QUALITATIVE ANALYSIS OF A SIMPLE TUMOR-IMMUNE SYSTEM WITH TIME DELAY OF TUMOR ACTION

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Abstract. In this paper, we propose a simple tumor-immune system model with time delay of tumor action, where two kinds of effects of the tumor cells (i.e. stimulation and neutralization) on the effector cells are considered. The local stability of the model is obtained by analyzing the characteristic equations of the model at the corresponding equilibria, the sufficient conditions on the global stability are found by applying the Fluctuation Lemma and constructing the different convergent sequences. The obtained results show that, compared to the results for the model without time delay, the time delay of tumor action can affect the stability of tumor equilibrium of the model as the stimulation effect of the tumor cells is strong enough, while the delay is harmless for the stability of tumor equilibrium under the neutralization of tumor cells. For the appropriate neutralization of tumor cells on effector cells, the bistability of the tumor free equilibrium and the stronger tumor equilibrium can appear. In the case of stimulation of tumor cells, the sufficiently large time delay can lead to the appearance of a stable periodic solution by Hopf bifurcation, and the numerical simulation illustrates that the amplitude of the periodic orbit increases with time delay. We also discuss the dependence of the tumor equilibrium and the time delay threshold, determining the stability of the tumor equilibrium, on tumor action. The related conditions determining dynamics of the model are expressed by certain formulae with biological meanings.

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1. **Introduction.** A tumor is an abnormal growth of body tissue, which can normally be controlled by the immune system under most cases. The formation of a tumor occurs often because there is problem in the body’s immune system. A number of mathematical models for the interactions between the immune system and a growing tumor have been developed [from [15]]. In [15], Kuznetsov et al. proposed the following mathematical model describing the interaction between effector cells (e.g. cytotoxic T lymphocytes (CTL) and natural killer (NK) cells) and tumor cells

\[
\begin{align*}
\frac{dT}{dt} &= rT \left( 1 - \frac{T}{K} \right) - nET, \\
\frac{dE}{dt} &= \sigma + \frac{pET}{g + T} - mET - \eta E,
\end{align*}
\]

where \( T = T(t) \) and \( E = E(t) \) are the concentrations of the tumor cells and the effector cells at time \( t \), respectively, \( r \) is the coefficient for the maximal growth of tumor cells, \( K \) is the carrying capacity of the biological environment for tumor cells, \( n \) is the rate coefficient at which the tumor cells are damaged by the effector cells, \( \sigma \) is the normal (non-enhanced by the presence of the tumor) rate of the inflow of mature effector cells into the tumor site, \( m \) is the coefficient of the decline rate of the effector cells neutralized by the tumor cells, and \( \eta \) is the natural elimination rate coefficient of the effector cells.

In model (1), it is assumed that, besides the natural inflow, the effector cells may be also recruited by stimulation of the tumor cells. The corresponding rate is described by the Michaelis-Menten function form \( \frac{pET}{g + T} \) in which \( p \) is the maximal coefficient and \( g \) is the associated constant.

Model (1) have at most three positive equilibria, and can exhibit complex phenomena including immunostimulation of tumor growth, “sneaking through” of the tumor, and formation of a tumor “dormant state”.

Following the line in this direction, Galach, in 2003, simplified model (1) by replacing the Michaelis-Menten function \( \frac{pET}{g + T} \) with a bilinear form \( pET \) from the simple mass action law[7]. Then model (1) is reduced to

\[
\begin{align*}
\frac{dT}{dt} &= rT \left( 1 - \frac{T}{K} \right) - nET, \\
\frac{dE}{dt} &= \sigma + pET - mET - \eta E = \sigma + \mu TE - \eta E,
\end{align*}
\]

where \( \mu = p - m \).

The middle two terms in the equation for \( E \) in model (1) reflect the effects of stimulation and neutralization of the tumor cells on the growth of the effector cells, respectively. Then the part \( \frac{pET}{g + T} - mET \) in model (1) can be referred to as the effect of the tumor cells on the effector cells. Thus, we refer to the parameter \( \mu \) in model (2) as the coefficient of action of the tumor cells on the effector cells. Specifically, \( \mu < 0 \) represents that, in the process of interaction between effector cells and tumor cells the neutralization of effector cells by tumor cells exceeds the stimulation; that is, the inhibiting effect of the tumor cells is dominant; on the contrary, the stimulating effect is dominant if \( \mu > 0 \). The case of \( \mu = 0 \) is trivial and thus is omitted.
Corresponding to model (1), Khajanchi and Banerjee [12] considered the tumor-immune interaction model with time delay

\[
\begin{cases}
\frac{dT(t)}{dt} = rT(t) \left(1 - \frac{T(t)}{K}\right) - nE(t)T(t), \\
\frac{dE(t)}{dt} = \sigma + \frac{pE(t-\tau)T(t-\tau)}{g + T(t-\tau)} - mE(t)T(t) - \eta E(t),
\end{cases}
\]

where the delay \( \tau \) reflects the time lag between the stimulated accumulation of effector cells in the vicinity of tumor cells, in interaction with tumor cells itself. They established the sufficient condition for local stability of the interior equilibrium, found that Hopf bifurcation occurs when the time delay passes a critical value, and estimated the length of delay to preserve stability.

In addition, Galach [7] included, in model (2), the time that develops a suitable response of effector cells after the appearance of tumor cells, which leads to the following delay differential system

\[
\begin{cases}
\frac{dT(t)}{dt} = rT(t) \left(1 - \frac{T(t)}{K}\right) - nE(t-\tau)T(t-\tau), \\
\frac{dE(t)}{dt} = \sigma + \mu T(t-\tau)E(t-\tau) - \eta E(t),
\end{cases}
\]

where \( \tau \) represents the time delay of the effector cell response after the appearance of tumor cells. In [22, 23, 24, 25], Yafia obtained the existence and stability of periodic solutions of models (2) and (4) through Hopf bifurcation. Based on models (2) and (4), Rihan et al. [18] introduced a family of ordinary differential equations (ODE) and delay differential equations (DDE) models which describe tumor-immune system interactions, and investigated bifurcations of these models to show the complexity of their dynamics. Bi and Xiao [2] also investigated the properties of Hopf bifurcated periodic solution and existence of the global Hopf bifurcation for model (4).

Further, Bi and Xiao [3] introduced the other time delay (\( \tau' \)) into model (2) to obtain the following model

\[
\begin{cases}
\frac{dT(t)}{dt} = rT(t) \left(1 - \frac{T(t)}{K}\right) - nE(t-\tau')T(t-\tau'), \\
\frac{dE(t)}{dt} = \sigma + \mu T(t-\tau)E(t-\tau) - \eta E(t),
\end{cases}
\]

and analyzed the codimension one and codimension two bifurcations, including Hopf bifurcation, steady-state bifurcation, and B-T bifurcation for model (5). Similar to models (3), (4) and (5), some discrete time delays are also included in other tumor-immune systems [1, 4, 5, 6, 13, 12, 20].

It was pointed out in [7] that, when \( \mu \geq 0 \), the solutions to model (4) are nonnegative for any nonnegative initial condition. However, there exist nonnegative initial conditions such that solution \( E(t) \) of model (4) becomes negative in a finite time interval if \( \mu < 0 \), which is evidently inconsistent with reality. For model (5), there is also the similar shortcoming.

We notice that the effects of the tumor on the immune system includes the stimulation and inhibition of the tumor for the effector cells, and the two effects are realized by the antigens released by the tumor cells.

On one hand, the antigen presenting cells of the immune system mediate the cellular immune response by processing and presenting antigens for recognition by
certain lymphocytes such as T cells, and activate the effector cells. On the other hand, the appearance of the antigens has certain negative effect on the growth of the effector cells, i.e. the effect of inhibition on the effector of cells. As is pointed in [11], the strength of the effector cell responses may be governed by antigen dose, localization, and costimulatory signals, and a fixed cumulative antigen dose was administered by different schedules to produce distinct dose-kinetics. Similar observations are also presented in [16, 17], where it shows that the immune response to cancer is determined by the balance between the antigenicity of the tumor and the microenvironment of cancer tissues. Thus, in many cases, it takes time for the tumor to progress to act on the immune system. More specifically, if we let the period of the time delay for the tumor cells to progress be $\tau$, the effector cells at time $t$ is essentially acted by the tumor cells originated at time $t - \tau$. Thus, different from models (3), (4) and (5), where it is assumed that the action from the tumor cells to the effector cells are instant but the appearance of the effects is delayed, we express the effect of the tumor cells on the effector cells by the term $\mu T(t - \tau)E(t)$. We then propose the following model for the interactive tumor cells and effector cells

\[
\begin{align*}
\frac{dT(t)}{dt} &= rT(t) \left(1 - \frac{T(t)}{K}\right) - nE(t)T(t), \\
\frac{dE(t)}{dt} &= \sigma + \mu T(t - \tau)E(t) - \eta E(t).
\end{align*}
\]

(6)

Obviously, solutions of model (6) with nonnegative initial conditions keep nonnegative for $t > 0$. If the time delay when the tumor acts on the immune system is ignored, that is, $\tau = 0$, model (6) is the same as model (2), and does not exhibit more complex dynamics such as the existence of periodic solutions produced by Hopf bifurcation. In contrast to model (2), the inclusion of the delay $\tau$ also changes the dependence of dynamics of model (6) on other parameters. Since the biological meaning of $\tau$ here is different from that in model (4), we call $\tau$ the time delay of tumor action. Accordingly, model (6) is subject to the initial condition

\[
\begin{align*}
T(\theta) &= \psi_1(\theta), \quad E(\theta) = \psi_2(\theta), \\
\psi_1(\theta) &\geq 0, \quad \theta \in [-\tau, 0], \quad \psi_1(0) > 0, \quad i = 1, 2,
\end{align*}
\]

(7)

where $(\psi_1(\theta), \psi_2(\theta)) \in \mathbb{C}([-\tau, 0], \mathbb{R}_{+0}^2)$, the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}_{+0}$ with norm $\|\psi\| = \sup_{-\tau \leq \theta \leq 0} |\psi_i(\theta)|$, $i = 1, 2$, and $\mathbb{R}_{+0}^2 = \{(x_1, x_2) | x_i \geq 0, i = 1, 2\}$.

