Asymptotic Behavior Analysis of a Fractional-Order Tumor-Immune Interaction Model with Immunotherapy

1. Introduction

Tumor or tumour is a term used to describe the name for a swelling or lesion formed by an abnormal growth of cells. A tumor can be benign, premalignant, or malignant, whereas cancer is by definition malignant and is used to describe a disease in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through blood and lymph systems [1], and so cancer is known as the leading cause of death in the world. During the last four decades, a large body of evidence has accumulated to provide support for the concept that the host immune system interacts with developing tumors and may be responsible for the arrest of tumor growth and for tumor regression [2].

Immunotherapy holds much promise for the treatment option and considered the fourth-line cancer therapy [3] by using cytokines and adoptive cellular immunotherapy (ACI) since adoptive immunotherapy using lymphokine-activated killer (LAK) cells or tumor-infiltrating lymphocytes (TIL) plus IL-2 has yielded positive results both in experimental tumor models and clinical trials [4].

The most current terminology used to describe cytokines is “immunomodulating agents” which are important regulators of both the innate and adaptive immune response. Examples of cytokines are protein hormones produced mainly by activated T cells (lymphocytes) in cell-mediated immunity, and interleukin-2 (IL-2), produced mainly by CD4+ T cells, is the main cytokine responsible for lymphocyte activation, growth, and differentiation. ACI refers to the injection of cultured immune cells that have antitumor reactivity into the tumor-bearing host, which is typically achieved in conjunction with large amounts of IL-2 by using the following two methods: LAK therapy and TIL therapy. For more information on cytokines and ACI, the reader is referred to [5] and the references therein.

By applying each therapy separately or by applying both therapies simultaneously, Kirschner and Panetta [6] considered a model describing tumor-immune dynamics together with the feature of IL-2 dynamics. They proposed a
model describing the interaction between the effector cells, tumor cells, and the cytokine (IL-2):

\[
\begin{align*}
\frac{dE}{dt} &= cT - \mu_2E + \frac{p_1EI_L}{g_1 + I_L} + s_1, \\
\frac{dT}{dt} &= r_2T(1 - bT) - \frac{aET}{g_2 + T}, \\
\frac{dI_L}{dt} &= \frac{p_2ET}{g_3 + T} - \mu_3I_L + s_2, \\
E(0) &= E_0, T(0) = T_0, I_L(0) = I_{L0},
\end{align*}
\]  

(1)

where \(E(t)\) represents the activated immune system cells (commonly called effector cells) such as cytotoxic T cells, macrophages, and natural killer cells that are cytotoxic to the tumor cells; \(T(t)\) represents the tumor cells; and \(I_L(t)\) represents the concentration of IL-2 in the single tumor-site compartment. The parameters and their biological interpretations are summarized in Table 1.

For the nondimensionalized model (1), we adopt the following scaling:

\[
\begin{align*}
\tilde{t} &= r_2t, \\
\tilde{u} &= E, \\
\tilde{v} &= \frac{T}{g_3}, \\
\tilde{w} &= \frac{I_L}{g_1}, \\
\tilde{b} &= bg_1, \\
\tilde{c} &= \frac{c_0}{r_2}, \\
\tilde{\mu}_2 &= \frac{\mu_2}{r_2}, \\
\tilde{p}_1 &= \frac{p_1}{r_2}, \\
\tilde{s}_1 &= \frac{s_1}{r_2}, \\
\tilde{s}_2 &= \frac{s_2}{g_1r_2}, \\
\tilde{a} &= \frac{a}{g_3r_2}, \\
\tilde{g} &= \frac{g_2}{g_3}, \\
\tilde{\mu}_3 &= \frac{\mu_3}{r_2}, \\
\tilde{\mu}_2 &= \frac{\mu_2}{r_2}.
\end{align*}
\]  

(2)

Then model (1) is converted into the following form (dropping the tilde):

\[
\begin{align*}
\frac{du}{dt} &= cv - \mu_2u + \frac{p_1uv}{1 + w} + s_1, \\
\frac{dv}{dt} &= v(1 - bv) - \frac{avu}{g + v}, \\
\frac{dw}{dt} &= \frac{p_2uv}{1 + v} - \mu_3w + s_2, \\
u(0) &= u_0, v(0) = v_0, w(0) = w_0.
\end{align*}
\]  

(3)

