Exploring dynamical complexity in a time-delayed tumor-immune model

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ABSTRACT

The analysis of dynamical complexity in nonlinear phenomena is an effective tool to quantify the level of their structural disorder. In particular, a mathematical model of tumor-immune interactions can provide insight into cancer biology. Here, we present and explore the aspects of dynamical complexity, exhibited by a time-delayed tumor-immune model that describes the proliferation and survival of tumor cells under immune surveillance, governed by activated immune-effector cells, host cells, and concentrated interleukin-2. We show that by employing bifurcation analyses in different parametric regimes and the 0–1 test for chaoticity, the onset of chaos in the system can be predicted and also manifested by the emergence of multi-periodicity. This is further verified by studying one- and two-parameter bifurcation diagrams for different dynamical regimes of the system. Furthermore, we quantify the asymptotic behavior of the system by means of weighted recurrence entropy. This helps us to identify a resemblance between its dynamics and emergence of complexity. We find that the complexity in the model might indicate the phenomena of long-term cancer relapse, which provides evidence that incorporating time-delay in the effect of interleukin in the tumor model enhances remarkably the dynamical complexity of the tumor-immune interplay.

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I. INTRODUCTION

Exploring the mechanisms in tumor-immune dynamics is of utmost importance in oncology. Typically, anti- and pro-tumor factors cause complex variations in the tumor-immune interplay. Here, we study a time-delay, tumor-immune model that consists of tumor cells, activated immune-effector cells, host cells, and concentrated interleukin-2. The time-delay in the model is introduced due to the delay in the stimulation and transportation of immune cells. We discuss the qualitative properties of the model and perform one- and two-parameter bifurcation analyses to identify regimes of regular and chaotic behavior. We verify the appearance of chaos by employing the 0–1 test and augment the study of the asymptotic behavior with the analysis of its behavior in appropriate parametric spaces. This is further corroborated by computing Poincaré maps and by means of weighted recurrence entropy calculations, both allowing for the study of dynamical complexity in the system. Our analysis shows the appearance of regular and chaotic dynamics and the emergence of complexity. We find that the complexity in the model might indicate the phenomena of long-term cancer relapse, which provides evidence that incorporating time-delay in the effect of interleukin in the tumor model enriches the dynamical complexity of the tumor-immune interplay.

I. INTRODUCTION

Complexity science has significantly contributed to improving and saving human lives over the last few decades.1−3 Indeed, understanding the complex mechanism of tumor-immune (TI) dynamics is a challenging task for bio-mathematicians, bio-physicists, and biomedical engineers4 alike. Modeling of TI dynamics is an interesting research topic on its own.4 The proliferation of tumor cells depends on immune-effector cells, i.e., on natural killer cells, macrophages, activated cytotoxic-T lymphocytes, tumor and host cells, cytokines (IL-2, IL-6, and IL-10), and the micro-environment of the tumor.2,4−10 Part of the proliferation process is the slow-fast stage. During that stage, routing imaging is essential for monitoring the recurrence of cancer, the so-called “tumor dormancy.”11 The immune system of a patient with tumor cells shows rather irregular and unpredictable behavior due to complex inter-cellular interactions in the
tumor. As time-delays affect the inter-cellular interactions and signaling, it is necessary to consider the delayed response when modeling tumor-immune interactions. Due to the diversity and non-linearity of cancer-immune interactions, different attractors (e.g., point attractors, strange attractors, limit cycles, etc.) have been observed. In fact, the existence of strange attractors was found to govern the chaotic behavior in dynamical systems at large. It is worth noting that, in the context of cancer dynamics, chaos has been studied in the time-delay TI system.

Chaos is attributed to sensitive dependence of the system on initial conditions. In the framework of TI dynamics, this sensitivity gives rise to local instability and invokes the proliferation of cancer-specific patterns. This translates to different development of tumors in patients. Consequently, understanding better TI dynamics is a challenging task for oncologists and clinicians but attractive to researchers working on the mathematical modeling of cancer dynamics. The study of the emergence of chaos in cancer dynamics can potentially illustrate advanced knowledge in cellular interactive processes. In this regard, Lyapunov exponents quantify the chaotic behavior in a dynamical system by providing the rate of divergence of trajectories that emanate from infinitesimally close initial conditions. The authors in Refs. and proposed the 0–1 test to characterize the dynamics in a system by utilizing the asymptotic growth of state-space trajectories. Complementary to these approaches, Poincaré maps prove useful in visualizing the qualitative properties of the dynamics in a system. Interestingly, as we study here for the time-delay TI system, the presence of chaos in the system gives rise to complex dynamics and to entropy increase.