It is easy to see that, whether $\mu > 0$ or not, model (6) with initial condition (7) can keep its solutions nonnegative for any nonnegative initial condition. The uniqueness of the solution to model (6) with initial condition (7) can be shown by using the theory of functional differential equations [9]. Our aim in this paper is to investigate the effects of the time delay $\tau$ and the interaction coefficient $\mu$ on the interactive dynamics between effector cells and tumor cells. To this end, based on the existing results on the existence and stability of equilibrium of model (2) without the time delay, we apply the bifurcation theory to discuss the local stability of equilibria of model (6) based on the characters of the corresponding characteristic equations, and determine the global stability by applying the Fluctuation Lemma and constructing different convergent sequences. The dependence of the eventual concentrations of tumor cells (corresponding to the stable tumor equilibrium) and the time delay threshold (determining the stability of the tumor equilibrium) on
tumor action is discussed theoretically. The impact of the time delay on dynamics of the model is investigated by numerical simulations. The related thresholds, which determine dynamics of the model, are expressed by certain formulas with biological meanings.

The organization of this paper is as follows. We introduce the main results for model (2) without time delay in Section 2. In Section 3, we investigate the local stability and the global stability of equilibria of model (6) and show the occurrence of Hopf bifurcation as the time delay increases. The effects of the action coefficient of the tumor cells ($\mu$) and the time delay ($\tau$) on dynamics of model (6) are analyzed in Sections 4 and 5, respectively. Finally, the biological meanings of the conditions determining the dynamics of the model are discussed.

2. Main results for model (2) without time delay. For model (2), some results have been shown in [7]. We list the main results for model (2) in Table 1 without giving details, where $P_0 = P_0 \left(0, \frac{2}{\eta} \right)$ denotes the tumor-free equilibrium, the positive equilibria $P^* = P^*(T^*, E^*)$, $P_* = P_*(T_*, E_*)$ and $P_*^* = P_*(T_*^*, E_*^*)$ all represent tumor equilibria, and

\[
T^* = \frac{K}{2\mu} \left[ \left( \mu + \frac{n}{\eta} \right) - \sqrt{\Delta} \right], \quad E^* = \frac{r}{2n\mu} \left[ \left( \mu - \frac{n}{\eta} \right) + \sqrt{\Delta} \right], \\
T_* = \frac{K}{2\mu} \left[ \left( \mu + \frac{n}{\eta} \right) + \sqrt{\Delta} \right], \quad E_* = \frac{r}{2n\mu} \left[ \left( \mu - \frac{n}{\eta} \right) - \sqrt{\Delta} \right], \\
T_*^* = \frac{K}{2\mu} \left( \mu + \frac{n}{\eta} \right), \quad E_*^* = \frac{r}{2n\mu} \left( \mu - \frac{n}{\eta} \right), \quad \Delta = \left( \mu - \frac{n}{\eta} \right)^2 + \frac{4n\sigma\mu}{K\tau}.
\]

The positive equilibria of model (2) can be found by directly solving the system

\[
\begin{cases}
    r \left( 1 - \frac{K}{\eta} \right) = nE, \\
    \sigma = (\eta - \mu T)E,
\end{cases}
\]
which is obtained by letting the right hand sides of (2) equal zeros. Their stability can be proved easily by analyzing the Jacobian matrix of model (2) at the corresponding equilibrium. That \( P^* \) is a saddle-node can be proved by means of the center manifold theory [8].

For Case C4 in Table 1, there are two tumor equilibria of model (2). Since \( T_* < T^* \), we refer to \( P_* \) as the weaker tumor equilibrium while \( P^* \) is called as the stronger tumor equilibrium.

3. Stability analysis of model (6) with time delay. It is obvious that the feasible equilibria of model (6) are the same as those of model (2). Then the existence of equilibria can be referred to Table 1. In this section, we first discuss the local stability of model (6), and then investigate the global stability in a feasible region.

3.1. Local stability of model (6). Linearizing (6) at any equilibrium \( \hat{P}(\hat{T}, \hat{E}) \) gives the system

\[
\begin{cases}
\frac{dx(t)}{dt} = \left( r - \frac{2r\hat{T}}{K} - n\hat{E} \right) x(t) - n\hat{T}y(t), \\
\frac{dy(t)}{dt} = \mu\hat{E}x(t - \tau) - (\eta - \mu\hat{T})y(t).
\end{cases}
\]  

(10)

Then the characteristic equation of (10) at the tumor-free equilibrium \( P_0 \left( 0, \frac{\eta}{\eta} \right) \) is

\[
\begin{bmatrix} \lambda - \left( r - \frac{n\sigma}{\eta} \right) \end{bmatrix} (\lambda + \eta) = 0.
\]

Therefore, \( P_0 \) is locally asymptotically stable as \( n\sigma > r\eta \), and unstable as \( n\sigma < r\eta \). This is the same as that without the time delay in Table 1.

For a tumor equilibrium \( \hat{P}(\hat{T}, \hat{E}) \) of model (6), \( \hat{T} \) and \( \hat{E} \) satisfy the system

\[
\begin{align*}
 r - \frac{\hat{c}_1}{K} - n\hat{E} &= 0, \\
 \eta - \mu\hat{T} &= \frac{\sigma}{\hat{E}},
\end{align*}
\]

which is obtained from (9). Then (10) can be rewritten as

\[
\begin{cases}
\frac{dx}{dt} = -\frac{r\hat{T}}{K} x - n\hat{T} y, \\
\frac{dy}{dt} = \mu\hat{E}x(t - \tau) - \frac{\sigma}{\hat{E}} y.
\end{cases}
\]  

(11)

By substituting \( x = c_1 e^{\lambda t} \) and \( y = c_2 e^{\lambda t} (c_1^2 + c_2^2 \neq 0) \) into the linear system (11), we can get the characteristic equation of the linear system (11) as

\[
\left( \lambda + \frac{r}{K} \hat{T} \right) \left( \lambda + \frac{\sigma}{\hat{E}} \right) + n\mu\hat{E}e^{-\lambda\tau} = 0,
\]

that is,

\[
\varphi(\lambda, \hat{T}, \hat{E}) := \lambda^2 + \left( \frac{r}{K} \hat{T} + \frac{\sigma}{\hat{E}} \right) \lambda + \hat{T} \left( \frac{r\sigma}{K\hat{E}} + n\mu\hat{E}e^{-\lambda\tau} \right) = 0.
\]  

(12)

Thus positive equilibrium \( \hat{P} \) is locally asymptotically stable if all roots of (12) have negative real parts.

Based on the representations in (8), direct calculation yields

\[
\varphi(0, T_*, E_*) = -rT_* \sqrt{\left( \mu - \frac{\eta}{K} \right)^2 + \frac{4n\sigma\mu}{K\tau}} < 0.
\]
Then, since \( \lim_{\lambda \to \infty} \varphi(\lambda, T^*_e, E^*_e) = +\infty \), there exists a positive root of equation \( \varphi(\lambda, T^*_e, E^*_e) = 0 \). Therefore, the weaker tumor equilibrium \( P_e^* \) is always unstable if it exists. This is also the same as that in Table 1.

For \( P_e^* \), the corresponding characteristic equation is

\[
\varphi(\lambda, T^*_e, E^*_e) = \lambda^2 + \left[ \frac{r}{2\mu} \left( \mu + \frac{\eta}{K} \right) + \frac{2\sigma n\mu}{r} \left( \mu - \frac{\eta}{K} \right) \right] \lambda + \frac{K r}{2} \left[ \mu^2 - \left( \frac{\eta}{K} \right)^2 \right] \left( 1 - e^{-\lambda \tau} \right).
\]

Since \( \lambda = 0 \) is a root of \( \varphi(\lambda, T^*_e, E^*_e) = 0 \), \( P_e^* \) is a higher order equilibrium. This happens rarely in reality. The further discussion is omitted.

For the stronger tumor equilibrium \( P^* \), Table 1 shows that it is locally asymptotically stable as \( \tau = 0 \). It implies that all roots of equation (12) have negative real parts for \( \tau = 0 \).