In recent years, fractional-order differential equations have attracted the attention of researchers due to their ability to provide a good description of certain nonlinear phenomena. The fractional-order differential equations are generalizations of ordinary differential equations to arbitrary (noninteger) orders. Some researchers studied the fractional-order differential equations to describe complex systems in different branches of physics, chemistry, and engineering [7]. In the last few years, many researchers have also employed fractional-order biological models [8]. This is because fractional-order differential equations are naturally related to systems with memory [8]. Many biological systems possess memory, and the conception of the fractional-order system may be closer to real-life situations than integer-order systems. The advantages of fractional-order systems are that they describe the whole time domain for physical processes, while the integer-order model is related to the local properties of a certain position, and they allow greater degrees of freedom in the model [9]. The relevant works related to the fractional modeling can be found in [10–13] and the references therein.

To the best of the authors’ knowledge, the dynamical analysis of a fractional-order tumor-immune interaction system with immunotherapy has not been performed before. Motivated by the above considerations, in this paper, we study a fractional-order tumor-immune interaction system by extending the integer order model (3) as follows:

### Table 1: Parameters and their biological meanings.

| Parameter | Biological meaning |
|-----------|--------------------|
| \(c\) \((1/\mu_2)\) | Antigenicity of the tumor | Natural average lifespan |
| \(p_1, a, p_2\) | Treatment by an external source of effector cells | Uptake velocity when all sites are saturated by the substrate |
| \(s_1\) | Treatment by an external input of IL-2 into the system (IL-2) | Net per capita growth rate |
| \(r_2\) | Environmental carrying capacity | Half saturation constant |
| \(g_i\) \((i = 1, 2, 3)\) | Loss/degraded rate of IL-2 | Natural average lifespan |
| \(\mu_3\) | |
| \(s_2\) | |
| \(|\mu_2|\) | |
| \(|a|\) | |
To prove the existence and uniqueness of the solution for model (4), we need the following lemma.

**Lemma 1** (see [8, 15]). Consider the system

$$
\begin{align*}
\dot{u}(t) &= cv - \mu_2 u + \frac{p_1 uw}{1 + w} + s_1, \\
\dot{v}(t) &= v(1 - bv) - \frac{auv}{g + v}, \\
\dot{w}(t) &= \frac{p_3 uv}{1 + v} - \mu_3 w + s_2,
\end{align*}
$$

(4)

with initial condition \( x(t_0) \), where \( \alpha \in (0, 1) \) and \( \frac{D^\alpha}{t^\alpha} \) is the standard Caputo differentiation. The Caputo fractional derivative of order \( \alpha \) is defined as \([9, 14]\)

$$
\frac{D^\alpha}{t^\alpha} f(t) = \frac{1}{\Gamma(n - \alpha)} \int_{t_0}^{t} (t - s)^{n - \alpha - 1} f^{(n)}(s) ds,
$$

(5)

where \( \alpha \in (0, 1) \) and \( \frac{D^\alpha}{t^\alpha} \) is the standard Caputo differentiation. The Caputo fractional derivative of order \( \alpha \) is defined as \([9, 14]\)

In this paper, we consider immunotherapy to be ACI and/or IL-2 delivery either separately or in combination in the interaction site among effector cells, the tumor, and IL-2. The organization of this paper is as follows. In Section 2, the existence, uniqueness, and nonnegativity of the fractional-order model (4) are presented. In Section 3, equilibria and existence and uniqueness of the solutions of the fractional-order model (4) are given. The numerical simulations are provided to verify the theoretical results of the fractional-order model (4) in Section 4. Finally, the study concludes with a brief discussion in Section 5.

### 2. Existence, Uniqueness, and Nonnegativity

This section studies the existence, uniqueness, and nonnegativity of the solutions of the fractional-order model (4).

For any \( X, \overline{X} \in \Omega \), it follows from (4) that

$$
\|F(X) - F(\overline{X})\| = \left| cv - \mu_2 u + \frac{p_1 uw}{1 + w} + s_1 - cv + \mu_2 \overline{u} - \frac{p_1 u \overline{w}}{1 + \overline{w}} - s_1 \right| + \left| v(1 - bv) - \frac{auv}{g + v} - (1 - bv) + \frac{a \overline{u} \overline{v}}{g + \overline{v}} \right|
$$

$$
+ \left| \frac{p_3 uv}{1 + v} - \mu_3 w + s_2 - \frac{p_3 \overline{u} \overline{v}}{1 + \overline{v}} + \mu_3 \overline{w} - s_2 \right| + \left| 1 - b(v + \overline{v}) - \frac{a \overline{u} \overline{v}}{(g + u)(g + \overline{u})} \right| (v - \overline{v}) + \frac{av}{g + v} (u - \overline{u})
$$

