED TIME DELAY

MIN YU
College of Science and Engineering
Aoyama Gakuin University
Sagamihara 252-5258, Japan

GANG HUANG
School of Mathematics and Physics
China University of Geoscience
Wuhan 430074, China

YUEPING DONG*
School of Mathematics and Statistics
Central China Normal University
Wuhan 430079, China

YASUHIRO TAKEUCHI
School of Mathematics and Physics
Aoyama Gakuin University
Sagamihara 252-5258, Japan

(Communicated by Christina Surulescu)

Abstract. In this paper, we propose a distributed delay model to investigate the dynamics of the interactions between tumor and immune system. And we choose a special form of delay kernel which combines two delay kernels: a monotonic delay kernel representing a fading memory and a nonmonotonic delay kernel describing a peaking memory. Then, we discuss the effect of such delay kernel on system dynamics. The results show that the introduction of nonmonotonic delay kernel does not change the stability of tumor-free equilibrium, but it can induce stability switches of tumor-presence equilibrium and cause a rich pattern of dynamical behaviors including stabilization. Moreover, our numerical simulation results reveal that the nonmonotonic delay kernel has more complicated effects on the stability compared with the monotonic delay kernel.

1. Introduction. A tumor (neoplasm) is an abnormal mass of tissue which can be benign, pre-malignant, or malignant. The immune response begins when tumor cells (TCs) are identified by many different kinds of immune cells: for example, B cells producing and secreting antibodies into the blood, cytotoxic T lymphocytes (CTLs) considered as effector cells (ECs) with the ability to kill TCs, Helper T cells (HTCs) secreting interleukins and hence stimulating both B and T cells, and so on.
Although the functions of the immune system during tumor development are very complicated, being nonlinear and evolutive in some extent [10], the mechanisms underlying the interactions between the tumor and immune system are critically important for understanding tumorigenesis and immunotherapy [15, 34].

Enormous modeling efforts have been made to explore the dynamics of tumor-immune system interaction since the early 1990s and have evolved to capture much more complex aspects of the immune response [1, 3, 4, 5, 6, 7, 25, 9, 10, 11, 12, 13, 14, 15, 8, 17, 18, 20, 22, 24, 26, 27, 28, 29, 30, 33, 34, 36]. For example, Kuznetsov et al. [22] presented a well-known model describing the CTL response to the growth of an immunogenic tumor, where the sneaking through mechanism was described: the tumor stays in a very small size for a relatively long time period, and subsequently grows dangerously large. Kirschner et al. [20] first introduced immunotherapy into their models which can explain both short-term tumor oscillations in tumor sizes as well as long-term tumor relapse. Galach [18] introduced the immune reaction time delay into the simplification of Kuznetsov-Taylor model [22] and observed a state of the “returning” tumor. d’Onofrio et al. [9] proposed a general scheme to model tumor-immune system competition and immunotherapy. To study the influence of Natural Killer (NK) cells and CTLs in tumor surveillance, de Pillis et al. [7] presented a mathematical model validating by both experimental and human data. Mallet et al. [25] considered a hybrid cellular automata model to investigate the interactions of a tumor and the host immune system that involved important signalling molecules. Dong et al. [12] developed a three dimensional ordinary differential equations (ODEs) model to describe the interactions among TCs, ECs and HTCs, and observed oscillated behaviours. Furthermore, Dong et al. [13] incorporated two immune activation delays into their previous model [12]. It is quite common that oscillations occur in the immune system [31], however, there is debate whether the immune response delay can cause the oscillations [5, 6, 11, 34]. Piotrowska et al. [28] took into account distributed time delays in a generalisation of tumor-immune system interaction model, and numerically solved the system with Erlang probability densities by applying the classic linear chain trick [23, 21]. Thurley et al. investigated simple cell-to-cell communication circuit motifs by using response-time distributions [32]. For good reviews in the modeling of tumor-immune system interaction, we refer to [1, 14] and references therein.

Recently, Yu et al. [36] formulated a three-dimensional tumor-immune system to study the interactions among TCs, ECs and HTCs as follows:

\[
\begin{align*}
\frac{dT(t)}{dt} &= aT(t)(1 - bT(t)) - nE(t)T(t), \\
\frac{dE(t)}{dt} &= s_1 - d_1E(t) + pE(t)H(t), \\
\frac{dH(t)}{dt} &= s_2 - d_2H(t) + k_2T(t)H(t),
\end{align*}
\]

(1)

with initial conditions \( T(0) = T_0 > 0, \ E(0) = E_0 \geq 0, \) and \( H(0) = H_0 \geq 0, \)

where \( T(t), \ E(t) \) and \( H(t) \) are the densities of TCs, ECs and HTCs, respectively. The logistic term \( aT(1 - bT) \) describes the growth of TCs, where \( a \) denotes the maximal growth rate of the TCs population and \( b^{-1} \) denotes the maximal tumor size/volume. \( n \) represents the loss rate of TCs by ECs interaction. \( s_1 \) is referred to as the constant rate flow of mature ECs into the region of TCs localization. ECs have a natural lifespan of an average \( 1/d_1 \) days. \( p \) is an activation rate of ECs by HTCs. \( s_2 \) is referred to as the birth rate of HTCs produced in the bone marrow. HTCs have a natural lifespan of an average \( 1/d_2 \) days. \( k_2 \) is HTCs stimulation rate by the presence of identified tumor antigens.
Following the method in [22], system (1) can be rescaled by introducing the new variables and parameters: $x = \frac{X}{T_0}$, $y = \frac{E}{T_0}$, $z = \frac{H}{T_0}$, $\tau = nT_0t$, $\alpha = \frac{nT_0}{\tau}$, $\beta = bT_0$, $\sigma_1 = \frac{b}{nT_0}$, $\delta_1 = \frac{\alpha}{nT_0}$, $\rho = \frac{\rho}{nT_0}$, $\sigma_2 = \frac{\sigma_2}{nT_0}$, $\omega = \frac{\omega}{nT_0}$, $\delta_2 = \frac{\delta_2}{nT_0}$. By replacing $\tau$ by $t$, system (1) becomes

$$\begin{align*}
\frac{dx(t)}{dt} &= \alpha x(t)(1 - \beta x(t)) - x(t)y(t), \\
\frac{dy(t)}{dt} &= \sigma_1 - \delta_1 y(t) + \rho y(t)z(t), \\
\frac{dz(t)}{dt} &= \sigma_2 - \delta_2 z(t) + \omega x(t)z(t),
\end{align*}$$

(2)

with initial conditions $x(0) > 0$, $y(0) \geq 0$, $z(0) \geq 0$, where $x(t)$, $y(t)$ and $z(t)$ denote the dimensionless density of TCs, ECs and HTCs population, respectively.