In the following, we only consider the stability of \( P^* \) for \( \tau > 0 \). As \( \tau \) varies, the stability of the tumor equilibrium \( P^* \) undergoes switches only when the transcendental equation (12) admits a pair of pure imaginary roots. Then, substituting \( \lambda = i\omega \) with \( \omega > 0 \) into (12) and separating the real and the imaginary parts, we obtain

\[
\begin{align*}
\omega^2 - \frac{r T^*_e}{K E^*} &= n\mu E^* T^* \cos(\omega \tau), \\
\left( \frac{r T^*_e}{K} + \frac{\sigma}{E^*} \right) \omega &= n\mu E^* T^* \sin(\omega \tau).
\end{align*}
\]

(13)

Squaring the two sides of (13) and then adding them up, we have

\[
F(\omega) := \omega^4 + \left[ \left( \frac{r T^*_e}{K} \right)^2 + \left( \frac{\sigma}{E^*} \right)^2 \right] \omega^2 + T^*^2 \left( \frac{r \sigma}{K E^*} + n\mu E^* \right) \left( \frac{r \sigma}{K E^*} - n\mu E^* \right) = 0.
\]

(14)

From (8) it follows that

\[
\frac{r \sigma}{K E^*} + n\mu E^* = \frac{r}{K} \sqrt{(\mu K - \eta)^2 + \frac{4n\sigma \mu K}{r}}
\]

and

\[
\frac{r \sigma}{K E^*} - n\mu E^* = -\frac{r(\mu K - \eta)}{K}.
\]

Then \( F(\omega) \) can be rewritten as

\[
F(\omega) = \omega^4 + \left( \frac{r T^*_e}{K} \right)^2 + \left( \frac{\sigma}{E^*} \right)^2 \omega^2 - \frac{r^2(\mu K - \eta) T^*^2}{K^2} \sqrt{(\mu K - \eta)^2 + \frac{4n\sigma \mu K}{r}}.
\]

(15)

Obviously, \( F(0) > 0 \) for Cases C2, C3 and C4 in Table 1 since \( \mu < 0 \). It implies that \( F(\omega) > 0 \) for Cases C2, C3 and C4. Then, for these cases, (12) has no pure imaginary roots as the time delay varies; that is, the local stability of \( P^* \) is independent of the time delay. Therefore, for these cases, \( P^* \) is absolutely stable.

When \( 0 < \mu K \leq \eta \), \( F(\omega) > 0 \) also holds for \( \omega > 0 \). Then, for Case C1, \( P^* \) is also absolutely stable when \( 0 < \mu K \leq \eta \).
For Case C1, when $\mu K > \eta$, $F(0) < 0$. It implies that $F(\omega) = 0$ has a unique positive root, denoted by $\omega_0$. Substituting $\omega = \omega_0$ into (13), we have $\sin(\omega_0 \tau) > 0$.

Further, from the first equation of (13), we obtain

$$\tau = \tau_j = \frac{1}{\omega_0} \arccos \left[ \frac{1}{\eta \mu E^* T^*} \left( \omega_0^2 - \frac{r \sigma T^*}{K E^*} \right) + \frac{2 j \pi}{\omega_0}, \quad j = 0, 1, 2, \cdots \right].$$

(16)

Therefore, when $\tau = \tau_j (j = 0, 1, 2, \cdots)$, the characteristic equation $\varphi(\lambda, T^*, E^*) = 0$ has a pair of pure imaginary roots $\pm \omega_0 t$. Thus, when $\tau$ increases and passes through $\tau = \tau_j$, the change of stability of $P^*$ is determined by the sign of $\text{Re} \left( \frac{d \lambda}{d \tau} |_{\tau = \tau_j} \right)$.

According to Theorem 4.1 in [14], $\text{Re} \left( \frac{d \lambda}{d \tau} |_{\tau = \tau_j} \right)$ has the same sign as $F'(\omega_0)$. It is obvious that $F'(\omega_0) > 0$. Then, the crossing direction is from the left to the right as $\tau$ increases and passes through $\tau = \tau_j$. Note that $\tau = \tau_0$ is the first time when the root of $\varphi(\lambda, T^*, E^*) = 0$ crosses the imaginary axis for increase of $\tau$. Then $P^*$ is locally asymptotically stable as $0 < \tau < \tau_0$ and unstable as $\tau > \tau_0$. Correspondingly, the Hopf bifurcation occurs at $\tau = \tau_0$ for model (6), and stable periodic solutions appear as $\tau > \tau_0$.

Summarizing the results above, we have the following results with respect to stability of model (6).

**Theorem 3.1.** For model (6), the tumor-free equilibrium $P_0$ is absolutely stable if $n \sigma > r \eta$ and unstable if $\sigma < r \eta$; the weaker tumor equilibrium $P_*$ (if it exists) is always unstable; the tumor equilibrium $P^*$ (if it exists) is absolutely stable as $\mu < 0$ or $0 < \mu K \leq \eta$, locally asymptotically stable as $\mu K > \eta$ and $\tau < \tau_0$, and unstable as $\mu K > \eta$ and $\tau > \tau_0$.

3.2. **Global stability of model (6).** In this section, we investigate the global stability of the tumor-free equilibrium $P_0$ and the tumor equilibrium $P^*$. Since their local stability has been obtained in the last subsection, it suffices to show that they are respectively globally attractive in the feasible region under the corresponding conditions.

To prove their attractiveness, we apply different methods for $P_0$ and $P^*$. For $P_0$, the fluctuation lemma in [10] is used. For $P^*$, its attractiveness is obtained via constructing a convergent sequences by the iteration technique, which generalizes the method in [21]. In [21], the Squeeze Theorem determining the convergence of a sequence is used. Here, the Monotone Boundedness Criterion is also applied in addition to the Squeeze Theorem since the structure of model (6) is different from those in [21].

Before proving the global stability of $P_0$, we first state the following Fluctuation Lemma from [10].

**Lemma 3.2.** Let $f : (t_0, \infty) \rightarrow R$ be bounded and continuously differentiable. Then there are sequences $t_n, s_n \rightarrow \infty$ with the following properties:

$$f(t_n) \rightarrow f^{\infty}, \quad f'(t_n) \rightarrow 0; \quad f(s_n) \rightarrow f_{\infty}, \quad f'(s_n) \rightarrow 0,$$

as $n \rightarrow \infty$, where

$$f^{\infty} = \limsup_{t \rightarrow \infty} f(t) \quad \text{and} \quad f_{\infty} = \liminf_{t \rightarrow \infty} f(t).$$

For the global stability of $P_0$, we have the following results.

**Theorem 3.3.** For model (6), the tumor-free equilibrium $P_0$ is globally asymptotically stable in the feasible region when one of the following conditions holds:
(i) \( \mu > 0 \) and \( n\sigma > r\eta \);
(ii) \( \mu < 0, \eta + \mu K \geq 0 \) and \( n\sigma \geq r\eta \);
(iii) \( \mu < 0, \eta + \mu K < 0 \) and \( n\sigma > -\frac{rK}{\eta} (\mu - \frac{\eta}{K})^2 \).

**Proof.** We discuss the globally asymptotical stability of \( P_0 \) for \( \mu > 0 \) and \( \mu < 0 \), respectively.

(i) When \( \mu > 0 \), from the second equation of model (6) we have \( E' \geq \sigma - \eta E \) due to the nonnegativeness of solutions. It follows that \( \lim \inf_{t \to \infty} E(t) \geq \frac{\sigma}{\eta} \). Therefore, when \( n\sigma > r\eta \), for number \( \varepsilon \) satisfying \( 0 < \varepsilon < \sigma - \frac{r\eta}{\eta} \), there is \( t_0 > 0 \) such that \( E(t) > \frac{\sigma - \varepsilon}{\eta} \) for \( t > t_0 \).

Further, for \( t > t_0 \), from the first equation of model (6) it follows that
\[
\frac{dT}{dt} \leq T \left[ r \left( 1 - \frac{T}{K} \right) - \frac{n(\sigma - \varepsilon)}{\eta} \right] \leq \left[ r - \frac{n(\sigma - \varepsilon)}{\eta} \right] T = \frac{n}{\eta} \left[ \varepsilon - \left( \sigma - \frac{r\eta}{\eta} \right) \right] T.
\]
That \( \varepsilon < \sigma - \frac{r\eta}{\eta} \) implies that \( \lim_{t \to \infty} T(t) = 0 \). Again, applying \( \lim_{t \to \infty} E(t) = \frac{\sigma}{\eta} \) by the theory of limit system [19]. Hence, when \( \mu > 0 \) and \( n\sigma > r\eta \), \( P_0 \) is globally attractive. Therefore, the local stability of \( P_0 \) implies its global stability if \( \mu > 0 \) and \( n\sigma > r\eta \).

(ii) For the case \( \mu < 0 \), we apply the Fluctuation Lemma 3.2 to prove the attractiveness of \( P_0 \).

When \( \mu < 0 \), according to the nonnegativeness of solutions of model (6), we have
\[
\frac{dT}{dt} \leq r T \left( 1 - \frac{T}{K} \right), \quad \text{and} \quad \frac{dE}{dt} \leq \sigma - \eta E.
\]
Then \( \lim \sup_{t \to \infty} T(t) \leq K \) and \( \lim \sup_{t \to \infty} E(t) \leq \frac{\sigma}{\eta} \). It implies that model (6) is bounded eventually for \( \mu < 0 \).