$$
= c(v - \overline{v}) + \left( \frac{p_1 u}{1 + w} - \mu_2 \right) (u - \overline{u}) + \frac{p_1 \overline{u}}{1 + \overline{w}} (w - \overline{w}) + \left( \frac{1 + 2bM + aM}{g} \right) (v - \overline{v}) + a|u - \overline{u}| + p_1 M |w - \overline{w}| + p_2 |u - \overline{u}| + p_2 M |v - \overline{v}| + \mu_3 |w - \overline{w}|
$$

$$
\leq c|v - \overline{v}| + (p_1 + p_2)|u - \overline{u}| + p_1 M |w - \overline{w}| + \left( 1 + 2bM + aM g \right) |v - \overline{v}| + a|u - \overline{u}| + p_2 |u - \overline{u}| + p_2 M |v - \overline{v}| + \mu_3 |w - \overline{w}|
$$

$$
= (p_1 + p_2 + a + p_2)|u - \overline{u}| + \left( c + 1 + 2bM + aM g + p_2 M \right) |v - \overline{v}| + (p_1 M + \mu_3)|w - \overline{w}|
$$

$$
\leq L\|X - \overline{X}\|,
$$

where \( L \) is the Lipschitz constant of the function \( F \).

**Theorem 1**. Let \( \Omega = \{(u, v, w) \in \mathbb{R}^3: \max\{|u|, |v|, |w| \} \leq M\} \). For each initial condition \( X_0 = (u_0, v_0, w_0) \in \Omega \), there exists a unique solution of the fractional-order model (4), which is defined for all \( t \geq 0 \).

**Proof**. Let \( 0 < T < \infty \). We seek a sufficient condition for existence and uniqueness of the solutions of the fractional-order model (4) in the region \( \Omega \times (0, T) \). We denote \( X = (u, v, w) \) and \( \overline{X} = (\overline{u}, \overline{v}, \overline{w}) \). Consider a mapping \( F(X) = (F_1(X), F_2(X), F_3(X)) \), where

$$
F_1(X) = cv - \mu_2 u + \frac{p_1 uw}{1 + w} + s_1,
$$

$$
F_2(X) = v(1 - bv) - \frac{auv}{g + v},
$$

$$
F_3(X) = \frac{p_3 uv}{1 + v} - \mu_3 w + s_2.
$$

(7)

For any \( X, \overline{X} \in \Omega \), it follows from (4) that

\[ \|F(X) - F(\overline{X})\| \leq L\|X - \overline{X}\|, \]

where \( L \) is the Lipschitz constant of the function \( F \).

Finally, the study concludes with a brief discussion in Section 5.
The cases (2) and (4) are realistic tumor-free equilibrium points. On the other hand, (1) and (3) are not realistic because the effector (or immune) cells do not disappear although the immune system can be weak. Thus, in this section, to investigate the tumor-free equilibrium points in (1), we examine the asymptotically stable behavior at the equilibrium points provided in the cases (2) and (4).

Next, we only provide the sufficient conditions of the existence of a unique positive equilibrium point $E_*$ to (4) and omit the proof process.

**Lemma 2** (Lemma 2.1, see [18]). If one of the following inequalities

1. $gc \geq (1 - bg)s_1$, $(\mu_2 - p_1)g > s_1$ and $\mu_2 > p_1$,
2. $gc > s_1$, $(\mu_2g/a) > s_1((s_2/\mu_2) + 1)$ and $\mu_2 = p_1$,

holds, then (4) has a unique positive equilibrium point $E_* = (u_*, v_*, w_*)$.

**Theorem 3.** Let $J(x^*)$ denote the Jacobian matrix of system (6) evaluated at equilibrium point $x^*$. The eigenvalues of $J(x^*)$ are $\lambda_i$, where $i = 1, \ldots, n$. Then, equilibrium point $x^*$ is locally asymptotically stable if and only if all eigenvalues $\lambda_i$ are $\lambda_i > 0$; equilibrium point $x^*$ is a saddle point if some eigenvalues $\lambda_i$ satisfy $|\arg(\lambda_i)| > (\alpha/2)$; and some others satisfy $|\arg(\lambda_i)| > (\alpha/2)$.

