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Review

Recent advances in ODEs modeling of tumor-immune responses: a focus on delay effects

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Abstract: This review examines recent developments in modeling the interaction between tumor cells and the immune system, with a specific focus on the application of delay differential equations (DDEs). The models serve as crucial tools to simulate and predict the immune response to tumor proliferation, thus facilitating a more effective evaluation of clinical and therapeutic strategies before their implementation. This approach enables the hypothetical testing of various interventions, thus resulting in significant time and resource savings. The central theme is the integration of DDEs to represent biologically realistic time delays. These delays—inherent in biological processes such as the activation and migration of immune cells to the tumor site—are essential for a more accurate and dynamic representation of the system. Furthermore, this document acknowledges the inherent limitations of these mathematical models, which are simplified representations of complex biological phenomena by nature. The precision and practical utility of these models depend on the use of biologically plausible delay formulations, the validation of parameters with empirical data, and the alignment of model predictions with clinical outcomes. Ultimately, this work underscores the considerable potential and significant challenges of employing mathematical models as a bridge between theoretical understanding and applied oncology.

Keywords: tumor-immune system; chemotheraphy; delay equation; periodic solutions

1. Introduction

A tumor (also known as a neoplasm) is an abnormal mass of tissue that forms when cells grow and divide more than they should or do not die when they should [1]. Malignant tumors have implications in cancer, whereas benign tumors are non-cancerous. Benign tumors may grow large but do not spread into or invade nearby tissues or other parts of the body, whereas malignant tumors can spread into or

invade nearby tissues. Additionally, they can spread to other parts of the body through the blood and lymphatic systems. Cancer encompasses over 100 distinct forms, which are classified either by their site of origin or by the specific cell type involved. The discussion of cancer has been studied from two major perspectives: solid tumors, that is, those that arise in tissues, and blood cancer cells.

Tumor growth represents a multifaceted biological phenomenon that involves intricate interactions between cancer cells, the surrounding tissues, and the immune system. While invaluable, traditional experimental methods often struggle to capture the full complexity of these processes. Mathematical models bridge this gap, thereby allowing researchers to simulate and predict tumor behavior on multiple scales–from cellular interactions to systemic progression. Those models that accurately represent tumor growth and its microenvironment can function as in silico clinical trials and provide valuable insights to select the appropriate therapeutic agents for human trials. Furthermore, they enable the optimization of treatment regimens by determining both the optimal dose schedules and the quantity of drug administration [2].

The investigation of tumor and immune interactions has a long theoretical history. Many mathematical models for tumor cell growth are delineated in the literature. Although a wealth of knowledge has been acquired to understand tumor initiation, development, progression, and the response to therapy, robust methods do not exist to reliably predict tumor growth and the response to specific therapeutic regimens for an individual patient. Unlike advances in cancer biology, investigators have developed a wealth of mathematical models and techniques to predict cancer development and the response to therapy [3]. The following selection of review-type documents presents some important examples, alongside the nearly five hundred references therein.

1) To get an idea of the significant human effort and economic resources dedicated to the fight against cancer throughout the past century, promptly up until 1997, the survey by Adam and Bellomo [4] explored mathematical modeling of tumor growth kinetics, tumor immune system interactions, kinetic cell theory, stages of tumor development, and tumor heterogeneity and growth control.
2) Contributions of mathematical modeling to the study of solid tumor growth with an argumentative view but without mathematical details can be found in the survey by Araujo and McElwain [5], where the authors offered a concise history of tumor growth research, highlighted influential mathematical models and their connections to experimental work, and showed how the interplay between theory and experimentation has advanced cancer research.
3) In contrast to the aforementioned authors, contributions of mathematical modeling to the study of tumor growth and treatment with detailed mathematical constructions can be found in the survey by Padikkamannil et al. [6], in which it is showed how certain models were made in ordinary and partial differential equations, with a specific focus on simulations and predictions of how tumors respond to various treatment strategies, thus facilitating the evaluation of hypotheses and therapeutic options before clinical application.
4) In the same line as above, in the survey by Yin et al. [7], the authors summarized mathematical models of tumor dynamics for solid tumors and of drug resistance evolution. Their models displayed a large number of basic functions that described natural tumor growth that can be implemented in ordinary and partial differential equation models, and a different set of functions specially designed for stochastic models that assumed a branching process. This article contains 100 references from which the selection of tumor growth functions that have historically been proposed.

5) The most common tumor growth functions for deterministic models are exponential, Mendelsohn, logistic, linear, surface, Gompertz, and Bertalanffy, and have been used to characterize cancer cell growth and proliferation. However, tumor development is influenced by unpredictable factors and environmental noise, such as cellular metabolism, energy demands, hormonal fluctuations, respiration, and patient-specific traits such as body mass index (BMI), genetics, smoking, and stress. Then, the survey by Tabassum et al. [8], focused on the idea that deterministic models alone cannot fully capture the dynamic nature of cancer progression, and it is necessary to develop stochastic versions of the logistic and Gompertz models to better reflect biological variability.
6) As different experimental methods allow researchers to analyze the temporal evolution of tumor growth in terms of both measurable dynamics and observable characteristics, in the paper by Benzekry et al. [9] performed a quantitative analysis of a classical model survey to explore the kinetics of tumor growth using the following: exponential, exponential linear, power law, Gompertz, logistic, generalized logistic, von Bertalanffy, and a dynamic loading model. These models were evaluated using data from two in vivo experimental systems: an ectopic syngeneic tumor and orthotopically xenografted human breast carcinoma. The authors presented how the prediction of solid tumor growth was addressed by each of the models mentioned.