Dynamical complexity is associated with structural disorder in a system and can be quantified by means of entropy computations. For example, the weighted entropy is a measure of uncertainty provided by probabilistic experiments on qualitative weights of possible events. Weights are computed by the inverse exponential of a distance metric, indicating the dispersion of points in the phase space of the system. Consequently, weighted entropy measures the complexity in a system, attributed to chaotic behavior. Moreover, entropic quantities based on recurrence plots have also been employed to quantify the recurrence properties of chaotic dynamics, which is an effective approach to determine the divergence of trajectories. Recurrence plots have been used to study heart beats, neural signals, biophysical systems, and ecosystems, and weighted recurrence plots and entropic measures have been proposed, for example, in Ref. 37.

This paper is organized as follows: In Sec. II, we discuss the time-delay TI model used in our study. The qualitative dynamics is investigated in Sec. III by performing bifurcation analyses. In Sec. IV, we focus on the dynamical complexity in the TI system and study the long-term behavior of its dynamics and weighted entropy in recurrence plots to measure the disorder produced in regimes related to cancer dynamics. Finally, in Sec. V, we discuss our work and compare it with the work in the field.

II. THE TIME-DELAY TI MODEL

In the last few decades, various mathematical models have been proposed to model cancer dynamics. and Khajanchi et al. studied a time-delay tumor model and observed that larger delay leads to stronger tumor proliferation and to long-term cancer relapse. They also suggested that the growth rate of immune-effector cells and the strength of host cells are necessary to develop in their competition against tumor cells. However, the effector cells are among the most significant cells in the human immune system as they fight viruses, foreign micro-organisms, and tumor cells. Natural killer cells, cytotoxic T-lymphocytes and cytokines, such as IL-2 and IL-6, are also involved in the tumor-immune interplay, that is in the interval between tumor and immune cells. Effector cells annihilate tumor cells by delivering biochemical signals. Moreover, the identification and annihilation of tumor cells by effector cells are not instantaneous processes. Cytokines play an important role in the activation of immune cells. Cytokine-mediated cell communication and orchestrated immune response are time dependent and, thus, necessitate the use of time-delay when modeling cancer dynamics at the cellular level.

Here, we consider the time-delay TI model proposed by Das et al.,

\[
\begin{align*}
\dot{T} &= \alpha_1 T(1 - \beta_1 T) - \frac{\gamma_1 E T}{k_1 + T^2} - r_1 H T, \\
\dot{H} &= \alpha_2 H(1 - \beta_2 H) - r_2 T H, \\
\dot{I}_L &= \frac{\gamma_2 E T}{k_3 + T^2} - \delta_2 I_L , \\
\dot{E} &= a T - \delta_3 E + \frac{\gamma_3 E(t - \tau) I_L(t - \tau)}{k_4 + I_L^2(t - \tau)},
\end{align*}
\]

with initial conditions

\[\eta(v) = (\eta_1(v), \eta_2(v), \eta_3(v), \eta_4(v)),\]

and \(\eta(v) \in C([-\tau, 0], \mathbb{R}^4)\) such a way that \(T(v) = \eta_1(v), H(v) = \eta_2(v), I_L(v) = \eta_3(v), \) and \(E(v) = \eta_4(v),\) where \(v \in [-\tau, 0].\) Here, \(C\) is a set of continuous maps on Banach space \([-\tau, 0] \rightarrow \mathbb{R}^4\) with norm defined by \(\|(\eta)\| = \sup_{[-\tau, 0]}\|\eta(t)\|,\) \(i = 1, 2, \ldots, 4\) and \(\tau \in [0, \infty).\) For biologically, practicality, \(t\) is assumed that \(\eta(0) > 0; i = 1, 2, \ldots, 4.\)

In system (1), \(T\) denotes the number of tumor cells in time, \(H\) denotes the number of host or normal cells in time, \(I_L\) denotes the change in cytokines in time, and \(E\) denotes the number of cancer-specific effector cells in time. Also, \(\tau\) is the time-delay introduced to the model to account for delayed interactions in the activation of immune cells, cytokine-mediated cell communication, and orchestrated immune response.