In reality, the transmission of signals and biological processes does not occur instantaneously, but rather depends on the influence of the past history of the system. Therefore, it is often necessary to incorporate time delays into model foundation to reflect the real system. As we know, the activation of immune response against the development of tumors is very complicated and often delayed, such as, the immune activation delays of ECs by TCs and HTCs by TCs [13], and the immune activation delay of ECs by HTCs [36] and so on. Since the immune activation delay of ECs by HTCs is relatively longer than the others, we only consider such delay in this study.

The time lags can be generally classified into two types: discrete delay and distributed delay [19]. Here we use the distributed immune activation delay $\int_{-\infty}^{t} F(t-s)z(s)ds$ to replace $z(t)$ in the second equation of (2), then we obtain the following system:

$$\begin{align*}
\frac{dx(t)}{dt} &= \alpha x(t)(1 - \beta x(t)) - x(t)y(t), \\
\frac{dy(t)}{dt} &= \sigma_1 - \delta_1 y(t) + \rho y(t)z(t), \\
\frac{dz(t)}{dt} &= \sigma_2 - \delta_2 z(t) + \omega x(t)z(t),
\end{align*}$$

(3)

where $F(t)$ is the distributed delay kernel. And we choose a special case of $F(t)$ as the convex combination of a monotonic delay kernel and a nonmonotonic delay kernel, that is $F(t) = c_1 F_1(t) + c_2 F_2(t)$, where $F_1(t) = be^{-bt}$, $F_2(t) = b^2 t e^{-bt}$, and $b, c_1, c_2 \geq 0$, $c_1 + c_2 = 1$.

$F_1(t)$ is a monotonic decreasing function describing a fading memory (see Figure 1(a)). It has a maximum value at the present time $t = 0$, that is to say, the present time has the greatest effect on the system. $F_2(t)$ is a nonmonotonic function describing a peaking memory (see Figure 1(b)). It has a maximum value at the past time $t = \frac{1}{b}$, that is to say, the past time $\frac{1}{b}$ has a greater effect on the system. From Figure 1(b), we can see that the peak can shift to the left as the increase of $b$. $F(t)$ is the linear combination of $F_1(t)$ and $F_2(t)$, and its properties are presented in Appendix A.

Let $G(t) = \int_{-\infty}^{t} F(t-s)z(s)ds$, where $G(t) = c_1 G_1(t) + c_2 G_2(t)$, $G_1(t) = \int_{-\infty}^{t} F_1(t-s)z(s)ds$ and $G_2(t) = \int_{-\infty}^{t} F_2(t-s)z(s)ds$. By using the linear chain trick [23, 21], system (3) can be transformed into the following system:

$$\begin{align*}
\frac{dx(t)}{dt} &= \alpha x(t)(1 - \beta x(t)) - x(t)y(t), \\
\frac{dy(t)}{dt} &= \sigma_1 - \delta_1 y(t) + \rho y(t)(c_1 G_1(t) + c_2 G_2(t)), \\
\frac{dz(t)}{dt} &= \sigma_2 - \delta_2 z(t) + \omega x(t)z(t), \\
\frac{dG_1(t)}{dt} &= b\dot{z}(t) - bG_1(t), \\
\frac{dG_2(t)}{dt} &= bG_1(t) - bG_2(t),
\end{align*}$$

(4)
where $b = 1/\tau$ is a positive constant, and $\tau$ represents average time delay. A relatively small $b$ indicates a strong delay effect, which means that the system is more dependent on the past time, while a relatively large $b$ indicates a weak delay effect, which means that the system is more dependent on the present time (see Figure 1).

When $\epsilon_2 = 0$, system (4) can be reduced to a four-dimensional system (with only a fading memory) which was well studied in [36] taking the following form:

$$
\begin{align*}
\frac{dx(t)}{dt} &= \alpha x(t)(1 - \beta x(t)) - x(t)y(t), \\
\frac{dy(t)}{dt} &= \sigma_1 - \delta_1 y(t) + \rho y(t)G(t), \\
\frac{dz(t)}{dt} &= \sigma_2 - \delta_2 z(t) + \omega x(t)z(t), \\
\frac{dG(t)}{dt} &= bz(t) - bG(t).
\end{align*}
$$

The analytical results on the stability of system (5) are summarized in Appendix B.

As far as we know, this is the first attempt to consider such nonmonotonic delay kernel in the modeling of tumor-immune system interaction. And we are aimed to investigate the impact of this nonmonotonic delay kernel on the dynamical behaviors of system (4). The rest of the paper is organized as follows. In Section 2, we discuss the local stability of tumor-free and tumor-presence equilibria of system (4). In Section 3, we perform the numerical simulations to draw the stability boundary curve for the tumor-presence equilibrium. In Section 4, we give a brief summary and a discussion of our findings.

2. Stability analysis. In order to investigate the steady states of system (4), we set $dx/dt = 0$, $dy/dt = 0$, $dz/dt = 0$, $dG_1/dt = 0$ and $dG_2/dt = 0$.