By Lemma 3.2 it follows that there exist two sequences \( \{t_n\} \) and \( \{s_n\} \) such that
\[
\lim_{n \to \infty} t_n = \infty, \quad \lim_{n \to \infty} T(t_n) = T, \quad \lim_{n \to \infty} \frac{dT(t_n)}{dt} = 0;
\]
\[
\lim_{n \to \infty} s_n = \infty, \quad \lim_{n \to \infty} E(s_n) = T, \quad \lim_{n \to \infty} \frac{dE(s_n)}{dt} = 0. \tag{17}
\]
From (6), we have
\[
\frac{dT(t_n)}{dt} = T(t_n) \left[ r \left( 1 - \frac{T(t_n)}{K} \right) - nE(t_n) \right],
\]
\[
\frac{dE(s_n)}{dt} = \sigma + \mu T(s_n - \tau) E(s_n) - \eta E(s_n).
\]
Then, letting \( n \to \infty \), from (17) and (18) we have
\[
0 \leq T \left[ r \left( 1 - \frac{T}{K} \right) - nE \right], \tag{19}
\]
\[
0 \geq \sigma + \mu T E - \eta E.
\]
We claim that \( T = 0 \). If not, \( T > 0 \) since \( 0 \leq T \leq K \). It follows from the first inequality of (19) that
\[
nE \leq r \left( 1 - \frac{T}{K} \right).
\]
Further, from the second inequality of (19) it follows that
\[ n\sigma + r (\mu T^\infty - \eta) \left( 1 - \frac{T^\infty}{K} \right) \leq 0. \] (20)

Note that, when either of the conditions (ii) and (iii) in Theorem 3.3 holds, the quadratic function of \( T, n\sigma + r (\mu T - \eta) \left( 1 - \frac{T}{K} \right) \), is positive in the interval \((0, K]\). Then inequality (20) does not hold under either of the conditions (ii) and (iii). Therefore, the claim is true. It implies that \( \lim_{t \to \infty} T(t) = 0 \).

Further, applying \( \lim_{t \to \infty} T(t) = 0 \) to the second equation of model (6), we can easily get \( \lim_{t \to \infty} E(t) = \frac{\sigma}{n} \) by the theory of limit system [19]. Therefore, for the cases (ii) and (iii), the local stability of \( P_0 \) also implies its global stability.

The proof of Theorem 3.3 is complete.

With respect to the global stability of \( P^* \) of model (6), we have the following results.

**Theorem 3.4.** The tumor equilibrium \( P^* \) of model (6) is globally asymptotically stable if either of the following two conditions holds: (i) \( \eta > \mu K > 0 \) and \( n\sigma < r\eta \); (ii) \( \mu < 0 \) and \( n\sigma < r\eta \).

In order to prove the global attractiveness of the tumor equilibrium \( P^* \) of model (6) under the conditions of Theorem 3.4, we need to construct two different convergent sequences corresponding to the two cases, \( \mu > 0 \) and \( \mu < 0 \), by the iteration technique. In the following, we define the two convergent sequences with the same general term but different first terms, and describe their properties with two lemmas. Since the proofs of the two lemmas are tedious, we put them in Appendix.

**Lemma 3.5.** Suppose \( n\sigma < r\eta \). Then the two sequences \( \{\tilde{T}_m\} \) and \( \{\tilde{E}_m\} \) \((m = 0, 1, 2, \cdots)\), defined by
\[
\tilde{E}_0 = \frac{\sigma}{\eta}, \quad \tilde{T}_m = K \left( 1 - \frac{n\tilde{E}_m}{r} \right), \quad \tilde{E}_{m+1} = \frac{\sigma}{\eta - \mu \tilde{T}_m},
\]
have the following properties.
(i) When \( 0 < \mu K < \eta \),
\[
0 < \tilde{T}_m < K \left( 1 - \frac{n\sigma}{r\eta} \right) < \frac{\eta}{\mu} \left( 1 - \frac{n\sigma}{r\eta} \right) < \frac{\eta}{\mu} < \tilde{E}_m < \frac{r}{n}, \quad m = 1, 2, \cdots.
\]
(ii) When \( \mu < 0 \),
\[
\tilde{T}_m > 0, \quad 0 < \tilde{E}_m < \frac{\sigma}{\eta} < \frac{r}{n}, \quad m = 1, 2, \cdots.
\]
(iii) For \( 0 < \mu K < \eta \) or \( \mu < 0 \),
\[
\lim_{m \to \infty} \tilde{T}_m = T^*, \quad \lim_{\mu \to \infty} \tilde{E}_m = E^*,
\]
where \( T^* \) and \( E^* \) are the corresponding coordinates of \( P^* \).

**Lemma 3.6.** When \( n\sigma < r\eta \) and \( \mu < 0 \), the two sequences \( \{\tilde{T}_m\} \) and \( \{\tilde{E}_m\} \) \((m = 0, 1, 2, \cdots)\), defined by
\[
\tilde{T}_0 = K, \quad \tilde{E}_0 = \frac{\sigma}{\eta - \mu \tilde{T}_1}, \quad \tilde{T}_{m+1} = K \left( 1 - \frac{n\tilde{E}_m}{r} \right), \quad \tilde{E}_{m+1} = \frac{\sigma}{\eta - \mu \tilde{T}_m},
\]

have the following properties.
have the following properties:

\[ \tilde{T}_m' > 0, \quad 0 < \tilde{E}_m' < \frac{\sigma}{\eta} < \frac{r}{n}, \]

and

\[ \lim_{m \to \infty} \tilde{T}_m' = T^*, \quad \lim_{\mu \to \infty} \tilde{E}_m' = E^*, \]

where \( T^* \) and \( E^* \) are the corresponding coordinates of \( P^* \).

**Proof of Theorem 3.4.** (i) When \( \mu > 0 \), from the second equation of model (6) we have \( E' \geq \sigma - \eta E \) due to the nonnegativeness of solutions of model (6). It follows that \( \liminf_{t \to \infty} E(t) \geq \frac{\sigma}{\eta} \). Then, for \( \varepsilon > 0 \), sufficiently small, there is \( t_0 > 0 \) such that \( E(t) > \frac{\sigma}{\eta} - \varepsilon := E_0(\varepsilon) \) for \( t > t_0 \).

Next, from the first equation of model (6) it follows that, for \( t > t_0 \),

\[ T' \leq T \left[ r \left( 1 - \frac{T}{K} \right) - nE_0(\varepsilon) \right] = \frac{rT}{K} \left[ \tilde{T}_0(\varepsilon) - T \right], \]

where \( \tilde{T}_0(\varepsilon) = K \left[ 1 - \frac{2E_0(\varepsilon)}{r} \right] \). Note that \( \lim_{\varepsilon \to 0} \tilde{T}_0(\varepsilon) = \tilde{T}_0 \in \left( 0, \frac{r}{2} \right) \) for \( n\sigma < r\eta \) and \( \eta > \mu K > 0 \), where \( \tilde{T}_0 \) is defined in (21). Then there is \( \varepsilon \), sufficiently small, such that \( \tilde{T}_0(\varepsilon) \in \left( 0, \frac{r}{2} \right) \). It follows that \( \limsup_{t \to \infty} T(t) \leq \tilde{T}_0(\varepsilon) \). Hence, there is \( t_0' \) (\( t_0' > t_0 \)) such that \( T(t) < \tilde{T}_0(\varepsilon) + \varepsilon := T_0(\varepsilon) \) for \( t > t_0' \).

Again, for \( t > t_0' + \tau \), from the second equation of (6) we have

\[ E' \leq \sigma - [\eta - \mu T_0(\varepsilon)] E = [\eta - \mu T_0(\varepsilon)] \left[ \tilde{E}_1(\varepsilon) - E \right], \]

where \( \tilde{E}_1(\varepsilon) = \frac{\sigma}{\eta - \mu T_0(\varepsilon)} \). Here, \( \lim_{\varepsilon \to 0} \tilde{E}_1(\varepsilon) = \tilde{E}_1 \in \left( \frac{\sigma}{\eta}, \frac{r}{2} \right) \), where \( \tilde{E}_1 \) is defined in (21). Similarly, there is a \( t_1 \) (\( t_1 > t_0' + \tau \)) such that \( E(t) < \tilde{E}_1(\varepsilon) + \varepsilon := E_1(\varepsilon) \) for \( t > t_1 \).

Further, for \( t > t_1 \), we get from the first equation of (6)

\[ T' \geq T \left[ r \left( 1 - \frac{T}{K} \right) - nE_1(\varepsilon) \right] = \frac{rT}{K} \left[ \tilde{T}_1(\varepsilon) - T \right], \]

where \( \tilde{T}_1(\varepsilon) = K \left[ 1 - \frac{nE_1(\varepsilon)}{r} \right] \). Similarly, there is \( t_1' \) (\( t_1' > t_1 \)) such that \( T(t) > \tilde{T}_1(\varepsilon) - \varepsilon := T_1(\varepsilon) \) for \( t > t_1' \).

So far, we get \( E_0(\varepsilon), T_0(\varepsilon), E_1(\varepsilon) \) and \( T_1(\varepsilon) \). Repeating the above process we can get the two sequences \( \{ E_m(\varepsilon) \} \) and \( \{ T_m(\varepsilon) \} \) \( (m = 0, 1, 2, \cdots) \). According to the process obtaining the two sequences, for given \( \varepsilon \), sufficiently small, and the corresponding sufficiently large \( t' \), we have, for \( t > t' \),

\[ cE_{2m}(\varepsilon) < E(t) < E_{2m+1}(\varepsilon), \]

\[ T_{2m+1}(\varepsilon) < T(t) < T_{2m}(\varepsilon), \]

\[ m = 0, 1, 2, \cdots. \] (23)

Note that \( \varepsilon \) is arbitrarily sufficiently small, and that \( \lim_{\varepsilon \to 0} E_m(\varepsilon) = \bar{E}_m \) and \( \lim_{\varepsilon \to 0} T_m(\varepsilon) = \bar{T}_m \), where \( \bar{E}_m \) and \( \bar{T}_m \) are defined in (21). Then, from (23) it follows that

\[ \bar{E}_{2m} \leq \liminf_{t \to \infty} E(t) \leq \limsup_{t \to \infty} E(t) \leq \bar{E}_{2m+1}, \]

\[ \bar{T}_{2m+1} \leq \liminf_{t \to \infty} T(t) \leq \limsup_{t \to \infty} T(t) \leq \bar{T}_{2m}, \]

\[ m = 0, 1, 2, \cdots. \] (24)
Lemma 3.5 shows that \( \lim_{m \to \infty} \hat{E}_m = E^* \) and \( \lim_{m \to \infty} \hat{T}_m = T^* \). Then it follows that

\[
\lim_{t \to \infty} E(t) = E^* \quad \text{and} \quad \lim_{t \to \infty} T(t) = T^* \quad \text{according to (24)}.
\]

That is, \( P^* \) is globally attractive.