The first equation in system (1) describes the growth dynamics of the number of tumor cells. In particular, the number of tumor cells, \(T,\) increases logistically with proliferation rate \(\alpha_1 > 0\) and reciprocal carrying capacity \(\beta_1 > 0.\) Immune-effector cells annihilate tumor cells with rate \(\gamma_1 > 0,\) governed by Monod–Haldane kinetics. The second equation describes the dynamics of the number of host or normal cells, \(H,\) which follows a logistic growth with rate \(\alpha_2 > 0\) and reciprocal carrying capacity \(\beta_2 > 0.\) The competition between tumor and host cells is described by the last two terms in the first two equations related to rates \(r_1 > 0\) and \(r_2 > 0,\) respectively. The third equation describes the rate of change in cytokines \(I_L,\) and \(\gamma_3 > 0\) indicates the recruitment rate in the presence of tumor cells by self-limiting production of \(I_L.\) Parameter \(\delta_2 > 0\) denotes the
decay rate of \(I_L\). The last equation corresponds to the number of cancer-specific effector cells, \(E\), changing in time, where tumor antigenicity, \(\alpha > 0\), increases the activation rate of effector cells at a rate of \(\gamma_3 > 0\). Here, \(\delta_I > 0\) indicates the decay rate of the effector cells. Moreover, \(I_L\) activates effector cells by a paracrine and autocrine process with a delayed interaction, \(\tau\). Figure 1 shows schematically the cellular interactions in the TI system \((1)\), and Table I summarizes the values and parameter ranges used.

### Table I. The values and ranges of the parameters used in the time-delay TI model \((1)\).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_1)</td>
<td>Growth rate of (T)</td>
<td>day(^{-1})</td>
<td>1</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>(Carrying capacity of (T))</td>
<td>(\text{cell} \cdot \text{day}^{-1})</td>
<td>0.1</td>
</tr>
<tr>
<td>(\gamma_1)</td>
<td>Decay rate of (T)</td>
<td>day(^{-1})</td>
<td>5.56</td>
</tr>
<tr>
<td>(k_1)</td>
<td>Half-saturation constant</td>
<td>volume</td>
<td>10</td>
</tr>
<tr>
<td>(r_1)</td>
<td>Fractional killing rate of (T) by (H)</td>
<td>(\text{cell} \cdot \text{day}^{-1})</td>
<td>([0.001, 0.2])</td>
</tr>
<tr>
<td>(\alpha_2)</td>
<td>Growth rate of (H)</td>
<td>day(^{-1})</td>
<td>1</td>
</tr>
<tr>
<td>(\beta_2)</td>
<td>(Carrying capacity of (H))</td>
<td>(\text{cell} \cdot \text{day}^{-1})</td>
<td>1</td>
</tr>
<tr>
<td>(r_2)</td>
<td>Fractional killing rate of (H) by (T)</td>
<td>(\text{cell} \cdot \text{day}^{-1})</td>
<td>0.55</td>
</tr>
<tr>
<td>(\gamma_2)</td>
<td>Recruitment rate of (I_L)</td>
<td>day(^{-1})</td>
<td>27.77</td>
</tr>
<tr>
<td>(k_2)</td>
<td>Half-saturation constant</td>
<td>volume</td>
<td>10</td>
</tr>
<tr>
<td>(\delta_2)</td>
<td>Decay rate of (I_L)</td>
<td>day(^{-1})</td>
<td>([0.2, 0.7])</td>
</tr>
<tr>
<td>(a)</td>
<td>Antigenicity of (T)</td>
<td>day(^{-1})</td>
<td>0.2</td>
</tr>
<tr>
<td>(\delta_3)</td>
<td>Decay rate of (E)</td>
<td>day(^{-1})</td>
<td>0.167</td>
</tr>
<tr>
<td>(\gamma_3)</td>
<td>Recruitment rate of (E)</td>
<td>(\text{cell} \cdot \text{day}^{-1})</td>
<td>1.1</td>
</tr>
<tr>
<td>(k_3)</td>
<td>Half-saturation constant</td>
<td>volume</td>
<td>10</td>
</tr>
<tr>
<td>(\tau)</td>
<td>Time delay</td>
<td>day</td>
<td>((0, 25])</td>
</tr>
</tbody>
</table>

Next, we perform a detailed numerical analysis of system \((1)\) for various combinations of the system parameters and initial conditions, which will show that the solution remains positive and bounded.

### III. QUALITATIVE ANALYSIS

We start our qualitative analysis by studying the dynamics of system \((1)\) and investigating its dynamical properties. In particular, we begin by analyzing the dynamical behavior in the neighborhood of its fixed points.