Substituting $x = 0$ leads to the tumor-free equilibrium,

$$
E^- = (x^-, y^-, z^-, G_1^-, G_2^-) = (0, \frac{\sigma_1 \delta_2}{\delta_1 \delta_2 - \rho \sigma_2}, \frac{\sigma_2}{\delta_2}, \frac{\sigma_2}{\delta_2}, \frac{\sigma_2}{\delta_2}).
$$

$E^-$ exists, when $\rho < \frac{\delta_1 \delta_2}{\sigma_2} \equiv \rho_0$.

Following the similar analysis in [36], we can also obtain the unique tumor-presence equilibrium $E^+ = (x^+, y^+, z^+, G_1^+, G_2^+) = (x^+, \alpha(1 - \beta x^+), \ldots)$.
The characteristic equation of \( J \), in order to ensure \( \alpha \delta_2 \rho \), the tumor-free equilibrium \( \delta_2 = \frac{\alpha_1 \delta_2 - \rho \sigma_2}{\delta_2 - \omega x} \), where \( x^+ = \frac{\alpha \beta (\delta_1 \delta_2 - \rho \sigma_2) + \alpha \delta_1 \omega - \omega x - \sqrt{\Delta}}{2 \alpha \beta \delta_1 \omega} \) and \( \Delta = \left( \omega (\sigma_1 - \alpha \delta_1) + \alpha \beta (\delta_1 \delta_2 - \rho \sigma_2) \right)^2 = 4 \alpha \beta \omega \sigma_1 \sigma_2 \). It is required to be \( \rho < \delta_1 \delta_2 - \frac{\alpha_1 \delta_2}{\sigma_2} \equiv \rho_1 \) in order to ensure \( E^+ > 0 \). Note that \( z^+ = G_1^+ = G_2^+ \).

Now we discuss the stability of two equilibria \( E^- \) and \( E^+ \) of system (4).

First, we compute the Jacobian matrix of system (4) at \( E^- \), denoted by

\[
J(E^-) = \begin{pmatrix}
\alpha - y^- & 0 & 0 & 0 & 0 \\
0 & -\frac{\sigma_1}{y^-} & \rho y^- c_1 & \rho y^- c_2 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
\end{pmatrix}
\]

The eigenvalues of \( J(E^-) \) are \( \lambda_1 = -\delta_2 < 0 \), \( \lambda_2 = \frac{\rho \omega \sigma_1}{\delta_2} - \delta_1 \delta_2 \), \( \lambda_3 = \alpha - \frac{\sigma_1 \delta_2}{\delta_2} \), \( \lambda_4 = -b < 0 \) and \( \lambda_5 = -b < 0 \). It can be seen that all the eigenvalues are negative if and only if \( \rho_1 < \rho < \rho_0 \).

Thus we have the following result.

**Theorem 2.1.** The tumor-free equilibrium \( E^- \) is locally asymptotically stable if \( \rho_1 < \rho < \rho_0 \).

Second, we compute the Jacobian matrix of system (4) at \( E^+ \), denoted by

\[
J(E^+) = \begin{pmatrix}
-\alpha \beta x^+ & -x^+ & 0 & 0 & 0 \\
0 & 0 & -\frac{\sigma_1}{y^+} & \rho y^+ c_1 & \rho y^+ c_2 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
\omega z^+ & 0 & 0 & 0 & 0 \\
\end{pmatrix}
\]

The characteristic equation of \( J(E^+) \) takes the form

\[
\lambda^5 + D_1 \lambda^4 + D_2 \lambda^3 + D_3 \lambda^2 + D_4 \lambda + D_5 = 0,
\]

where

\[
\begin{align*}
D_1 &= 2b + b_1 = b + B_1, \\
D_2 &= b^2 + 2b_1 b + b_2 = bB_1 + B_2, \\
D_3 &= b_1 b^2 + 2b_2 b + b_3 - b_4 = bB_2 + B_3, \\
D_4 &= b_2 b^2 + (2b_3 - b_4 - c_2 b_4) b = bB_3 + B_4 - c_2 b_4 b, \\
D_5 &= b_3 b^2 = bB_4,
\end{align*}
\]

and

\[
\begin{align*}
B_1 &= b + b_1 > 0, \\
B_2 &= bb_1 + b_2 > 0, \\
B_3 &= bb_2 + b_3 - b_4 > 0, \\
B_4 &= bb_3 > 0,
\end{align*}
\]

while

\[
\begin{align*}
b_1 &= \alpha \beta x^+ + \frac{\sigma_1}{y^+} + \frac{\sigma_2}{z^+} > 0, \\
b_2 &= \alpha \beta x^+ \frac{\sigma_1}{y^+} + \alpha \beta x^+ \frac{\sigma_2}{z^+} + \frac{\sigma_1 \sigma_2}{y^+ z^+} > 0, \\
b_3 &= \alpha \beta x^+ \frac{\sigma_1}{y^+ z^+} + \rho \omega x^+ y^+ z^+ > 0, \\
b_4 &= \alpha \beta x^+ \frac{\sigma_1}{y^+ z^+} > 0.
\end{align*}
\]
Applying the Routh-Hurwitz criterion, we know that all roots of (6) have negative real parts if and only if
\[ D_1, D_2, D_3, D_4, D_5 > 0, \quad D_1D_2D_3 > D_3^2 + D_4^2D_5 - D_1D_5 \]
and
\[ (D_1D_4 - D_5)(D_1D_4D_3 - D_3^2 - D_4^2D_5 + D_1D_5) > D_5(D_1D_2 - D_3)^2. \]
Following we choose the parameters which locate in the stability regions of \( E_* = (x^+, y^+, z^+, \mathbb{Z}^+) \) of system (2) and \( E^* = (x^+, y^+, z^+, \mathbb{Y}^+) \) of system (5). That is, we have \( P = b_1b_2 - b_3 > 0 \) (ensured by Lemma B.1) and \( Q = B_1B_2B_3 - B_3^2 - B_4^2B_5 > 0 \) (ensured by Lemma B.2).