Now, we determine the local stability of the equilibrium points of model (4) using the linearization method. The Jacobian matrix of the system evaluated at point $X = (u, v, w)$ is given by

$$J(X) = F_X(X) = \begin{bmatrix}
-\mu_2 + \frac{p_1w}{1 + w} & c & \frac{p_1u}{(1 + w)^2} \\
\frac{-av}{g + v} & 1 - 2bv & \frac{agu}{(g + v)^2} - 0 \\
\frac{p_2v}{1 + v} & \frac{p_2u}{(1 + v)^2} & -\mu_3
\end{bmatrix}$$

where $F(X)$ is defined in the proof of Theorem 1.

**Theorem 3.** Equilibrium point $E_2 = ((s_1/\mu_2), 0, 0)$ of (4) is locally asymptotically stable if $a_{s_1} > g\mu_2$ and is unstable, which is a saddle point, if $a_{s_1} < g\mu_2$.

**Proof.** By (9), the Jacobian matrix of model (4) evaluated at equilibrium point $E_2 = ((s_1/\mu_2), 0, 0)$ is given by

$$J(E_2) = \begin{bmatrix}
-\mu_2 & c & \frac{p_1s_1}{\mu_2} \\
0 & 1 - \frac{as_1}{g\mu_2} & 0 \\
0 & \frac{p_2s_1}{\mu_2} & -\mu_3
\end{bmatrix}$$

where $F(X)$ is defined in the proof of Theorem 1.
Hence, the eigenvalues of $J(E_2)$ are $\lambda_1 = -\mu_2$, $\lambda_2 = -\mu_2$, and $\lambda_3 = 1 - (as_1/g\mu_2)$. Consequently, $\arg(\lambda_1) = \arg(\lambda_2) = \pi$ and $\arg(\lambda_3) = \pi$ if $as_1 > g\mu_2$, which leads to $|\arg(\lambda_i)| > (\alpha\pi/2)$, for $0 < \alpha < 1$. Therefore, according to Lemma 3, the equilibrium point $E_2$ is locally asymptotically stable.

If $as_1 < g\mu_2$, then $\arg(\lambda_3) = 0$. Thus, $|\arg(\lambda_i)| < (\alpha\pi/2)$ for $0 < \alpha < 1$, which yields that the equilibrium point $E_3$ is unstable and is a saddle point. □

**Theorem 4.** Equilibrium point $E_4 = ((s_1(\mu_3 + s_2)/(\mu_2\mu_3 + s_2(\mu_2 - p_1)), 0, 1(s_2/\mu_3))$ of (4) is locally asymptotically stable if $p_1s_2 > \mu_2(s_2 + \mu_3)$ and $as_1(s_2 + \mu_3 > g[\mu_2\mu_3 + s_2(\mu_2 - p_1)]$; equilibrium point $E_4$ is a saddle point, if $p_1s_2 < \mu_2(s_2 + \mu_3)$ or $as_1(s_2 + \mu_3 < g[\mu_2\mu_3 + s_2(\mu_2 - p_1)]$.

**Proof.** By (9), the Jacobian matrix of model (4) evaluated at equilibrium point $E_4 = ((s_1/\mu_2), 0, 0)$ is given by

$J(E_4) = \begin{bmatrix} -\mu_2 + \frac{p_1s_2}{s_2 + \mu_3} & c \\ 0 & \mu_2s_3 + s_2(\mu_2 - p_1) \end{bmatrix}$

Hence, the eigenvalues of $J(E_4)$ are $\lambda_1 = -\mu_3$, $\lambda_2 = -\mu_2 + (p_1s_2/(s_2 + \mu_3))$, and $\lambda_3 = 1 - (a/g) \cdot (s_1(\mu_3 + s_2)/(\mu_2\mu_3 + s_2(\mu_2 - p_1)))$. Consequently, $\arg(\lambda_1) = \pi$ and $\arg(\lambda_2) = \arg(\lambda_3) = \pi$ if $p_1s_2 > \mu_2(s_2 + \mu_3)$ and $as_1(s_2 + \mu_3 > g[\mu_2\mu_3 + s_2(\mu_2 - p_1)]$, which leads to $|\arg(\lambda_i)| > (\alpha\pi/2)$, for $0 < \alpha < 1$. Therefore, according to Lemma 3, the equilibrium point $E_4$ is locally asymptotically stable.