#### A. Linear stability analysis of fixed points

System \((1)\) admits the following four fixed points:

- The trivial or no-living cell fixed point \(E^{(0)} = (0, 0, 0, 0, 0)\).
- The axial or only host-cell-present fixed point \(E^{(1)} = (0, \frac{1}{\beta_1}, 0, 0)\).
- The host-cell-free fixed point \(E^{(2)} = (0, 0, \frac{1}{\alpha_2}, 0)\).
- The cancer-present fixed point \(E^{(3)} = (0, \frac{1}{\alpha_2}, 0, 0)\).

To study the stability of the fixed points, we employ the Jacobian matrix \(J\) of system \((1)\):

\[
J = \begin{pmatrix}
g_{11} & -r_1 T & 0 & 0 & g_{14} \\
r_1 H & 0 & 0 & 0 & 0 \\
g_{31} & 0 & -\delta_2 & g_{34} & 0 \\
0 & g_{43} e^{-\lambda t} & -\delta_3 & g_{44} e^{-\lambda t} & 0 \\
a & 0 & 0 & 0 & -\delta_3 + g_{44} e^{-\lambda t}
\end{pmatrix},
\]

where \(g_{11} = \alpha_1(1 - 2\beta_1 T) - \frac{\gamma_2(\xi_1 - T^2)}{(\xi_1 + T^2)^2} - r_1 H\), \(g_{14} = -\frac{\gamma_2(\xi_1 - T^2)}{(\xi_1 + T^2)^2}\), \(g_{31} = \alpha_2(1 - 2\beta_2 H) - \frac{\gamma_2(\xi_2 - T^2)}{(\xi_2 + T^2)^2}\), \(g_{34} = -\frac{\gamma_2(\xi_2 - T^2)}{(\xi_2 + T^2)^2}\), \(g_{43} = -\frac{\gamma_2(\xi_1 - E^*)}{(\xi_1 + E^*)}\), and \(g_{44} = -\frac{\gamma_2(\xi_2 - E^*)}{(\xi_2 + E^*)}\).

Next, we compute the eigenvalues of \(J\) at four fixed points in the absence of time-delay, i.e., for \(\tau = 0\), considering the instantaneous interaction between \(I_L\) and \(E\) as an easier case to treat semi-analytically. We will get back to the study of the dynamics of system \((1)\) for \(\tau > 0\) in Subsection III B. To calculate the eigenvalues for \(\tau = 0\), we used the parameter values in Table I, keeping \(r_1\) and \(\delta_2\) fixed at 0.05 and 0.65, respectively. These values are within the ranges for \(r_1\) and \(\delta_2\) reported in the table.

The eigenvalues at the fixed point \(E^{(0)}\) are \(\lambda_1^{(0)} = \alpha_1 > 0, \lambda_2^{(0)} = \alpha_2 > 0, \lambda_3^{(0)} = -\delta_2 < 0, \lambda_4^{(0)} = -\delta_3 < 0, \lambda_5^{(0)} = -\delta_3 < 0\), as \(\alpha_1, \alpha_2, \delta_2, \delta_3\) are all positive. Therefore, there are stable and unstable manifolds emanating from \(E^{(0)}\), and thus, it is a saddle fixed point.

The eigenvalues at the fixed point \(E^{(1)}\) are \(\lambda_1^{(1)} = \alpha_1 - \frac{1}{\beta_1}\), \(\lambda_2^{(1)} = 0, \lambda_3^{(1)} = -\delta_2 < 0, \lambda_4^{(1)} = -\delta_3 < 0, \lambda_5^{(1)} = -\delta_3 < 0\). Thus, system \((1)\) undergoes a transcritical bifurcation at the critical point \(\alpha_1 = \frac{1}{\beta_1}\) as \(r_1 \in [0.001, 0.2]\) (see Table I).
The eigenvalues at the fixed point $E^{(2)}$ are $\lambda_1 \approx 0.894648$, $\lambda_2 \approx -0.719801$, $\lambda_3 \approx -0.0083286 - 0.267752i$, and $\lambda_4 \approx -0.0083286 + 0.267752i$. Consequently, $E^{(2)}$ is a saddle-focus fixed point and, thus, unstable.

B. Bifurcation analysis

To do so, we compute one- and two-parameter bifurcation diagrams for different settings. We start by keeping all parameters as in Table 1 and vary the interaction rate between tumor and host cells, $r_1$ in $(0, 0.2]$ in Fig. 2(a), the decay rate of $I_1$ cells, $\delta_1$ in $[0.2, 0.7]$ in panel (b), and the time-delay of $I_2$ activation of the effector cells, $\tau$ in $(0, 25]$ in panel (c). In Fig. 3, we plot two-parameter bifurcation diagrams for $r_1$ and $\delta_1$ in panel (a), for $r$ and $r_1$ in panel (b), and for $\delta_1$ and $\tau$ in panel (c), keeping $\tau = 23$ in panel (a), $\delta_1 = 0.65$ in panel (b), and $r_1 = 0.05$ in panel (c).