Since \( 0 < c_2 \leq 1, b_3 - b_4 = \rho \omega x^+ y^+ z^+ > 0 \) and \( 2b_3 - b_4 - c_2b_4 = (b_3 - b_4) + (b_3 - c_2b_4) > 0 \), we can conclude that \( D_1D_4 - D_5 = 2b_2b_3^2 + [2(2b_3 - b_4 - c_2b_4) + (b_1b_2 - b_3)]b_2^2 + b_2(2b_3 - b_4 - c_2b_4) > 0 \). Hence \( (D_1D_4 - D_5)(D_1D_4D_3 - D_3^2 - D_4^2D_5 + D_1D_5) > D_5(D_1D_2 - D_3)^2 \) implies that \( D_1D_2D_3 - D_3^2 - D_4^2D_5 + D_1D_5 > 0. \)

Therefore, the sufficient condition for the stability of \( E^+ \) is given by
\[
(D_1D_4 - D_5)(D_1D_2D_3 - D_3^2 - D_4^2D_5 + D_1D_5) - D_5(D_1D_2 - D_3)^2
= D_1[-D_2^2D_4^2 + (D_1D_2D_3 - D_3^2 + 2D_1D_5)D_4 - D_5(D_1D_2^2 - D_2D_3 + D_5)]
\]
\[
\Delta = D_1H(D_4) > 0.
\]

Note that \( D_4 = bB_3 + B_2 - c_2b_4b = bB_3 + b(b_3 - c_2b_4) > 0 \) for \( 0 \leq c_2 \leq 1, \) because of \( b_3 > b_4. \) Since \( B_1B_2 - B_3 > 0 \) (because \( Q > 0 \) implies that \( B_3(B_1B_2 - B_3) > B_2^2B_4 > 0 \)), we have \( D_1D_2 - D_3 = b^2B_1 + bB_2^2 + (B_1B_2 - B_3) > 0. \) In fact, \( H(D_4) \) can be written as
\[
H(D_4) = h_2D_4^2 + h_1D_4 + h_0,
\]
where
\[
h_2 = -D_2^2 < 0,
\]
\[
h_1 = D_1D_2D_3 - D_3^2 + 2D_1D_5 = D_3(D_1D_2 - D_3) + 2D_1D_5 > 0,
\]
\[
h_0 = -D_5(D_1D_2^2 - D_2D_3 + D_5) = -D_5[D_2(D_1D_2 - D_3) + D_5] < 0.
\]

It is easy to see that equation \( H(D_4) = 0 \) has two positive roots \( D_4^* = \frac{-h_1 - \sqrt{h_1^2 - 4h_0h_2}}{2h_2} \) and
\[
D_4^{**} = \frac{-h_1 + \sqrt{h_1^2 - 4h_0h_2}}{2h_2} \quad \text{if} \quad h_1^2 > 4h_0h_2.
\]

Note that \( D_4 \) is a decreasing function with respect to \( c_2 \) (see Figure 2(a)), and \( H(D_4) \) is a quadratic function with respect to \( D_4 \) (see Figure 2(b)). We define \( \overline{d} = bB_3 + B_4 \) and \( \underline{d} = bB_3 + B_4 - b_4b = b_2b_3^2 + 2(b_3 - b_4)b > 0, \) then we have \( \underline{d} < D_4 < \overline{d} \) (see Figure 2(a)). To check the sign of \( H(D_4), \) we just need to know the signs of

---

Figure 2. (a) The monotonic decreasing function \( D_4 \) with respect to \( c_2. \) (b) The quadratic function \( H(D_4) \) with respect to \( D_4. \)
$H(d)$ and $H(\bar{d})$. Remember, we have assumed that the conditions $P > 0$ and $Q > 0$ are satisfied. By calculations, we have $H(d) = T_4 b^4 + T_3 b^3 + T_2 b^2 + T_1 b + T_0 > 0$, since

$$
T_4 = B_1 B_2 B_3 - B_3^2 - B_4^2 B_4 = Q > 0, \\
T_3 = B_1^2 B_2 B_3 - B_1 B_3^2 - B_4^2 B_4 = B_1 Q > 0, \\
T_2 = B_1 B_2^2 B_3 - B_2 B_3^2 - B_4^2 B_2 B_4 = B_2 Q > 0, \\
T_1 = B_1 B_2 B_3^2 - B_3^3 - B_3^2 B_3 B_4 = B_3 Q > 0, \\
T_0 = B_1 B_2 B_3 B_4 - B_3^2 B_4 - B_4^2 B_4^2 = B_4 Q > 0.
$$

From $H(\bar{d}) > 0$, we have $\bar{d} < D_4^*$ (see Figure 2(b)). The remaining matter is to determine the sign of $H(d)$. In summary, we have two cases:

**Case (I).** If $d > D_4^*$, then we have $H(d) > 0$. So $H(D_4) > 0$ when $d < D_4 < \bar{d}$ for any $0 \leq c_2 \leq 1.$

**Case (II).** If $d < D_4^*$, then we have $H(d) < 0$. So $H(D_4) > 0$ when $D_4 < D_4 < \bar{d}$, and $H(D_4) < 0$ when $d < D_4 < D_4^*$. There must exist a root $c_2^*$ which satisfies $D_4(c_2^*) = D_4^*$.

Thus we have the following result.

**Theorem 2.2.** System (4) has a unique tumor-presence equilibrium $E^+$ if $0 < \rho < \rho_1$, which is locally asymptotically stable if the inequality $H(d) > 0$ holds.

3. **Numerical results.** In this section, we provide some numerical simulations to illustrate that the stability can be changed at the branch of the tumor-presence equilibrium $E^+$. The parameters are taken from [12]: $\alpha = 1.636$, $\beta = 0.002$, $\sigma_1 = 0.1181$, $\delta_1 = 0.3743$, $\sigma_2 = 0.38$, $\delta_2 = 0.055$. After some calculations, we obtain $\rho_0 = \frac{1}{16} \approx 0.054175$, $\rho_1 = \frac{1}{16} \approx 0.0437267$. Note that $E^+$ exists when $\rho < \rho_1$. We draw the stability boundary curve of $E^+$ by using AUTO as incorporated in XPPAUT [16].