If $p_1s_2 < \mu_2(s_2 + \mu_3)$ or $as_1(s_2 + \mu_3 < g[\mu_2\mu_3 + s_2(\mu_2 - p_1)]$, then $\arg(\lambda_2) = 0$ or $\arg(\lambda_3) = 0$. Thus, $|\arg(\lambda_i)| < (\alpha\pi/2)$ for $0 < \alpha < 1$, which yields that the equilibrium point $E_4$ is a saddle point. □

**Remark 1.** Note that equilibrium points $E_1$ and $E_3$ are not of biological significance since the effector (or immune) cells do not disappear although the immune system can be weak. As a supplement, we point out a fact that $E_1$ and $E_3$ are saddle in mathematics since the Jacobian matrix of model (4) evaluated at equilibrium points $E_1$ and $E_3$ are as follows:

$J(E_1) = \begin{bmatrix} -\mu_2 + \frac{p_1s_2}{s_2 + \mu_3} & c \\ 0 & \mu_2s_3 + s_2(\mu_2 - p_1) \end{bmatrix}$

$J(E_3) = \begin{bmatrix} -\mu_2 + \frac{p_1s_2}{s_2 + \mu_3} & c \\ 0 & \mu_2s_3 + s_2(\mu_2 - p_1) \end{bmatrix}$
The eigenvalues of Jacobian matrix $J(E_*)$ are the roots of the following equation:

$$P(\lambda) = \lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0,$$

(14)

where

$$a_1 = \left( \mu_2 - \frac{\mu^* \ln \left( 1 + v^* \right)}{g + v^*} \right) + \mu_3,$$

$$a_2 = \mu^* \ln \left( 1 + v^* \right) + \left( \mu_2 - \frac{\mu^* \ln \left( 1 + v^* \right)}{g + v^*} \right) + \mu_3,$$

$$a_3 = \mu^* \ln \left( 1 + v^* \right) + \left( \mu_2 - \frac{\mu^* \ln \left( 1 + v^* \right)}{g + v^*} \right) + \mu_3.$$

The discriminant of $D(P)$ (see [19], Definition 1) is

$$D(P) = 18a_1 a_2 a_3 - a_2^2 a_3^2 - 4a_1^2 a_3 - 4a_1 a_2^2 - 27a_1^2.$$

(16)

By the Routh–Hurwitz conditions for fractional-order differential equations defined in [19], Proposition 1, we obtain the following results.

**Theorem 5** (1) If $D(P) > 0$ and $a_1 > 0, a_2 > 0, a_3 > 0$, then $E_*$ is locally asymptotically stable for $\alpha \in (0, 1)$.

(2) If $D(P) < 0$ and $a_1 \geq 0, a_2 \geq 0, a_3 > 0$, then $E_*$ is locally asymptotically stable for $\alpha \in (0.5, (2/3))$.

(3) If $D(P) < 0$ and $a_1 < 0, a_2 < 0$, then $E_*$ is unstable for $\alpha > (2/3)$.

(4) If $D(P) < 0$ and $a_1 > 0, a_2 > 0, a_3 = 0$, then $E_*$ is locally asymptotically stable for $\alpha \in (0, 1)$.

**Remark 2.** It follows from Lemmas 2.2 and 2.3 in [18] that $\mu_2 - \left( (p_1 u_1 - (1 + w_1))^2 + (p_1 u_1 - (1 + v_1))^2 \right)$ and $\left( \frac{\mu_2 - \mu^* \ln \left( 1 + v^* \right)}{g + v^*} \right) + \left( \frac{\mu_2 - \mu^* \ln \left( 1 + w^* \right)}{g + w^*} \right)$ for the terms of some of the terms of $a_i$, $i = 1, 2, 3$, could be determined.

We next investigate the global stability of the positive equilibrium point $E_*$ by introducing the following Lyapunov function:

$$E(t) = E(u(t), v(t), w(t)) = \frac{1}{2}(u - u_*)^2 + \left( v - v_* - v_* \ln \frac{v}{v_*} \right) + \frac{1}{2}(w - w_*)^2,$$

(17)

for the solution $(u, v, w)$ to (4). Note that $E(t) \geq 0$ for all $t \geq 0$, and thus, if $\int_0^t D^\alpha E(t) \leq 0$ can be derived, then we obtain the desired result from the well-known Lyapunov stability.

**Lemma 4** (see [20]). Let $x(t) \in \mathbb{R}_+$ be a continuous and derivable function. Then, for any time instant $t > t_0$.

$$\int_{t_0}^t D^\alpha x(t) \leq \int_{t_0}^t x(t) \left(1 - \frac{x^*}{x(t)}\right),$$

(18)

where $x^* \in \mathbb{R}_+$ and $\alpha \in (0, 1)$.