We compute the local maxima of the tumor variable $T$, $T_{\text{max}}$, for $r_1 \in (0, 0.2]$, $\delta_1 \in [0.2, 0.7]$, and $\tau \in (0, 25]$ in panels (a), (b), and (c) in Fig. 2, respectively. Figure 2(a) shows the one-parameter bifurcation diagram varying $r_1$ for fixed $\delta_1 = 0.65$ and $\tau = 23$. Chaotic and periodic dynamics of different periods can be seen as $r_1$ increases in $(0, 0.2]$. On the other hand, the increase in the decay rate $\delta_1$ in $[0.2, 0.7]$ of interleukin-2 promotes instability and periodic behavior in the system as seen in Fig. 2(b). Similarly, a period-doubling route to chaos can be seen in Fig. 2(c) with the increase in the time-delay $\tau \in (0, 25]$. This shows that large time-delay is not enough to instigate effector cells against tumor cells. In all cases, system (1) exhibits multi-periodic states and chaotic behavior as can be seen in the bifurcation diagrams in Fig. 2, depending on the values of the bifurcation parameters.

Furthermore, to study the effects of $r_1$, $\delta_1$, and $\tau$ on the qualitative behavior of system (1), we plot in Fig. 3 two-parameter bifurcation diagrams of $T_{\text{max}}$ by varying $\delta_1$ and $r_1$ in $[0.2, 0.7]$ and $(0, 0.5]$ [panel (a)], $\tau$ and $r_1$ in $(0, 25]$ and $(0, 0.5]$ [panel (b)], and $\tau$ and $\delta_1$ in $[0, 25]$ and $(0.2, 0.7]$ [panel (c)]. The color bar represents different orders of periodic behavior. The results in Fig. 3 signify the existence of higher-order periodicity in system (1). Consequently, higher-order periodic behavior leads to period doubling cascade to chaos as these parameters vary. These results show rich dynamical behavior that we explore next.

C. Dynamical behavior analysis employing the 0–1 test

Here, we complement the qualitative analysis in Sec. III by studying the chaotic behavior of the time-delay TI model (1) and employing the 0–1 test,\textsuperscript{28,29} a method that can discriminate effectively between regular and chaotic dynamics.

According to the 0–1 test,\textsuperscript{28,29} one considers the solution $y(j), j = 1, \ldots, N$, where $N$ is the length of the trajectory $y$, and constructs the two variables,

$$p_n(n) = \sum_{i=1}^{n} y(i) \cos(i\alpha),$$

$$q_n(n) = \sum_{i=1}^{n} y(i) \sin(i\alpha),$$

where $\alpha \in (0, \pi)$ and $n \in [1, \frac{N}{2}]$. In the numerical computations, we have considered $\alpha = \pi/5$. Regular geometric structures in the $(p_n, q_n)$ plane correspond to regular dynamics and Brownian-like motion to chaotic dynamics. From now on, we will drop the dependence of $p$ and $q$ on $\alpha$ and will refer to the $(p, q)$ plane for simplicity.

By applying the 0–1 test in our case, we consider $y$ the solution $T$ to system (1) that represents the evolution of the number of...
tumor cells in time. In Fig. 4, we plot \((p, q)\) for \(\delta_2 = 0.23\) [panel (a)] and \(\delta_1 = 0.65\) [panel (c)], both for fixed \(\tau = 6\), and \((p, q)\) for \(\tau = 8\) [panel (b)] and \(\tau = 23\) [panel (d)], both for fixed \(\delta_2 = 0.65\). Regular dynamics are depicted by regular geometric structures, such as those seen in panels (a) and (c). On the other hand, chaotic dynamics is depicted by Brownian-like, irregular motion as can be seen in panels (b) and (d). These results show the potential of the 0–1 test to discriminate effectively between regular and chaotic dynamics in the case of the time-delay TI system (1).

Subsequently, the diffusive behavior on the \((p, q)\) plane can be measured by means of the square dispersion,

\[
M_n = \lim_{N \to \infty} \frac{1}{N} \sum_{i=1}^{N} \left( (p_n(i+n) - p_n(i))^2 + (q_n(i+n) - q_n(i))^2 \right),
\]

where \(n\) is very small compared to the length of the trajectory \(N\) (i.e., \(n \ll N\)). The limit is assured by computing \(M_n\) only for \(n \leq n_{\text{cut}}\), where \(n_{\text{cut}} \ll N\). In particular, as the test for chaos depends on the growth rate of \(M_n\) as a function of \(n\), we consider \(n_{\text{cut}} \approx \frac{N}{1000}\).