Since the condition $c_1 + c_2 = 1$ is satisfied, we choose $c_2$ as a bifurcation parameter. The stability boundary curves in Figure 3 are derived from $H(c_2, b) = 0$ for each fixed $\rho$ and $\omega$. Note that function $H$ given by (9) is now a function of $c_2$ and $b$, since $E^+$ does not depend on $c_2$ and $b$. In Figure 3(a), two stability boundary curves are drawn for system (4) in the $c_2 - b$ parameter plane when $\rho = 0.01$ and $\omega = 0.00035$ are fixed. $E^+$ is stable in the area outside these two stability boundary curves, while $E^+$ is unstable in the area between these two stability boundary curves. Particularly, when we fix $c_2 = 0$ (that is, $c_1 = 1$: case for a fading memory of system (5)), we can see that $E^+$ is stable, and becomes unstable, and then becomes stable again as the increase of $b$ (decrease of delay effect), which is in accordance with the previous observations (dual role of delay effect) in [36]. Actually, system (4) can be reduced to system (5) when $c_2 = 0$. In this case, we observe that the instability region increases as the increase of $c_2$. In Figure 3(b), one stability boundary curve is drawn for system (4) in the $c_2 - b$ parameter plane when $\rho = 0.03$ and $\omega = 0.00035$ are fixed. $E^+$ is stable in the area below the stability boundary curve, while $E^+$ is unstable in the area above the stability boundary curve. Similarly, when we fix $c_2 = 0$, we can see that $E^+$ is stable, and becomes unstable with increasing $b$, which is in accordance with the previous observations in [36]. Note that we observe the dual role of delay effect when an activation rate $\rho$ of ECs by HTCs is relatively small even under a peaking memory (see Figure 3(a)).
Figure 3. Log plots for the stability regions of tumor-presence equilibrium $E^+$ and stability boundary curves representing by black curves in $c_2-b$ parameter plane. (a) $E^+$ is stable in the area outside these two stability boundary curves, while $E^+$ is unstable in the area between these two stability boundary curves. (b) $E^+$ is stable in the area below the stability boundary curve, while $E^+$ is unstable in the area above the stability boundary curve.
Figure 4. Stability boundary curves of $E^+$ are shown in $\rho - \omega$ parameter plane for different $b$. $E^+$ is stable below each stability boundary curve, while $E^+$ is unstable above each stability boundary curve. (a) We fix $c_2 = 0.2(< 0.5)$. (b) We fix $c_2 = 0.8(> 0.5)$. 
Figure 5. Stability boundary curves of $E^+$ are shown in $\rho - \omega$ parameter plane for different $c_2$. $E^+$ is stable below each stability boundary curve, while $E^+$ is unstable above each stability boundary curve. (a) We fix $b = 0.001$. (b) We fix $b = 0.1$. 
In order to check how the parameter $c_2$ affects the stability of $E^+$, we choose two representative values $c_2 = 0.2$ (the distributed delay kernel dominated by a fading memory) and $c_2 = 0.8$ (the distributed delay kernel dominated by a peaking memory) to draw stability boundary curves of $E^+$ in $\rho - \omega$ parameter plane for different $b$ (see Figure 4). $E^+$ is stable in the area below the stability boundary curve, while $E^+$ is unstable in the area above the stability boundary curve. These curves satisfy $H(\rho, \omega) = 0$ for each fixed $c_2$ and $b$. For the both cases $c_2 = 0.2$ and $0.8$, we find that the stability region decreases first, and then increases with increasing $b$, which is similar to the system (5) with only a fading memory. This means that the introduction of $c_2$ does not change the variation tendency of stability, but it causes the change of stability region inducing the possibility of stability switch (see Figure 4(a) and (b)). In general, the increasing delay gives the tendency to promote the instability of the system. But for both cases in Figure 4, when $b$ is relatively small ($b < 0.1$, indicating that delay effect is stronger), the stability region decreases with the increase of $b$, which is counterintuitive (against the general tendency). On the other hand, when $b$ is relatively large ($b > 0.1$, indicating that delay effect is weaker), the stability region increases with the increase of $b$, which agrees to intuitive sense. Now let us compare two cases in Figure 4. When we fix $b$ for the same value in Figure 4(a) and (b), we find the stability region for relatively small $c_2$ (the case dominated by a fading memory) is smaller than one for relatively large $c_2$ (the case dominated by a peaking memory). This implies that a peaking memory will make the system more stable. We now observe this is true or not by Figure 5.

We draw the stability boundary curves in $\rho - \omega$ parameter plane as $c_2$ varies for fixed $b = 0.001$ and $b = 0.1$. The stability boundary curves satisfy $H(\rho, \omega) = 0$ for each fixed $c_2$ and $b$. From Figure 5(b), when $b$ is relatively large (weak delay effect: $b = 0.1$), the stability region decreases monotonically as $c_2$ increases. This agrees to an intuitive sense of delay effects. That is, a peaking memory promotes the instability of the system. On the other hand, from Figure 5(a), when $b$ is relatively small (strong delay effect: $b = 0.001$), the stability region becomes larger when $c_2$ increases as $c_2 = 0$(cyan curve), 0.2(magenta curve), 0.5(green curve), 0.8(yellow curve) for $0 < \rho < 0.04$ and the stability region turns to be much smaller for $c_2 = 1$(red curve). The former phenomenon is also true for any $\rho < \rho_1$, $0 < c_2 < 0.5$. This implies that a peaking memory promotes the stability of the system when a fading memory is dominated ($c_2 < 0.5$) under any activation rate $\rho$ of ECs by HTCs. After the peaking memory becomes dominant ($c_2 > 0.5$), still it promotes the stability under small $\rho(< 0.04)$, but hinders the stability for large $\rho$. It is shown that the delay distribution function $F(t)$ has a maximum peak $F_{max}$ only for $c_2 > 0.5$. Hence, dominated peaking memory brings instability under large activation rate $\rho$ of ECs by HTCs. It is interesting to observe in Figure 5(a) that the stability region becomes smallest when $c_2$ reaches at its maximum ($c_2 = 1$). This suggests that there may exist an optimal value $c_2$ which gives the maximum stability region at $c_2 = c_2$ satisfying $0.5 < c_2 < 1$. This also shows that a peaking memory can promote the stability of the system.