**Lemma 5** (see [21, 22]). Let $\alpha \in (0, 1), x \in C^0([0, T]: \mathbb{R})$, and $x^* \in L^1(0, T; \mathbb{R})$. Then,

$$\int_{t_0}^t D^\alpha x^2(t) \leq 2x(t) D^\alpha x(t), \quad t \in (0, T).$$

(19)

**Theorem 6.** Assume that $gc \geq (1 - bg)s_1$ and $(\mu_2 - p_1)/(a g) > s_1$ where $\mu_2 > p_1$. Then, the positive equilibrium point $E_*$ to (4) is globally asymptotically stable if

$$\mu_2 \geq p_1 + \frac{c + (a/g)}{2} + \frac{1}{2} \left[ (c/b) + \frac{1}{s_1} \right] \mu_2 - p_1,$$

$$b \geq \frac{1}{g} \left( 1 + \frac{(c + (a/g))}{2} + \frac{p_1}{c} \frac{(c/b) + s_1}{\mu_2 - p_1} \right),$$

$$\mu_3 \geq \frac{1}{2} \left( p_2 + p_1 \frac{(c/b) + s_1}{\mu_2 - p_1} \right) + \frac{p_2}{2} \frac{(c/b) + s_1}{\mu_2 - p_1},$$

(20)

Proof. Calculating the $\alpha$-order derivative of $E(t)$ along the solution of model (4), it follows Lemmas 4 and 5 that
In this section, numerical simulations of the fractional-order tumor-immune interaction model (4) are conducted to illustrate the theoretical results obtained before. The predictor-corrector PECE method of Adams–Bashforth–Moulton type [23] and some implicit fractional linear multistep methods (FLMMs) of the second order [24] are applied in order to find an approximate solution for our fractional-order model.
and consider the asymptotic stability of the realistic tumor-free equilibria $E_2$ and $E_4$. This yields that under some conditions, the tumor can be cured thoroughly, by the therapy (ACI or ACI plus IL-2). Following Theorem 3, when $s_1 = 3$ and $s_2 = 0$, the realistic tumor-free equilibrium $E_2 = ((s_1/\mu_2), 0, 0) = (3, 0, 0)$ of the fractional-order model (4) is locally asymptotically stable as indicated in Figure 1.

Following Theorem 4, when $s_1 = 3$ and $s_2 = 0.5$, the realistic tumor-free equilibrium $E_4 = ((s_1 (\mu_3 + s_2)/(\mu_2 + s_2 (\mu_2 - p_1)), 0, I(s_2/\mu_3)) = (3.6, 0, 0.5)$ of the fractional-order model (4) is locally asymptotically stable as indicated in Figure 2.

For better visualization of the impact of $\alpha$ on the asymptotic rate of convergence of the realistic tumor-free equilibria $E_2$ and $E_4$, Figure 3 indicates that with the higher value of $\alpha$, the asymptotic rate of convergence of $E_2$ and $E_4$ will be larger.

Note that $\nu$ represents the tumor cells and $s_1$ and $s_2$ represent the treatment by an external source of effector

Figure 2: Time series (a) and phase diagram (b) of the fractional-order model (4) with $c = 0.9, \mu_2 = 1, p_1 = 0.5, s_1 = 3, b = 3, a = 1, g = 2.5, p_2 = 1, \mu_3 = 1, \alpha = 0.9$, and $s_2 = 0.5$.

Figure 3: Time series of the fractional-order model (4) with $c = 0.9, \mu_2 = 1, p_1 = 0.5, s_1 = 3, b = 3, a = 1, g = 2.5, p_2 = 1, \mu_3 = 1$, and different values of the order $\alpha$ of the Caputo fractional derivative. (a)$s_2 = 0$ and (b)$s_2 = 0.5$. 
cells and the treatment by an external input of IL-2 into the system, respectively. For better visualization of the effects of two types of immunotherapy, we consider the rate of tumor extinction under two cases: $s_2$ with different $s_1$, or $s_1 = 3$ with different $s_2$. Figure 4 implies the former case, Figures 5 and 6 imply the latter case. The results show

(1) Tumor treatment by an external source of effector cells, i.e., $s_2 = 0$ with different $s_1$. Figure 4 shows that the higher the value of $s_1$, the asymptotic rate of convergence of $v$ or the rate of tumor extinction will be larger; however, the variations are not obvious when $s_1$ reaches a critical value.