Following Refs. 27 and 28, regular and chaotic dynamics can be quantified by the asymptotic growth rate of

\[
K_n = \lim_{n \to \infty} \frac{\log(M_n(n))}{\log(n)},
\]

where \(n \to \infty\) implies that all possible time lags are considered in the computation of \(M_n\). Consequently, \(K_n \approx 0\) denotes regular and \(K_n \approx 1\) denotes chaotic behavior.

To quantify the dynamics of the time-delay TI system (1), we compute \(K_n\) in Fig. 5 as a function of \(\delta_2\) in [0.2, 0.7] for fixed \(\tau = 23\) [panel (a)], as a function of \(\tau\) in (0, 25] for fixed \(\delta_2 = 0.65\) [panel (b)], and in the parameter space \((\tau, \delta_2)\) in (0.25) \times [0.2, 0.7] in panel (c). Panel (a) shows that depending on \(\delta_2\), \(K_n\) fluctuates around 0.5 or increases to 1, indicating regular or chaotic dynamics, respectively. A similar situation appears for \(K_n\) in Fig. 5(b) where again, depending on \(\tau\), the system either lies in a regime of regular behavior depicted by \(K_n < 0.5\) or \(K_n\) around 1 after about \(\tau \approx 10\), signaling chaotic dynamics.

Finally, Fig. 5(c) shows how \(K_n\) varies in the parameter space \((\tau, \delta_2)\), similarly to our study in Fig. 3(c) for the two-parameter bifurcation diagram. Comparing the results in Fig. 5(c) with those of the two-parameter bifurcation diagram in Fig. 3(c), one can appreciate high resemblance and similar conclusions with respect to the dynamical properties of system (1). Concluding, these results show that the 0–1 test can successfully discriminate between regular and chaotic dynamics in the time-delay TI system (1).

IV. DYNAMICAL COMPLEXITY ANALYSIS

Here, we investigate the dynamical complexity in system (1) by means of weighted recurrence plots and weighted entropy. Before doing so, however, we will start by discussing our results on the long-term behavior of representative trajectories of system (1) and their connection to cancer dynamics.

A. Phase space analysis and connection to cancer dynamics

We start by studying the asymptotic behavior of system (1). In particular, panels (a), (b), and (c) in Fig. 6 show three-dimensional projections of regular and chaotic trajectories. Panels (a) and (b) show, for \(\delta_2 = 0.65\) and \(\tau_1 = 0.05\), period 1 and 2 trajectories for \(\tau = 5\) and \(\tau = 11\), respectively, which correspond to tumor-immunoediting that goes through an equilibrium process of dual host protection and tumor-promoting actions in the immune system. Panel (c) shows a chaotic structure for \(\tau = 23\). These results provide evidence of a nonlinear relation among immune, host, and tumor cells. In Fig. 6(c), it can be observed that host cells, \(H\), and tumor cells, \(T\), nearly attain their maximum cell numbers, i.e., their carrying capacity. This represents a long-term, chaotic, and
thus unpredictable growth in the number of tumor cells, pinpointing to cancer dynamics.

We complement these results by studying the Poincaré map of the local maxima, $T_{\text{max}}$, of the chaotic solution $T$ in panel (c) that represents the evolution of the number of tumor cells in time. In particular, the Poincaré map of the chaotic structure in panel (c) for $\tau = 23$, $\delta_k = 0.65$, and $r_1 = 0.05$ shows scattered points in panels (d), providing further evidence of its chaotic nature. These results are in line with those from the 0–1 test in Subsection III C.

B. Weighted recurrence entropy analysis

Finally, we turn to the study of dynamical complexity in system (1) by employing the computation of weighted entropy based on weighted recurrence plots.\[1,7]

In particular, in an $m$-dimensional space, for a given trajectory $y \in \mathbb{R}^m$, the weighted recurrence is defined as the matrix $W$, where its entries, $w_{ij}$, are defined by

$$w_{ij} = e^{-\|y_i - y_j\|^2}, i,j = 1, \ldots, N,$$

where $\| \cdot \|$ denotes the Euclidean distance and $N$ denotes the length of the trajectory $y$. Here, $w_{ij}$ is the inverse exponential of the Euclidean distance between pairs of points $y_i$ and $y_j$ at times $i$ and $j$, respectively.