4. Conclusion and discussion. In this study, we employed a special form of distributed delay with the kernel, $F(t) = c_2 F_1(t) + c_2 F_2(t)$, $(c_1, c_2 \geq 0, c_1 + c_2 = 1)$, consisting of a monotonic delay kernel $F_1(t) = be^{-bt}$ representing a fading memory and a nonmonotonic delay kernel $F_2(t) = b^2 te^{-bt}$ illustrating a peaking memory to model the time lag of the immune activation of ECs by HTCs. A relatively
small $b$ indicates a strong delay effect, while a relatively large $b$ indicates a weak delay effect. $c_2 = 0.5$ is a threshold determining which delay kernel is dominated. When $c_2$ is relatively small ($< 0.5$), $F(t)$ is dominated by $F_1(t)$. In this case, $F(t)$ has the maximum value at $t = 0$ denoted by $F_{\text{max}} = F(0) = (1 - c_2)b$.

The immune activation of ECs mainly depends on the density of HTCs at the present time $t = 0$. On the other hand, when $c_2$ is relatively large ($> 0.5$), $F(t)$ is dominated by $F_2(t)$. In this case, $F(t)$ has the maximum value at $t = t^*$ denoted by $F_{\text{max}} = F(t^*) = bc_2 e^{-bt}$. The immune activation of ECs mainly depends on the density of HTCs at the past time $t = t^*$. From Figure 3, we showed the effect of $c_2$ on the stability of $E^+$ (see Figures 4 and 5) and suggest the existence of an optimal $c_2$ to make the stability region maximum. From Figure 7, we know that $t^*$ (the time giving maximum value of delay kernel $F(t)$) is increasing with respect to increasing of $c_2$, but $F_{\text{max}}$ is decreasing with respect to $c_2$. This will give an optimal $c_2$ to ensure the stability region maximum.

Note that we only considered the model with the special delay kernel $F(t) = c_1 F_1(t) + c_2 F_2(t)$, $(c_1, c_2 \geq 0, c_1 + c_2 = 1)$). In general, the delay kernel can be defined as $F(t) = \sum_{j=1}^{n} c_j F_j(t)$, where $c_j \geq 0, F_j(t) = \frac{b^j}{j!} t^j e^{-bt}$, $b > 0$, $j = 1, 2, \ldots, n$ and $\sum_{j=1}^{n} c_j = 1$. Finally, we have to point out that how to analyze the original system (3) is still an open problem.

Besides, in this study, we only consider the anti-tumor immunity factors, such as ECs and HTCs. However, the pro-tumor immunity factors, such as Th17 cells and regulatory T lymphocytes are also present in the tumor microenvironment [35]. So it is important to consider the dual role of the immune response: tumor-inhibiting and tumor-promoting in the modeling of tumor immune system interaction [2].

Appendix A. Properties of delay kernel $F(t)$. By calculating the derivative of $F(t)$ with respect to $t$, we have $\frac{dF(t)}{dt} = \frac{d}{dt}(c_1 be^{-bt} + c_2 b^2 t e^{-bt}) = b^2 e^{-bt}(2c_2 - 1 - c_2 bt)$. Define

$$t^* = \frac{2c_2 - 1}{c_2 b} = \frac{1}{b} \left( 2 - \frac{1}{c_2} \right).$$

Then we have $\frac{dF(t)}{dt} \big|_{t=t^*} = 0$. From (10), we can see that $t^*$ is a monotonic increasing function of $c_2$, while it is a monotonic decreasing function of $b$. There exists a critical threshold $c_2 = 0.5$ that can determine the sign of $t^*$. If $c_2 \leq 0.5$, we have $t^* \leq 0$, further if $t \geq 0$, then we have $t \geq t^*$ and $\frac{dF(t)}{dt} \leq 0$. So $F(t)$ is a monotonic decreasing function for all $t \geq 0$. If $c_2 > 0.5$, we have $t^* > 0$, and when $t < t^*$ we have $\frac{dF(t)}{dt} > 0$, and when $t > t^*$ we have $\frac{dF(t)}{dt} < 0$. So $F(t)$ is a nonmonotonic function with a peak at $t = t^*$. For relatively small $c_2 (< 0.5)$, the curve shape of function $F(t)$ is very similar to function $F_1(t)$, which means that $F(t)$ is dominated
Figure 6. The function $F(t)$ with respect to $t$. The black curves are given for relatively small $b$ and imply strong delay. The red curves are given for relatively large $b$ and imply weak delay. (a) We fix $c_2 = 0.2 (< 0.5)$. The dashed curves correspond to relatively small $c_2$. (b) We fix $c_2 = 0.8 (> 0.5)$. The solid curves correspond to relatively large $c_2$.