(2) Tumor treatment by an external source of effector cells without or with an external input of IL-2 into the system, i.e., $s_1 = 3$, $s_2 = 0$ or $s_1 = 3$, $s_2 = 0.5$. Figure 5 shows that the introduction of new immunotherapy methods has accelerated the asymptotic rate of convergence of $v$ or the rate of tumor extinction.

(3) Tumor treatment by an external source of effector cells and an external input of IL-2 into the system, i.e., $s_1 = 3$ with different $s_2$. Figure 6 shows that with the same value of $s_1$ and higher value of $s_2$, the asymptotic rate of convergence of $v$ or the rate of tumor extinction will be larger; however, the
variations are not obvious when $s_2$ reaches a critical value.

In other words, the desired best effects can be achieved by combining the two types of immunotherapy.

Second, we choose the following set of parameters:

$$c = 1, \quad \mu_2 = 1, \quad p_1 = 0.5, \quad s_1 = 1, \quad s_2 = 0.5,$$

and consider the asymptotic stability of the unique interior equilibrium $E_*$. This yields that under some conditions, combination therapy (ACI plus IL-2) can achieve satisfactory and stable tumor control; however, the tumor is incurable.

Figures 7 and 8 indicate that the unique interior equilibrium

$$E_* = (7.2036, 3.1197, 5.9551) \text{ or } (2.5191, 0.7481, 1.5781),$$

is asymptotically stable when $b = 0.3, a = 0.05, g = 2.5, p_2 = 1, \mu_3 = 1$, and $\alpha = 0.9 \text{ or } b = 0.3, a = 1, g = 2.5, p_2 = 1, \mu_3 = 1$, and $\alpha = 0.6$, respectively, concurring with the results of Theorem 5 (1) and (2).

Figure 9 indicates that all trajectories with different positive initial conditions converge to the unique interior equilibrium $E_* = (0.8463, 0.5880, 0.3283)$ when $b = 1.5, a = 0.5, g = 3, p_2 = 0.5, \mu_3 = 2$, and $\alpha = 0.9$, which indicates that $E_*$ is globally asymptotically stable, concurring...
with the results of Theorem 6. This situation means that the tumor will exist indefinitely, which will be incurable in medicine.

5. Concluding Remarks

In this paper a fractional-order tumor-immune interaction model with immunotherapy is discussed. The existence, uniqueness, and nonnegativity of the solutions are proved. The local and global asymptotic stability of some equilibrium points are investigated. Unfortunately, by the fractional calculation, we cannot obtain the boundedness of solutions to the fractional-order tumor-immune model (4) with \( \alpha \in (0, 1) \).

In addition, numerical simulations are conducted to illustrate the analytical results. This yields that under some conditions, the tumor can be cured thoroughly, by the therapy (ACI or ACI plus IL-2); under some other conditions, combination therapy (ACI plus IL-2) can achieve satisfactory and stable tumor control; however, the tumor is incurable. The results indicate that the sufficiently large order \( \alpha \) of the Caputo fractional derivative has a stabilization effect, and it may help to control the tumor extinction, in the tumor-immune model with immunotherapy.
Data Availability
The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Acknowledgments
The work was supported by National Natural Science Foundation of China (no. 81571731), Key Research and Development Program of Shaanxi (no. 2018SF-161), Natural Science Basic Research Plan in Shaanxi Province of China (no. 2020JM-569), and Scientific Research Program Funded by Shaanxi Provincial Education Department (no. 19J0792).