The weights $w_{ij}$ encode the information whether points $i$ and $j$ are close in the $m$-dimensional space at times $i$ and $j$ by measuring the distances $\|y_i - y_j\|$, computed as the inverse of the exponential function, normalized in $[0, 1]$. In this context, 0 corresponds to divergent and 1 to identical states. Consequently, the weights $w_{ij}$ describe the disorder in the system.

For periodic trajectories, the occurrence of identical states results in $w_{ij} = 1$, and for chaotic trajectories, $w_{ij}$ tends to zero due to exponential divergence. We note that definition (3) results in a symmetric matrix $W$. Thus, different dynamical behaviors can be encoded in the weighted matrix $W$ with entries in $[0, 1]$, and dynamical complexity can be observed based on the entries of $W$, as we discuss below.

In the following, we consider $T$-solution component of system (1) as the trajectory $y$ and compute $W$ using Eq. (3). We then use the function `imagesc` in Matlab to scale the data in $W$ as a coloreful image. Each entry of $W$ specifies the color for one pixel of the image. The resulting image is an $N \times N$ grid of pixels, where $N = 1000$. The results of the weighted-recurrence computations are presented in Fig. 7, where panel (a) shows a periodically repeated pattern for $\delta_k = 0.23$ and $\tau = 6$, for the regular dynamics discussed in Subsection III C. This pattern is due to the periodic trajectory visiting the same region in the state-space over and over in time, what is a recurrence. On the other hand, panel (b) shows different morphological patterns for $\delta_k = 0.23$ and $\tau = 23$, which amount to chaotic dynamics and indicate a disordered structure (see Subsection III C). It is worth noting that the results from the recurrence plots are in agreement with the regular and chaotic nature of the trajectories depicted by the 0–1 test in Subsection III C and Poincaré maps in Subsection IV A.

Next, we proceed to the study of the dynamical complexity in system (1) and introduce the weighted entropy, $E_{\text{wr}}$, based on the weighted recurrence matrix $W$ in Eq. (3). The weighted entropy $E_{\text{wr}}$ is defined by

$$E_{\text{wr}} = -\sum_{c_k \in E} p(c_k) \log p(c_k),$$

where $p(c_k)$ is the probability of $c_k$ to occur in $E$, where

$$E = \left\{ c_k : c_k = \frac{1}{N} \sum_{i=1}^{N} w_{ki}, k = 1, \ldots, N \right\}.$$

For the computation of $E_{\text{wr}}$, the probabilities in Eq. (4) were computed by constructing the histogram of the values of the set $E$ using the bin-counting method and 20 bins. The histogram was
Further normalized so that the probabilities sum up to 1. The dependence of $E_{wr}$ on $\delta_1$ and $\tau$ is shown in panels (a) and (b) in Fig. 8. Panel (a) shows the dependence of $E_{wr}$ on $\delta_1$ in $[0.2, 0.7]$ for fixed $\tau = 23$, and panel (b) shows the dependence on $\tau$ in $[0, 25]$ for fixed $\delta_1 = 0.65$. A similar trend in fluctuations can be seen in panels (a) and (c) in Fig. 5, showing that chaotic behavior corresponds to higher entropy, depicted by $E_{wr}$. We also plot the weighted recurrence entropy $E_{wr}$ in Fig. 8(c) to study its dependence on $\tau$ and $\delta_1$ on $[0, 25] \times [0.2, 0.7]$. Comparing Figs. 5(c) and 8(c), we observe similar pattern variations between $K_{u}$ and $E_{wr}$. These results provide additional evidence of the dynamical complexity in the system for different parameter regimes and settings.

Our study has shown that the chaotic behavior in system (1) is the result of disorder and chaotic oscillations, which are associated with the dynamics of cancerous cells.\(^{14}\) In contrast, regular dynamics, as those discussed for system (1), are indicative of dual host protection and tumor-promoting action that lead to cancer immunoeediting. Disorderly rapid oscillations of cancerous cells are related to increased rates of entropy production and complexity in the tumor-immune interaction.\(^{39}\) This is corroborated by our finding that the rate of entropy production of the cancerous cells is higher than that of the immune and healthy cells. Thus, the increase in entropy production, driven by chaoticity, is related to the increased level of proliferation of cancerous cells. Consequently, higher entropies reflect rapid and highly uncontrolled proliferation of cancer cells.\(^{30,40}\)

**V. DISCUSSION**

Cellular interactions in the cancer-immune system give rise to different cancer-growth patterns and contribute to highly complicated and not well-understood processes. Here, we sought to explore the dynamics and complexity of a time-delay TTI system. To this end, we have performed stability and bifurcation analyses for different parameter settings. The bifurcation diagrams show a stable, periodic, and chaotic behavior. Furthermore, two-dimensional bifurcation diagrams in the form of parametric plots revealed regions of periodic and chaotic behavior that were further explored.