Therefore, the local stability of \( P^* \) implies that \( P^* \) is globally asymptotically stable as \( n\sigma < r\eta \) and \( \eta > \mu K > 0 \).

(ii) When \( \mu < 0 \), by the derivation similar to the above case that \( \mu > 0 \), for the same two sequences \( \{E_m(\varepsilon)\}\) and \( \{T_m(\varepsilon)\} \) \( (m = 0, 1, 2, \ldots) \), we know that there is a \( t'_m > t_m \) such that \( E(t) < E_m(\varepsilon) \) and \( T(t) > T_m(\varepsilon) \) for \( t > t'_m \). Thus, since \( \varepsilon \) is arbitrarily sufficiently small, we have \( E(t) \leq \hat{E}_m \) and \( T(t) \geq \hat{T}_m \). Further, it follows that

\[
\limsup_{t \to \infty} E(t) \leq E^* \quad \text{and} \quad \liminf_{t \to \infty} T(t) \geq T^* \quad \text{since} \quad \lim_{m \to \infty} \hat{E}_m = E^* \quad \text{and} \quad \lim_{m \to \infty} \hat{T}_m = T^* \quad \text{by Lemma 3.6.}
\]

On the other hand, in order to get \( \lim \inf_{t \to \infty} E(t) \geq E^* \) and \( \lim \sup_{t \to \infty} T(t) \leq T^* \), we construct other two sequences \( \{E'_m(\varepsilon)\}\) and \( \{T'_m(\varepsilon)\} \) \( (m = 0, 1, 2, \ldots) \) as follows.

From the first equation of model (6) we have \( T' \leq r T \left( 1 - \frac{T}{K} \right) \). It follows that

\[
\limsup_{t \to \infty} T(t) \leq K.
\]

Then, for \( \varepsilon > 0 \), sufficiently small, there is a \( t_0 > 0 \) such that \( T(t) < K + \varepsilon := t_0 \) for \( t > t_0 \).

For \( \mu < 0 \), from the second equation of model (6) we have, for \( t > t_0 + \tau \),

\[
E' \geq \frac{\eta}{\mu T_0^*} - \frac{\eta}{\mu T_0^*} \frac{[\hat{E}_0^*(\varepsilon) - E]}{[\hat{E}_0^*(\varepsilon) - \hat{E}_0^*(\varepsilon)]},
\]

where \( \hat{E}_0^*(\varepsilon) = \frac{\eta}{\mu T_0^*} \). Note that \( \lim_{t \to \infty} \hat{E}_0^*(\varepsilon) = \hat{E}_0^* \) with \( 0 < \hat{E}_0^* < \frac{\eta}{\mu} \), where \( \hat{E}_0^* \) is defined in (22).

Then there is \( \varepsilon_0 \), sufficiently small, such that \( \hat{E}_0^*(\varepsilon) \leq \frac{\eta}{\mu} \).

It follows that \( \liminf_{t \to \infty} E(t) \geq \hat{E}_0^*(\varepsilon) \).

Thus, there is \( t_0 \) \( (t_0 > t_0) \) such that \( E(t) > \hat{E}_0^*(\varepsilon) \).

Further, for \( t > t_0 + \tau \), we get from the first equation of (6)

\[
T' \leq T \left[ r \left( 1 - \frac{T}{K} \right) - n E'(\varepsilon) \right] = \frac{r T}{K} \left[ \hat{T}_1(\varepsilon) - T \right],
\]

where \( \hat{T}_1(\varepsilon) = K \left[ 1 - \frac{n \hat{E}_0^*(\varepsilon)}{\tau} \right] \). Similarly, there is \( t_1 \) \( (t_1 > t_0) \) such that \( T(t) < \hat{T}_1(\varepsilon) + \varepsilon := T_1(\varepsilon) \) for \( t > t_1 \).

Again, for \( t > t_1 + \tau \), from the second equation of (6) we have

\[
E' \geq \frac{\eta}{\mu T_1^*(\varepsilon)} - \frac{\eta}{\mu T_1^*(\varepsilon)} \frac{[\hat{E}_1^*(\varepsilon) - E]}{[\hat{E}_1^*(\varepsilon) - \hat{E}_1^*(\varepsilon)]},
\]

where \( \hat{E}_1^*(\varepsilon) = \frac{\eta}{\mu T_1^*(\varepsilon)} \). Repeating the above process, there is a \( t_1 \) \( (t_1 > t_1) \) such that \( E(t) > \hat{E}_1^*(\varepsilon) \).

Thus, we get \( T_0^*(\varepsilon), T_1^*(\varepsilon), T_2^*(\varepsilon) \) and \( E_0^*(\varepsilon) \). Continuing in this manner, we can get the two sequences \( \{T_0^*(\varepsilon)\} \) and \( \{E_0^*(\varepsilon)\} \) \( (m = 0, 1, 2, \ldots) \), and there is \( t_m \) such that

\[
E(t) > E_m(\varepsilon) \quad \text{and} \quad T(t) < T_m(\varepsilon) \quad \text{for} \quad t > t_m.
\]

It implies that \( \liminf_{t \to \infty} E(t) \geq E_m(\varepsilon) \) and \( \limsup_{t \to \infty} T(t) \leq T_m(\varepsilon) \). Since \( \varepsilon \) is arbitrarily sufficiently small, we have that \( \liminf_{t \to \infty} E(t) \geq \hat{E}_m^* \) and \( \limsup_{t \to \infty} T(t) \leq \hat{T}_m^* \), where \( \hat{E}_m^* \) and \( \hat{T}_m^* \) are defined in (22).

Note that Lemma 3.6 shows that \( \lim_{m \to \infty} \hat{E}_m^* = E^* \) and \( \lim_{m \to \infty} \hat{T}_m^* = T^* \).

Then, \( \liminf_{t \to \infty} E(t) \geq E^* \) and \( \limsup_{t \to \infty} T(t) \leq T^* \).

By constructing the two different sequences, the above inferences have shown that \( \limsup_{t \to \infty} E(t) \leq E^* \) and \( \liminf_{t \to \infty} T(t) \geq T^* \), and that \( \liminf_{t \to \infty} E(t) \geq E^* \) and \( \limsup_{t \to \infty} T(t) \leq T^* \). Therefore, \( \lim_{t \to \infty} E(t) = E^* \) and \( \lim_{t \to \infty} T(t) = T^* \).

This completes the proof of Theorem 3.4. \qed
4. Impact of the time delay of tumor action and numerical simulation.

In this section, we illustrate the effect of the time delay of tumor action on model (6) when there is a tumor equilibrium, and show the dynamical behavior of (6) by numerical simulations. The following discussion is considered for the three cases: (i) $\mu K > \eta$, (ii) $0 < \mu K < \eta$, and (iii) $\mu < 0$.

The structure of model (6) shows that the existence of its equilibria is independent of the time delay, and the results obtained in the previous section illustrate that the time delay can affect the stability of model (6) only when $\mu K > \eta$ and $n\sigma < r\eta$ such that the tumor equilibrium $P^*$ exists. That is, under the condition that $\mu K > \eta$ and $n\sigma < r\eta$, there is $\tau_0$ (defined in (16)) such that $P^*$ is stable as $\tau < \tau_0$ and unstable as $\tau > \tau_0$. Here, Hopf bifurcation occurs for model (6) as $\tau$ increases and crosses $\tau_0$. Correspondingly, a stable periodic solution appears for $\tau > \tau_0$ (Figure 1), and the bifurcation diagram of model (6) is displayed in Figure 2. In Figures 1 and 2, the values of parameters of model (6) are $r = 2.5$, $K = 2$, $n = 0.8$, $\sigma = 0.5$, $\mu = 4$, and $\eta = 1.5$. These parameter values satisfy the conditions $\mu K > \eta$ and $n\sigma < r\eta$. In this case, the tumor equilibrium is $P^*(0.3272, 2.6138)$, and the threshold determining the stability of $P^*$ is $\tau_0 = 0.1943$ from (16). In Figure 1, $\tau = 0.3$. Figure 2 shows that, when $\tau > \tau_0$, the amplitude of the periodic solution increases with the time delay.

When $0 < \mu < \frac{r}{\eta}$, the tumor equilibrium $P^*$ is absolutely stable by Theorem 3.1 if it exists (i.e. $n\sigma < r\eta$). By taking three different values of the time delay, $\tau = 1, 5, 10$, respectively, Figure 3 shows that the delay slows convergence of solutions to $P^*$ of model (6). Here, $r = 2.5$, $K = 2$, $n = 0.8$, $\sigma = 0.5$, $\mu = 0.4$ and $\eta = 1.5$, and model (6) has a unique tumor equilibrium $P^*(1.6238, 0.5879)$ which is globally asymptotically stable.
Figure 2. The bifurcation diagram of model (6) with respect to the time delay $\tau$ when $\mu K > \eta$ and $n \sigma < r \eta$. Here, except for the time delay $\tau$, the values of other parameters are the same as those for Figure 1.