References
[1] J. Marx, “How cancer cells spread in the body,” Science, vol. 244, no. 4901, pp. 147-148, 1989.
[2] G. P. Dunn, A. T. Bruce, H. Ikeda, L. J. Old, and R. D. Schreiber, “Cancer immunoediting: from immunosurveillance to tumor escape,” Nature Immunology, vol. 3, no. 11, pp. 991-998, 2002.
[3] N. P. Restifo, M. E. Dudley, and S. A. Rosenberg, “Adaptive immunotherapy for cancer: harnessing the T cell response,” Nature Reviews Immunology, vol. 12, no. 4, pp. 269–281, 2012.
[4] W. H. West, K. W. Tauer, J. R. Yannelli et al., “Constant-infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer,” New England Journal of Medicine, vol. 316, no. 15, pp. 898–905, 1987.
[5] F. K. Nani and M. N. Oğuztöreli, “Modelling and simulation of Rosenberg-type adaptive cellular immunotherapy,” Mathematical Medicine and Biology, vol. 11, no. 2, pp. 107–147, 1994.
[6] D. Kirschner and J. C. Panetta, “Modeling immunotherapy of the tumor–immune interaction,” Journal of Mathematical Biology, vol. 37, no. 3, pp. 235–252, 1998.
[7] N. Heymans and I. Podlubny, “Physical interpretation of initial conditions for fractional differential equations with Riemann-Liouville fractional derivatives,” Rheologica Acta, vol. 45, no. 5, pp. 765–771, 2006.
[8] H.-L. Li, L. Zhang, C. Hu, Y.-L. Jiang, and Z. Teng, “Dynamical analysis of a fractional-order predator-prey model incorporating a prey refuge,” Journal of Applied Mathematics and Computing, vol. 54, no. 1-2, pp. 435–449, 2017.
[9] I. Petriä, Fractional-order Nonlinear Systems: Modeling, Analysis and Simulation, Springer Science & Business Media, Berlin, Germany, 2011.
[10] M. A. Khan, M. Ismail, S. Ullah, and M. Farhan, “Fractional order sir model with generalized incidence rate,”AIMS Mathematics, vol. 5, no. 3, pp. 1856–1880, 2020.
[11] M. A. Khan, A. Khan, A. Elsonbaty, and A. A. Elsayadny, “Modeling and simulation results of a fractional dengue model,” The European Physical Journal Plus, vol. 134, no. 8, p. 379, 2019.
[12] S. Ullah, M. A. Khan, M. Farooq, T. Gul, and F. Hussain, “A fractional order HBV model with hospitalization,” Discrete & Continuous Dynamical Systems-S, vol. 13, no. 3, pp. 957–974, 2019.
[13] M. A. Khan, S. Ullah, and M. Farhan, “The dynamics of zika virus with caputo fractional derivative,”AIMS Mathematics, vol. 4, no. 1, pp. 134–146, 2019.
[14] A. A. Kilbas, H. M. Srivastava, and J. J. Trujillo, Theory and Applications of Fractional Differential Equations, vol. 204, Elsevier Science Limited, Amsterdam, Netherlands, 2006.
[15] Y. Li, Y. Chen, and I. Podlubny, “Stability of fractional-order nonlinear dynamic systems: Lyapunov direct method and generalized Mittag-Leffler stability,” Computers & Mathematics with Applications, vol. 59, no. 5, pp. 1810–1821, 2010.
[16] B. Bandopadhyay and S. Kamal, Stabilization and Control of Fractional Order Systems: A Sliding Mode Approach, vol. 317, Springer, Berlin, Germany, 2015.
[17] S. K. Choi, B. Kang, and N. Koo, “Stability for caputo fractional differential systems,” Abstract and Applied Analysis, vol. 2014, Article ID 631419, 6 pages, 2014.
[18] W. Ko and I. Ahn, “Stationary patterns and stability in a tumor-immune interaction model with immunotherapy,” Journal of Mathematical Analysis and Applications, vol. 383, no. 2, pp. 307–329, 2011.
[19] E. Ahmed, A. M. A. El-Sayed, and H. A. A. El-Saka, “On some Routh-Hurwitz conditions for fractional order differential equations and their applications in Lorenz, Rössler, Chua and Chen systems,” Physics Letters A, vol. 358, no. 1, pp. 1–4, 2006.
[20] C. Vargas-De-León, “Volterra-type Lyapunov functions for fractional-order epidemic systems,” Communications in Nonlinear Science and Numerical Simulation, vol. 24, no. 1–3, pp. 75–85, 2015.
[21] J. I. Diaz, T. Pierantozzi, and L. Vazquez, “Finite time extinction for nonlinear fractional evolution equations and related properties,”Electronic Journal of Differential Equations, vol. 2016, no. 239, pp. 1–13, 2016.
[22] A. Alsaedi, B. Ahmad, and M. Kirane, “A survey of useful inequalities in fractional calculus,”Fractional Calculus and Applied Analysis, vol. 20, no. 3, pp. 574–594, 2017.
[23] K. Diethelm, N. J. Ford, and A. D. Freed, “A predictor-corrector approach for the numerical solution of fractional differential equations,”Nonlinear Dynamics, vol. 29, no. 1–4, pp. 3–22, 2002.
[24] R. Garrappa, “Trapezoidal methods for fractional differential equations: theoretical and computational aspects,”Mathematics and Computers in Simulation, vol. 110, pp. 96–112, 2015.