Figure 7. Schematic diagram of $F(t)$ with respect to $t$ for different $c_2$ and fixed $b$.

by $F_1(t)$ (see Figure 6(a)), while for relatively large $c_2 (> 0.5)$, the curve shape of function $F(t)$ is very similar to function $F_2(t)$, which means that $F(t)$ is dominated by $F_2(t)$ (see Figure 6(b)). For any $0 < c_2 \leq 1$, $F(t)$ always has the maximum value at $t = t^\ast$. Denote

$$F_{\text{max}} = F(t^\ast) = c_2b e^{-2 + \frac{1}{c_2}}.$$  \hspace{1cm} (11)

By calculating the derivative of $F_{\text{max}}$ with respect to $c_2$, we have $\frac{dF_{\text{max}}}{dc_2} = b(1 - \frac{1}{c_2})e^{-2 + \frac{1}{c_2}} \leq 0$. So $F_{\text{max}}$ is a monotonic decreasing function of $c_2$. From (11), we can see that $F_{\text{max}}$ is a monotonic increasing function of $b$. We can conclude that $c_2$ has an opposite role on $t^\ast$ and $F_{\text{max}}$ compared to the role of $b$. Large $t^\ast$ or small $F_{\text{max}}$ indicates that the system depends on the past time more than the present time. Note that $F = c_1F_1 + c_2F_2 = (bt - 1)be^{-bt}c_2 + be^{-bt}$. We define $\hat{t} = \frac{b}{c_2}$, then we have $F(\hat{t}) = \frac{b}{c_2}$. From (10), we can see that the limit of $t^\ast$ is $\hat{t}$ as $c_2$ approaches 1. When $t < \hat{t}$, $F$ is a monotonic decreasing function of $c_2$. And when $t > \hat{t}$, $F$ is a monotonic increasing function of $c_2$ (see Figure 7).
Appendix B. Summary of previous stability results of systems (2) and (5). We summarize the stability results from [36] which are used in this study.

Three-dimensional system (2) has a tumor-free equilibrium

\[ E_0 = (x^-, y^-, z^-) = \left( 0, \frac{\sigma_1 \delta_2}{\delta_1 \delta_2 - \rho \sigma_2}, \frac{\sigma_2}{\delta_2} \right). \]

\( E_0 \) exists when \( \rho < \rho_0 \). And system (2) has a unique tumor-presence equilibrium

\[ E_* = (x^+, y^+, z^+) = (x^+, \alpha(1 - \beta x^+), \frac{\sigma_2}{\delta_2 - \omega x^+}). \]

\( E_* \) exists when \( \rho < \rho_1 \). We define \( P = b_1 b_2 - b_3 \), where \( b_1, b_2, b_3 \) are given in (8).

Then we have the following result.

**Lemma B.1.** \( E_0 \) is locally asymptotically stable if \( \rho_1 < \rho < \rho_0 \), and \( E_* \) is locally asymptotically stable if \( P > 0 \) holds.

Four-dimensional system (5) has a tumor-free equilibrium

\[ E^0 = (x^-, y^-, z^-, G^-) = \left( 0, \frac{\sigma_1 \delta_2}{\delta_1 \delta_2 - \rho \sigma_2}, \frac{\sigma_2}{\delta_2}, \frac{\sigma_2}{\delta_2} \right). \]

\( E^0 \) exists when \( \rho < \rho_0 \). And system (5) has a unique tumor-presence equilibrium

\[ E^* = (x^+, y^+, z^+, G^+_1) = (x^+, \alpha(1 - \beta x^+), \frac{\sigma_2}{\delta_2 - \omega x^+}, \frac{\sigma_2}{\delta_2 - \omega x^+}). \]

\( E^* \) exists when \( \rho < \rho_1 \). We define \( Q = (B_1 B_2 - B_3) B_3 - B_1^2 B_4 = P_3 b^3 + P_2 b^2 + P_1 b + P_0 \), where \( B_i \) are given in (7), \( b_i \) are given in (8), \( i=1,2,3,4 \), and

\[
\begin{align*}
P_3 & = b_1 b_2 - b_3, \\
P_2 & = b_1 (b_1 b_2 - b_3 - b_4), \\
P_1 & = b_2 (b_1 b_2 - b_3 + b_4 (b_2 - b_4^2)), \\
P_0 & = (b_3 - b_4) (b_1 b_2 - b_3 + b_4).
\end{align*}
\]

Then we have the following result.

**Lemma B.2.** \( E^0 \) is locally asymptotically stable if \( \rho_1 < \rho < \rho_0 \), and \( E^* \) is locally asymptotically stable if \( Q > 0 \) holds.

**Acknowledgments.** We would like to thank the editor and two anonymous referees for their valuable comments and suggestions which helped to improve the manuscript. This work was partially supported by the National Natural Science Foundation of China (Nos. 11571326, 11901225), the Natural Science Foundation of Hubei Province (No. 2019CFB189), the Fundamental Research Funds for the Central Universities (No. CCNU18XJ041) and by Aoyama Gakuin University research grant “Ongoing Research Support”.

**REFERENCES**

[1] J. A. Adam and N. Bellomo, *A Survey of Models for Tumor-Immune System Dynamics*, Birkhauser, Boston, 1997.

[2] A. Arabameri, D. Asemani and J. Hadjati, A structural methodology for modeling immune-tumor interactions including pro- and anti-tumor factors for clinical applications, *Math. Biosci.,* 304 (2018), 48-61.

[3] S. Banerjee and R. R. Sarkar, Delay-induced model for tumor-immune interaction and control of malignant tumor growth, *BioSystems,* 91 (2008), 268–288.

[4] P. Bi and S. G. Ruan, Bifurcations in delay differential equations and applications to tumor and immune system interaction models, *SIAM J. Appl. Dyn. Syst.,* 12 (2013), 1847–1888.
[5] P. Bi, S. G. Ruan and X. N. Zhang, Periodic and chaotic oscillations in a tumor and immune system interaction model with three delays, *Chaos*, 24 (2014), 023101, 16 pp.

[6] M. Bodnar and U. Foryś, Delays do not cause oscillations in a corrected model of humoral mediated immune response, *Appl. Math. Comput.*, 289 (2016), 7–21.

[7] L. G. de Pillis, A. E. Radunskaya and C. L. Wiseman, A validated mathematical model of cell-mediated immune response to tumor growth, *Cancer Res.*, 65 (2005), 7950–7958.

[8] L. G. de Pillis and A. E. Radunskaya, Modeling tumor-immune dynamics, in *Mathematical Modeling of Tumor-Immune System Dynamics*, Springer Proc. Math. Stat., Springer, New York, 107 (2014), 59–108.