Figure 3. The trajectories of $T = T(t)$ and $E = E(t)$ of model (6) corresponding to three delays $\tau = 1, 5, 10$ in case of $0 < \mu < \frac{2}{K}$ and $n \sigma < r \eta$, respectively. Other parameter values are $r = 2.5, K = 2, n = 0.8, \sigma = 0.5, \mu = 0.4$ and $\eta = 1.5$.

For the case $\mu < 0$, Theorem 3.1 shows that the time delay does not affect the stability of equilibria of model (6), but, similarly as in the case $0 < \mu < \frac{2}{K}$, it could play a role affecting the convergence of solutions of (6). Here, we display the effects of the delay on solutions of model (6) only for Case C4 in Table 1; that is, there are two tumor equilibria $P^*$ and $P_*$ of model (6) (Figure 4). For Figure 4, $r = 2.5, K = 4, n = 0.8, \sigma = 6.2, \mu = -1.2$ and $\eta = 1.5$, which satisfy the condition.
C4 in Table 1. Corresponding to the set of parameter values, model (6) has two positive equilibria $P^*(1.9016, 1.6394)$ and $P_*(0.8484, 2.4622)$ with $P^*$ stable and $P_*$ unstable. In this case, where the tumor cells neutralizes the effector cells and model (6) has two tumor equilibria, a number of numerical simulations also show that the delay slows the convergence of solution to $P^*$ of model (6). Figure 4 displays the orbits of model (6) corresponding to the different values of delay $\tau$, where the left column is for $\tau = 0.3$, the right column is for $\tau = 2.0$.

![Image](image_url)

**Figure 4.** The trajectories of model (6) with two delays $\tau = 0.3, 2.0$ in Case C4 of Table 1, where the left column is for $\tau = 0.3$, the right column is for $\tau = 2.0$, and the initial conditions of model (6) are the same in the two columns. The first row is the orbits of model (6) in the $T$-$E$ plane, the second row is the trajectories of $T = T(t)$, and the third row is those of $E = E(t)$.

The numerical simulations above show that the time delay of tumor action can slow the convergence of tumor cells to the steady state when the tumor equilibrium $P^*$ is stable, and can increase the amplitude of the periodic solution as the periodic solution appears.

5. **Impact of the tumor action coefficient.** In model (6), the effect of the tumor cells on the immune system is reflected by two parameters, the action coefficient of the tumor cells on the effector cells ($\mu$) and the time delay of tumor action ($\tau$). In the last section, we have discussed the effect of the time delay ($\tau$) on dynamics of model (6) by numerical simulation. In this section, we theoretically investigate the impact of the tumor action coefficient ($\mu$). Its impact is discussed in two respects.
One is on the concentrations of the tumor cells and the effector cells at the steady state (i.e. the eventual concentrations), and the other is on the time delay threshold determining the stability of the tumor equilibrium \( P^* \). The impacts are shown by the following two propositions.

**Proposition 1.** For the tumor equilibrium \( P^*(T^*, E^*) \), \( T^* \) is deceasing with \( \mu \), whereas \( E^* \) is increasing with \( \mu \).

**Proof.** Note that \( E^* = \frac{r}{n} \left( 1 - \frac{T^*}{K} \right) \). Then, it suffices to prove that \( T^* = T^*(\mu) \) is decreasing with \( \mu \).

The expression of \( T^* \) in (8) can be rewritten as
\[
T^*(\mu) = \frac{2(\eta r - n\sigma)}{2\phi(\mu)},
\]
where \( \phi(\mu) = (\mu + \frac{n}{K}) + \sqrt{(\mu - \frac{n}{K})^2 + \frac{4n\sigma \mu}{K\tau}}. \) Direct calculation gives
\[
\frac{d\phi}{d\mu} = 1 + \frac{(\mu - \frac{n}{K}) + \frac{2n\sigma}{K\tau}}{\sqrt{(\mu - \frac{n}{K})^2 + \frac{4n\sigma \mu}{K\tau}}}
\]

When \( \mu > 0 \), from \( |\mu - \frac{n}{K}| < \sqrt{(\mu - \frac{n}{K})^2 + \frac{4n\sigma \mu}{K\tau}} \) it follows that \( \phi'(\mu) > 0 \). Then \( T^*(\mu) < 0 \) for \( \mu > 0 \) and \( n\sigma < \eta r \), which responds to Case C1 in Table 1.

When \( \mu < 0 \), we reexpress \( \phi'(\mu) \) as
\[
\frac{d\phi}{d\mu} = \frac{\hat{\phi}(\mu)}{\sqrt{(\mu - \frac{n}{K})^2 + \frac{4n\sigma \mu}{K\tau}}},
\]
where
\[
\hat{\phi}(\mu) = \sqrt{(\mu - \frac{n}{K})^2 + \frac{4n\sigma \mu}{K\tau} + (\mu - \frac{n}{K}) + \frac{2n\sigma}{K\tau}}
\]
\[
= \frac{2n\sigma}{K\tau} \cdot \sqrt{(\mu - \frac{n}{K})^2 + \frac{4n\sigma \mu}{K\tau} - (\mu - \frac{n}{K}) - (\mu - \frac{n}{K})^2}
\]

It is obvious that \( \hat{\phi}(\mu) > 0 \) when \( \frac{n}{K} + \mu \geq 0 \), which responds to Case C2 in Table 1. Therefore, that \( T^*(\mu) < 0 \) holds for Case C2 since \( \hat{\phi}(\mu) > 0 \) implies that \( \phi'(\mu) > 0 \).

Note that
\[
\left[ \sqrt{(\mu - \frac{n}{K})^2 + \frac{4n\sigma \mu}{K\tau}} \right]^2 - \left( \mu + \frac{n}{K} \right)^2 = \frac{4\mu(n\sigma - r\eta)}{K\tau}.
\]
Then, for \( \mu + \frac{n}{K} < 0 \) and \( n\sigma < r\eta \), the last expression is positive. It implies that \( \hat{\phi}(\mu) > 0 \). Thus, \( T^*(\mu) < 0 \) for Case C3 in Table 1.

When \( \mu + \frac{n}{K} < 0 \) and \( n\sigma > r\eta \), the expression (25) is negative; that is, \( \phi'(\mu) < 0 \) for Case C4 in Table 1. Further, \( n\sigma > r\eta \) implies that \( T^*(\mu) < 0 \) also holds for Case C4 in Table 1.

The above inference shows that, no matter \( \mu > 0 \) or not, \( T^*(\mu) < 0 \) as \( P^* \) exists. Therefore, \( T^* \) decreases as \( \mu \) increases.

The proof of Proposition 1 is complete.
According to Theorem 3.1, $\tau_0$ is a threshold determining the stability of the tumor equilibrium $P^*$ as $\mu K > \eta$ and $n \sigma < r \eta$. It is evident that the value of $\tau_0$ depends on $\mu$. With respect to the dependence of $\tau_0$ on $\mu$, we have the following results.

**Proposition 2.** When $n \sigma < r \eta$ and $\mu K > \eta$, $\tau_0$ defined in (16) is decreasing with $\mu$.

**Proof.** Note that $n \sigma < r \eta$ assures the existence of the tumor equilibrium $P^*$ of model (6), and $\mu K > \eta$ makes equation (14) have a positive root, $\omega_0$. In order to show that $d \tau_0 / d \mu < 0$, we first prove that $d \omega_0 / d \mu > 0$ and $d^2 / d \mu \left( \frac{\omega_0^2}{n \mu E^* T^*} \right) > 0$ when $n \sigma < r \eta$ and $\mu K > \eta$, where $\omega_0$ is determined by (14).

By the Implicit Function Theorem, the derivative of function $\omega_0(\mu)$ determined by (14) is given by

$$\frac{d \omega_0(\mu)}{d \mu} = -\frac{\omega_0^2 \frac{d}{d \mu} \left( \left( \frac{r \sigma T^*}{K E^*} \right)^2 + \left( \frac{\sigma}{E^*} \right)^2 \right) + \frac{d}{d \mu} \left( \frac{T^*}{n \mu E^* T^*} \left( \frac{\omega_0^2}{n \mu E^* T^*} \right)^2 \right)}{2 \omega_0^2 \left( \frac{r \sigma T^*}{K E^*} \right)^2 + 2 \left( \frac{\omega_0}{n \mu E^* T^*} \right)^2 - \left( \frac{\omega_0}{n \mu E^* T^*} \right)^2}.$$  \hspace{1cm} (26)

Since $\mu E^* T^* = \eta E^* - \sigma$ according to the second equation of (9), then

$$T^* \left( \frac{r \sigma}{K E^*} \right)^2 - (n \mu E^*)^2 = \left( \frac{r \sigma T^*}{K E^*} \right)^2 - n^2 (\eta E^* - \sigma)^2.$$

Thus, by Proposition 1 we can see from (26) that $d \omega_0(\mu) / d \mu > 0$.