The appearance of chaotic behavior pinpoints the existence of metastatic cancer in the viewpoint of oncology.\(^{13}\) Two-dimensional bifurcation diagrams have identified regions of low- and high-order periodic behavior leading to period-doubling cascades to chaos. In our work, the regular and chaotic behavior revealed in the bifurcation diagrams was further corroborated by performing 0–1 tests for trajectories in the characteristic of regular and chaotic regimes. In this context, regular dynamics indicates an equilibrium state of cancer immunoeediting on the simultaneous stage in host-protective and cancer-promoting actions of the immune system. Further clinical investigation is thus necessary.\(^{12}\) Interestingly, chaotic dynamics is also found here and corresponds to long-term phenomena of cancer relapse.\(^{14,39}\)

From the viewpoint of dynamical systems, regular patterns correspond to self-organization. This means that cellular interactions are more robust. On the other hand, complex behavior is associated with weak interactions generating irregular patterns.\(^{40}\) The entropy computed from recurrence plots provides further evidence of the structural disorder in the delayed system studied here. Our work provides evidence that high entropy production, driven by chaoticity, corresponds to higher complexity, which leads to abrupt, rapid proliferation of cancer cells. This is the result of the loss of autonomic and synchronized balance in the tumorigenic (low energetic) and tumoroidal (high energetic) properties of immunity in defending cancerous cells.\(^{30,40}\)

Here, we have shown that our model exhibits regular and chaotic dynamics, depending on the choice of parameters and time-delay. Chaos is attributed to sensitive dependence of the trajectories of the system on initial conditions. This sensitivity gives rise to local instability. Chaotic behavior gives rise to increased entropy production (as opposed to entropy production in regular dynamics) and to complexity in the system. Thus, higher entropy production is driven by chaotic dynamics, which produces complexity in the system. In the case of chaotic trajectory in our model, the ability to predict the proliferation rate of tumor cell is lost, and thus, the behavior of the trajectory becomes unpredictable. However, the trajectories do not escape to infinity due to bounded solutions for all finite times. Chaoticity, thus, means that the evolution of the number of tumor cells, $T$, becomes unpredictable in time. Typically, the innate and adaptive immune cells suppress the progression of tumor proliferation by either eliminating tumor cells or by attempting to regulate their outgrowth (tumor-immune interplay). When the competition between tumor cells and their micro-environment (attributed to host cells, effector cells, and cytokines) starts to lose its efficiency, the proliferation of tumor cells is no longer strongly maintained, and thus, fast tumor growth is possible. Thus, in the framework of tumor-immune dynamics, sensitivity to initial conditions gives rise to local instability, which leads to unpredictability, increased production of entropy, complexity, and invokes the uncontrollable, unpredictable, proliferation of cancer-specific patterns\(^{42-43}\) and also to long-term cancer relapse.\(^{40}\)

On the other hand, regular dynamics indicates an equilibrium state of cancer immunoeediting on the simultaneous process in host-protective and cancer-promoting actions.\(^{11}\) This might lead to tumor dormancy, i.e., to a non-cancerous stage. Our study has shown that the chaotic behavior in our system is the result of disorder and chaotic oscillations that are associated with the dynamics of cancerous cells. In contrast, regular dynamics are indicative of dual host protection and tumor-promoting action that lead to cancer immunoeediting. Disorderly rapid oscillations of cancerous cells are related to increased rates of entropy production and complexity in the tumor-immune interaction.\(^{36}\) This is corroborated by our finding that the rate of entropy production of the cancerous cells...
is higher than that of the immune and healthy cells. Thus, the increase in entropy production, driven by chaoticity, is related to the increased level of proliferation of cancerous cells. Consequently, higher entropies reflect rapid and highly uncontrolled proliferation of cancer cells.\textsuperscript{11,40}

Finally, our study has revealed that the complexity of the tumor-immune interaction builds up with the increase in entropy production of cancerous cells attributed to unpredictable growth in the number of tumor cells, that is to chaotic dynamics. The production of oscillation patterns and variations in parameters to develop cancer treatments and novel drug therapies. Thus, it would be useful in a future publication to compare model solutions studied here with oncology and immunological data to see how closely they match.

**DATA AVAILABILITY**

The data that support the findings of this study are available within the article.

**REFERENCES**