[9] A. d’Onofrio, A general framework for modeling tumor-immune system competition and immunotherapy: Mathematical analysis and biomedical inferences, *Physica D*, 208 (2005), 220–235.

[10] A. d’Onofrio, Metamodeling tumor-immune system interaction, tumor evasion and immunotherapy, *Math. Comput. Model.*, 47 (2008), 614–637.

[11] A. d’Onofrio, F. Gatti, P. Cerrai and L. Freschi, Delay-induced oscillatory dynamics of tumour-immune system interaction, *Math. Comput. Model.*, 51 (2010), 572–591.

[12] Y. P. Dong, R. Miyazaki and Y. Takeuchi, Mathematical modeling on helper T cells in a tumor immune system, *Discrete Continuous Dynam. Systems-B*, 19 (2014), 55–72.

[13] Y. P. Dong, G. Huang, R. Miyazaki and Y. Takeuchi, Dynamics in a tumor immune system with time delays, *Appl. Math. Comput.*, 252 (2015), 99–113.

[14] R. Eftimie, J. L. Bramson and D. J. D. Earn, Interactions between the immune system and cancer: A brief review of non-spatial mathematical models, *Bull. Math. Biol.*, 73 (2011), 2–32.

[15] S. Eikenberry, C. Thalhauser and Y. Kuang, Tumor-immune interaction, surgical treatment, and cancer recurrence in a mathematical model of melanoma, *PLoS Comput. Biol.*, 5 (2009), e1000362, 18 pp.

[16] B. Ermentrout, *Simulating, Analyzing, and Animating Dynamical Systems: A Guide to XPPAUT for Researchers and Students*, Software, Environments, and Tools, 14. Society for Industrial and Applied Mathematics (SIAM), Philadelphia, PA, 2002.

[17] U. Foryś, J. Waniewski and P. Zhivkov, Anti-tumor immunity and tumor anti-immunity in a mathematical model of tumor immunotherapy, *J. Biol. Syst.*, 14 (2006), 13–30.

[18] M. Galach, Dynamics of the tumor-immune system competition-the effect of time delay, *Int. J. Appl. Math. Comput. Sci.*, 13 (2003), 395–406.

[19] M. Iannelli and A. Pugliese, *An Introduction to Mathematical Population Dynamics*, Along the Trail of Volterra and Lotka. Unitext, 79. La Matematica per il 3+2. Springer, Cham, 2014.

[20] D. Kirschner and J. C. Panetta, Modeling immunotherapy of the tumor-immune interaction, *J. Math. Biol.*, 37 (1998), 235–252.

[21] Y. Kuang, *Delay Differential Equations: With Applications in Population Dynamics*, Mathematics in Science and Engineering, 191. Academic Press, Inc., Boston, MA, 1993.

[22] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor and A. S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, *Bull. Math. Biol.*, 56 (1994), 295–321.

[23] N. MacDonald, *Biological Delay Systems: Linear Stability Theory*, Cambridge Studies in Mathematical Biology, 8. Cambridge University Press, Cambridge, 1989.

[24] K. J. Mahasa, R. Ouifki, A. Eladdadi and L. de Pillis, Mathematical model of tumor-immune surveillance, *J. Theor. Biol.*, 404 (2016), 312–330.

[25] D. G. Mallet and L. G. de Pillis, A cellular automata model of tumor-immune system interactions, *J. Theor. Biol.*, 239 (2006), 334–350.

[26] M. J. Pietrowska, M. Bodnar, J. Poleszczuk and U. Forsy, Mathematical modelling of immune reaction against gliomas: sensitivity analysis and influence of delays, *Nonlinear Anal. Real World Appl.*, 14 (2013), 1601–1620.

[27] M. J. Pietrowska, An immune system-tumour interactions model with discrete time delay: Model analysis and validation, *Commun. Nonlinear Sci. Numer. Simulat.*, 34 (2016), 185–198.

[28] M. J. Pietrowska and M. Bodnar, Influence of distributed delays on the dynamics of a generalized immune system cancerous cells interactions model, *Commun. Nonlinear Sci. Numer. Simulat.*, 54 (2018), 389–415.
[29] F. A. Rihan, D. H. Abdel Rahman, S. Lakshmanan and A. S. Alkhajeh, A time delay model of tumour-immune system interactions: global dynamics, parameter estimation, sensitivity analysis, Appl. Math. Comput., 232 (2014), 606–623.

[30] E. D. Sontag, A dynamic model of immune responses to antigen presentation predicts different regions of tumor or pathogen elimination, Cell Syst., 4 (2017), 231–241.

[31] J. Stark, C. Chan and A. J. T. George, Oscillations in the immune system, Immunol. Rev., 216 (2007), 213–231.

[32] K. Thurley, L. F. Wu and S. J. Altschuler, Modeling cell-to-cell communication networks using response-time distributions, Cell Syst., 6 (2018), 355–367.

[33] A. Tsygvintsev, S. Marino and D. E. Kirschner, A mathematical model of gene therapy for the treatment of cancer, Mathematical Methods and Models in Biomedicine, Lect. Notes Math. Model. Life Sci., Springer, New York, (2013), 367–385.

[34] L. Wenbo and J. Wang, Uncovering the underlying mechanism of cancer tumorogenesis and development under an immune microenvironment from global quantification of the landscape, J. R. Soc. Interface, 14 (2017), 20170105.

[35] K. P. Wilkie and P. Hahnfeldt, Modeling the dichotomy of the immune response to cancer: Cytotoxic effects and tumor-promoting inflammation, Bull. Math. Biol., 79 (2017), 1426–1448.

[36] M. Yu, Y. P. Dong and Y. Takeuchi, Dual role of delay effects in a tumor-immune system, J. Biol. Dyn., 11 (2017), 334–347.

Received April 2019; revised August 2019.

E-mail address: yumin8618@gmail.com
E-mail address: huanggang@cug.edu.cn
E-mail address: ypdong@mail.ccnu.edu.cn
E-mail address: takeuchi@gem.aoyama.ac.jp