On the other hand, equation (14) can be rewritten as

$$\left( \frac{\omega_0^2}{n \mu E^* T^*} \right)^2 + \frac{1}{n \mu E^* T^*} \left( \frac{r T^*}{K} \right)^2 + \left( \frac{\sigma}{E^*} \right)^2 \left( \frac{\omega_0^2}{n \mu E^* T^*} \right)$$

$$+ \left( \frac{r \sigma}{n \mu K E^* T^*} \right)^2 - 1 = 0.$$

Applying again $\mu E^* T^* = \eta E^* - \sigma$ to the last equation yields

$$\left( \frac{\omega_0^2}{n \mu E^* T^*} \right)^2 + \frac{1}{n (\eta E^* - \sigma)} \left( \frac{r T^*}{K} \right)^2 + \left( \frac{\sigma}{E^*} \right)^2 \left( \frac{\omega_0^2}{n \mu E^* T^*} \right)$$

$$+ \left( \frac{r \sigma}{n \mu K E^* T^*} \right)^2 - 1 = 0.$$  \hspace{1cm} (27)

Similarly as in calculating the derivation of $d \omega_0(\mu) / d \mu > 0$, from (27) it can be found that $d / d \mu \left( \frac{\omega_0^2}{n \mu E^* T^*} \right) > 0$. For

$$\tau_0 = \frac{1}{\omega_0} \arccos \left( \frac{\omega_0^2}{n \mu E^* T^*} \left( \omega_0^2 - \frac{r \sigma T^*}{K E^*} \right) \right) = \frac{1}{\omega_0} \arccos \left( \frac{\omega_0^2}{n \mu E^* T^*} - \frac{r \sigma}{n \mu K E^* T^*} \right),$$

it is easy to know that $d \tau_0 / d \mu < 0$ by Proposition 1 and $d \omega_0 / d \mu > 0$ and $d / d \mu \left( \frac{\omega_0^2}{n \mu E^* T^*} \right) > 0$.

This completes the proof of Proposition 2. \hfill $\Box$

Up to now, we have known the monotonicity of $T^*$, $E^*$ and $\tau_0$ with respect to $\mu$ when $n \sigma < r \eta$ and $\mu K > \eta$. Further, by a straightforward calculation, we can get
the following limits

\[
\lim_{\mu \to \eta} T^* = K \left(1 - \sqrt{\frac{n\sigma}{r\eta}} \right), \quad \lim_{\mu \to \infty} T^* = 0;
\]

\[
\lim_{\mu \to \eta} E^* = \frac{r}{n} \sqrt{\frac{n\sigma}{r\eta}}, \quad \lim_{\mu \to \infty} E^* = \frac{r}{n}.
\]

It follows from (14) and (15) we have

\[
\lim_{\mu \to \eta} \omega_0 = 0, \quad \lim_{\mu \to \infty} \omega_0 = \sqrt{\Theta},
\]

where \(\Theta = \frac{1}{2} \left[ \left(\frac{n\sigma}{r}\right)^4 + 4r^2 \left(\eta - \frac{n\sigma}{r}\right)^2 - \left(\frac{n\sigma}{r}\right)^2 \right],\) since

\[
\lim_{\mu \to \eta} [(\mu K - \eta)T^*] = 0, \quad \lim_{\mu \to \infty} [(\mu K - \eta)T^*] = K \left(\eta - \frac{n\sigma}{r}\right).
\]

Thus, from (16) it follows that

\[
\lim_{\mu \to \eta} \tau_0 = +\infty, \quad \lim_{\mu \to \infty} \tau_0 = \frac{1}{\sqrt{\Theta}} \arccos \frac{\Theta}{r\eta - n\sigma}.
\]

The above results including the monotonicity of \(T^*\) and \(E^*\) with respect to \(\mu\) and the related limit can be verified by numerical simulation. The relation between \(\tau_0\) and \(\mu\) can also be used to determine the stability of the tumor equilibrium \(P^*\) for a given \(\tau\). The graph of the curve \(\tau_0 = \tau_0(\mu)\) is displayed in Figure 5. That is, fixing the values of parameters \(r, K, n, \sigma\) and \(\eta\) (except for \(\mu\)) satisfying \(n\sigma < r\eta\), and letting \(\mu\) increase from \(\frac{\eta}{K}\), the curve of \(\tau_0 = \tau_0(\mu)\) divides the region \(D = \{(\mu, \tau) : \mu > \frac{\eta}{K}, \tau > 0\}\) into two parts, \(D_1\) and \(D_2\), where \(D_1\) is below the curve, whereas \(D_2\) is above the curve. Under this case, \(P^*\) is locally asymptotically stable for \((\mu, \tau) \in D_1\), and unstable for \((\mu, \tau) \in D_2\).

6. **Conclusion and discussion.** In this paper, we present a simple tumor-immune system for the different biological situation, where the time delay of tumor action is included, and the effect of tumor cells on the effector cells is reflected by the corresponding coefficient and the time delay of tumor action. Solutions of the model with feasible initial conditions are all nonnegative. The dynamic behavior of the model is analyzed by constructing iteration sequences, applying the Fluctuation Lemma and the bifurcation theory, and is also illustrated by numerical simulation. The impact of the tumor action on dynamics of the model is also investigated. We notice that, in the obtained results, the signs of the expressions \(r\eta - n\sigma\) and \(\eta - |\mu|K\) play an important role in determining final outcomes of the interaction between tumor cells and effector cells. In order to understand biologically the conditions on the obtained results, in the following, we give biological meanings of the two expressions according to the biological meanings of the parameters of model (6), and then explain the associated results.

For model (6), \(\frac{\sigma}{n}\) is the concentration of effector cells at the steady state in the absence of tumor cells. Then \(n \cdot \frac{\sigma}{n}\) approximately represents the damage rate of tumor cells by effector cells at the steady state where the concentration of the tumor cells is sufficiently low. Further, \(r - \frac{n\sigma}{\eta}\) can be referred to as the net growth rate of the tumor cells with its concentration sufficiently low. Thus the condition \(r\eta < n\sigma\) has a clear biological meaning since \(r\eta < n\sigma\) is equivalent to \(r - \frac{n\sigma}{\eta} < 0\).
On the other hand, $K$ is the maximum carrying capacity of tumor cells in the biological environment. Then $|\mu|K$ reflects the maximum effect of tumor cells on effector cells, and $\eta - |\mu|K$ is the difference between the natural losing rate of effector cells and the action effect of tumor cells. Here, the effect of tumor action is a neutralization action if $\mu < 0$, and a stimulation action as $\mu > 0$.

In view of the biological meanings of $r - \frac{na}{\eta}$ and $\eta - |\mu|K$ explained above, we may have the following statements according to the results obtained in the previous sections.

When the tumor cells play a stimulation role for the growth of the effector cells (i.e. $\mu > 0$), sufficiently strong stimulation, compared with the natural death rate of the effector cells, can lead to the instability of the tumor equilibrium and the appearance of periodic solutions if the net growth rate of the tumor cells with its sufficiently low concentration is positive. Meanwhile, a sufficiently long time delay of tumor action is required for the occurrence of these phenomena. The specific conditions refer to the results in Sections 2 and 3.

For the case $\mu < 0$, that is, the effect of tumor action on the effector cells is neutralization, the results obtained in Section 3 show that the time delay of tumor action has no effect on the stability of equilibria of model (6). Here, we give an explanation with biological meaning for the condition of Case C4 in Table 1, under which the bistability of the tumor-free equilibrium and the tumor equilibrium of model (6) could occur.

For Case C4, the inequality $na < -\frac{rK}{4\rho} (\mu - \frac{\eta}{K})^2$ is equivalent to

$$-\left(\sqrt{\frac{na}{r}} - \eta + \sqrt{\frac{na}{r}}\right)^2 < \mu K < -\left(\sqrt{\frac{na}{r}} - \eta - \sqrt{\frac{na}{r}}\right)^2.$$
Note that \((\frac{n\sigma}{r} - \eta - \sqrt{\frac{n\sigma}{r}})^2 < \eta\) as \(n\sigma > r\eta\). Then the condition on Case C4 in Table 1 can be reexpressed with \(\mu < 0\) and \(r\eta < n\sigma\) as

\[-(\frac{n\sigma}{r} - \eta + \sqrt{\frac{n\sigma}{r}})^2 < \mu < -\eta, \quad \text{i.e.} \quad \eta < |\mu|K < \tilde{\eta},\]

where \(\tilde{\eta} = (\frac{n\sigma}{r} - \eta + \sqrt{\frac{n\sigma}{r}})^2\). Therefore, for this case, when the net growth rate of the tumor cells with its sufficiently low concentration, \(r - n\sigma\eta\), is negative, the appropriate neutralization, the effect of which is between \(\eta\) and \(\tilde{\eta}\), can result in the bistability of model (6), and make the extinction of tumor cells depending on the initial conditions.

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Appendix. Proof of Lemma 3.5. (i) First, when \(n\sigma < r\eta\) and \(0 < \mu K < \eta\), we have

\[0 < \tilde{T}_0 = K \left(1 - \frac{n\sigma}{r\eta}\right) < \frac{n}{\mu} \left(1 - \frac{n\sigma}{r\eta}\right) < \frac{\eta}{\mu}.\]

From (21), \(0 < \tilde{T}_0 < \frac{n}{\mu}\) implies \(\tilde{E}_1 > \frac{\sigma}{\eta}\), and \(\tilde{T}_0 < \frac{n}{\mu} \left(1 - \frac{n\sigma}{r\eta}\right)\) implies \(\tilde{E}_1 < \frac{r}{\eta}\). That is, \(\frac{\sigma}{\eta} < \tilde{E}_1 < \frac{r}{\eta}\). It then follows that \(0 < \tilde{T}_1 < K \left(1 - \frac{n\sigma}{r\eta}\right) < \frac{n}{\mu} \left(1 - \frac{n\sigma}{r\eta}\right) < \frac{\eta}{\mu}\).

By further induction, we know that \(0 < \tilde{T}_m < K \left(1 - \frac{n\sigma}{r\eta}\right) < \frac{n}{\mu} \left(1 - \frac{n\sigma}{r\eta}\right) < \frac{\eta}{\mu}\) and \(\frac{\sigma}{\eta} < \tilde{E}_m < \frac{r}{\eta}\) \((m = 1, 2, 3, \ldots)\), when \(n\sigma < r\eta\) and \(0 < \mu K < \eta\).

Next, we prove the existence of the limits of sequences \(\{\tilde{T}_m\}\) and \(\{\tilde{E}_m\}\). Straightforward calculation shows

\[\tilde{E}_{m+2} = \frac{\sigma}{\eta} \left(\frac{\mu n K}{r\eta} \tilde{E}_m + \left(1 - \frac{\mu K}{\eta}\right)\right)}{(1 - \frac{nK}{\eta}) \frac{\mu n K}{r\eta} \tilde{E}_m + \left(1 - \frac{\mu K}{\eta}\right)^2 + \frac{\mu n\sigma K}{r\eta^2}}. \quad (28)\]

and

\[\tilde{E}_{m+2} - E^* = \frac{\left[\frac{\sigma}{\eta} - \left(1 - \frac{\mu K}{\eta}\right) E^*\right] \left(\frac{\mu n K}{r\eta} \tilde{E}_m + 1 - \frac{\mu K}{\eta}\right) - \frac{\sigma}{\eta} \frac{\mu n K}{r\eta} E^*}{\left(1 - \frac{nK}{\eta}\right) \frac{\mu n K}{r\eta} \tilde{E}_m + \left(1 - \frac{\mu K}{\eta}\right)^2 + \frac{\mu n\sigma K}{r\eta^2}}. \quad (29)\]

According to (9), \(E^*\) is the positive root of equation

\[h(E) = \frac{\mu n K}{r\eta} E^2 + \left(1 - \frac{\mu K}{\eta}\right) E - \frac{\sigma}{\eta} = 0,\]

i.e.,

\[\frac{\sigma}{\eta} = \frac{\mu n K}{r\eta} E^{*2} + \left(1 - \frac{\mu K}{\eta}\right) E^*.\]

Then

\[\tilde{E}_{m+2} - E^* = \frac{(\mu n K)^2 E^{*2} \left(\tilde{E}_m - E^*\right)}{(r\eta)^2 \left(1 - \frac{nK}{\eta}\right) \frac{\mu n K}{r\eta} \tilde{E}_m + \left(1 - \frac{\mu K}{\eta}\right)^2 + \frac{\mu n\sigma K}{r\eta^2}}. \quad (29)\]
Note that
\[ h(\tilde{E}_0) = \frac{\mu K}{\eta} \tilde{E}_0 \left( \frac{n}{r} \tilde{E}_0 - 1 \right) = \frac{\mu \sigma K}{\eta^2} \left( \frac{n \sigma}{r \eta} - 1 \right), \]

and
\[ h(\tilde{E}_1) = \frac{\mu K}{\eta} \tilde{E}_1 \left( \frac{n}{r} \tilde{E}_1 - 1 \right) + \left( \tilde{E}_1 - \frac{\sigma}{\eta} \right) \]
\[ = \frac{\mu K}{\eta} \cdot \frac{\sigma}{\eta - \mu T_0} \left( \frac{n}{r} \cdot \frac{\sigma}{\eta - \mu T_0} - 1 \right) + \left( \frac{\sigma}{\eta - \mu T_0} - \frac{\sigma}{\eta} \right) \]
\[ = \frac{n \mu^2 \sigma^2 K T_0}{r \eta^2 (\eta - \mu T_0)^2} > 0. \]

Then \( \tilde{E}_0 < E^* < \tilde{E}_1 \) according to the property of function \( h(E) \). Further, the recursion from (29) shows that \( 0 < \tilde{E}_{2k} < E^* < \tilde{E}_{2k-1} \) \((k = 1, 2, \cdots)\).

On the other hand,
\[ \tilde{E}_{m+2} - \tilde{E}_m = -\left( 1 - \frac{\mu K}{\eta} \right) \left( \frac{n \mu K}{r \eta} \tilde{E}_m + \left( 1 - \frac{\mu K}{\eta} \right) \tilde{E}_m - \frac{\sigma}{\eta} \right) \]
\[ = -\left( 1 - \frac{\mu K}{\eta} \right) \frac{n \mu K}{r \eta} \tilde{E}_m + \left( 1 - \frac{\mu K}{\eta} \right)^2 + \frac{n \sigma K}{r \eta^2}. \]

Then, \( 0 < \tilde{E}_{2k} < E^* < \tilde{E}_{2k-1} \) implies \( h(\tilde{E}_{2k}) < 0 \) and \( h(\tilde{E}_{2k-1}) > 0 \) \((k = 1, 2, \cdots)\).

Hence, sequence \( \{\tilde{E}_{2k}\} \) is monotone increasing, and sequence \( \{\tilde{E}_{2k-1}\} \) is monotone decreasing. Therefore, when \( n \sigma < r \eta \) and \( 0 < \mu K < \eta \), the limits of sequences \( \{\tilde{E}_{2k}\} \) and \( \{\tilde{E}_{2k-1}\} \) both exist.

Lastly, letting \( m \to \infty \) for the two sides of (28) gets that the limits of \( \{\tilde{E}_{2k}\} \) and \( \{\tilde{E}_{2k-1}\} \) both satisfy \( h(E) = 0 \). Thus we know that \( \lim_{k \to \infty} \tilde{E}_{2k} = \lim_{k \to \infty} \tilde{E}_{2k-1} = E^* \) since \( E^* \) is the unique positive root of equation \( h(E) = 0 \).

Further, from \( \tilde{T}_m = K \left( 1 - \frac{n \tilde{E}_m}{r} \right) \) it follows that \( \lim_{m \to \infty} \tilde{T}_m = T^* \).

(ii) From \( n \sigma < r \eta \) and \( \mu < 0 \) it follows that
\[ \tilde{T}_0 = K \left( 1 - \frac{n \tilde{E}_0}{r} \right) = K \left( 1 - \frac{n \sigma}{r \eta} \right) > 0, \]

and
\[ \tilde{E}_1 = \frac{\sigma}{\eta - \mu T_0} < \frac{\sigma}{\eta} < \frac{r}{n}. \]

Again, \( \tilde{E}_1 < \frac{r}{n} \) implies \( \tilde{T}_1 > 0 \). Therefore, by induction we know \( \tilde{E}_m < \frac{\sigma}{\eta} < \frac{r}{n} \) and \( \tilde{T}_m > 0 \) \((m = 1, 2, \cdots)\) as \( n \sigma < r \eta \) and \( \mu < 0 \). On the other hand, \( \tilde{T}_m > 0 \) implies \( \tilde{E}_{m+1} > 0 \).

Straightforward calculation shows
\[ \tilde{E}_{m+2} - \tilde{E}_{m+1} = \frac{\sigma \mu \left( \tilde{T}_{m+1} - \tilde{T}_m \right)}{(\eta - \mu T_{m+1})(\eta - \mu \tilde{T}_m)} = \frac{\sigma \mu K \left( \tilde{E}_m - \tilde{E}_{m+1} \right)}{r \left( \eta - \mu \tilde{T}_{m+1} \right)(\eta - \mu \tilde{T}_m)}. \]
Then $\tilde{E}_1 < \tilde{E}_0$ implies $\tilde{E}_2 < \tilde{E}_1$. By recursion, $T_m > 0$ implies that sequence $\{\tilde{E}_m\}$ is monotone decreasing. Therefore, the limit of $\tilde{E}_m$ exists. Similarly, for the case $n\sigma < r\eta$ and $0 < \mu K < \eta$, we have $\lim_{m \to \infty} T_m = T^*$ and $\lim_{m \to \infty} \tilde{E}_m = E^*$.

The proof of Lemma 3.5 is complete. □

Proof of Lemma 3.6. Notice that the recursive relations between the two sequences defined in Lemmas 3.5 and 3.6 are the same, but their initial terms are different.

For Lemma 3.6, $0 < \tilde{E}_0' = \frac{\sigma}{\eta - \mu K} < \frac{\sigma}{\tilde{E}}$. Correspondingly, $T_1^* > 0$. Then from induction for the two sequences we can show easily that $\tilde{T}_m' > 0$ and $0 < \tilde{E}_m' < \frac{\sigma}{\eta} < \frac{\sigma}{\tilde{E}}$ ($m = 0, 1, 2, \cdots$) when $n\sigma < r\eta$ and $\mu < 0$.

Note that

$$\tilde{E}_1' - \tilde{E}_0' = \frac{\sigma \mu (\tilde{T}_1' - \tilde{T}_0')}{(\eta - \mu \tilde{T}_0') (\eta - \mu \tilde{T}_0')} = \frac{\sigma \mu n K \tilde{E}_0'}{r (\eta - \mu \tilde{T}_0') (\eta - \mu \tilde{T}_0')} > 0.$$ 

Then, from

$$\tilde{E}_{m+2}' - \tilde{E}_{m+1}' = \frac{\sigma \mu (\tilde{T}_{m+2}' - \tilde{T}_{m+1}')}{(\eta - \mu \tilde{T}_{m+2}') (\eta - \mu \tilde{T}_{m+1}')} = \frac{\sigma \mu n K (\tilde{E}_m' - \tilde{E}_{m+1}')}{r (\eta - \mu \tilde{T}_{m+2}') (\eta - \mu \tilde{T}_{m+1}')} ,$$

we know that the sequence $\{\tilde{E}_m\}$ is monotone increasing by recursion. Therefore, similarly as in the proof of Lemma 3.5, $\lim_{m \to \infty} \tilde{T}_m' = T^*$ and $\lim_{m \to \infty} \tilde{E}_m' = E^*$.

This completes the proof of Lemma 3.6. □

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