As can be seen in this summary, research in the field of tumor growth modeling has only increased over the years in a variety of mathematical scenarios. In particular, mathematical modeling of tumor-immune interactions and time-delay differential equation models emerge almost naturally. Perhaps one of the first works in this direction was written by Bodnar and Fory's [10], where they proposed a discrete-time delay differential equation system inspired by Marchuk's model [11]. In this context, the time delay parameter corresponds to the time delay between the production of the immune cell and the stimulation of the effector cell. Time-delay models to study the dynamics of tumor growth have been explored in several papers; for example, see [12–16] and the references therein. Our main objective is to delve deeper into this type of model and establish their main scope.

The paper is organized as follows: Section 2 is devoted to the examination of continuous models represented by ordinary differential equations (ODEs) that confront a proliferating population, thereby representing actively dividing cells in both the nucleus and the periphery of the tumor, which interacts with other populations that may incorporate therapy-resistant quiescent cells; Section 3 presents a curated overview of tumor growth models that explicitly incorporate time-delay mechanisms, specifically focusing on the role and implementation of delays within each model, rather than providing comprehensive technical details; in Section 4, we present several established and contemporary planar differential equations with delay that characterize the dynamic interactions between effector cells ($E(t)$) and tumor cells ($T(t)$); finally, Section 5 explores a set of open problems in delay differential equation models for tumor immune interactions, and provides an executive summary of the main questions arising from the study presented in this paper.

2. A first glance at tumor immune interaction models

The availability of validated mathematical models that can predict the spatio-temporal evolution of tumor growth would allow oncologists to intervene in an optimal way for the individual patient. The landscape of mathematical modeling in cancer encompasses a diverse range of approaches, each addressing unique aspects of tumor dynamics. These models range from continuous deterministic

frameworks to discrete stochastic simulations, each offering distinct perspectives on how tumors develop, spread, and respond to interventional strategies.

First, we must first examine continuous models represented by ODEs to discuss classical mathematical approaches that describe the dynamics of the tumor cell population. These models capture the temporal evolution of cell populations through fundamental growth principles. In general, the first models are expressed as follows:

$$\frac{dT(t)}{dt} = f(t, T(t)).$$

Over the years, the growth function $f(t, T)$ has had different expressions. An interesting catalog of these functions can be found in [7–9].

Starting with the most popular simple case. The first and foundational assumption for $f(t, T)$ is to consider an exponential-type function; in such a case, we have the following:

$$\frac{dT(t)}{dt} = g(t)T(t), \tag{1}$$

where $T(t)$ represents the population of tumor cells at time t, and $g(t)$ denotes the instantaneous growth rate, which can be a time-dependent function reflecting complex biological dynamics.

This simple yet powerful differential equation encapsulates the basic mechanism of population expansion, where the rate of change in cell number is proportional to the current population size. By allowing $g(t)$ to be a function rather than a constant, the model can incorporate sophisticated biological parameters such as nutrient availability, microenvironmental constraints, or cellular interactions. The function $T(t)$, which describes the tumor cell population, is the most crucial component of the mathematical model given in (1) for almost any population growth study, especially in oncology. It corresponds to a dynamic representation of cellular proliferation that can capture various biological phenomena. An easy integration provides the general solution given by the following:

$$T(t, T_0) = T_0 \exp\left(\int_0^t g(s)ds\right), \tag{2}$$

where T_0 is the initial population of tumor cells in $t = 0$, and $\int_0^t g(s)ds$ accounts for the cumulative growth effects. The complexity of $T(t)$ can be expanded to incorporate multiple biological and external constraints, with the corresponding cost in the mathematical complexity of the model. For example, the second simple model is a general logistic growth constraint [1], which can be written as follows:

$$\frac{dT(t)}{dt} = g(t)T(t)\left(1 - \frac{T(t)}{K(t)}\right), \tag{3}$$

where $K(t)$ represents the environmental carrying capacity of tumor cells, thus modeling resource-limited growth. In general, $K(t)$ is a positive and bounded function, for example, a positive constant function $K(t) = K > 0$ or a positive p-periodic function $K(t + p) = k(t) > 0$ for all $\in t \in \mathbb{R}$ with $p > 0$ the minimal period.

Let us see an explicit solution of (3) for a particular case of $g(t)$ and $K(t)$. This solution is obtained as a direct application of the result given in [17]

Lemma 1. *Regarding Eq* (3)*, suppose that*

$$g(t) = a \quad \textit{and} \quad K(t) = K_{\max}(1 - be^{-\delta t}),$$

where $K_{\max}$ *is the saturation level of the carrying capacity of tumor cells,* a, δ *are positive constants with* δ *being the intrinsic growth rate of* $K(t)$*, and* $b = 1 - K(0)/K_{\max}$ *with* $0 < b < 1$*. Then, the exact solution of* (3) *satisfying* $T(0) = T_0$ *is given by*

$$T(t, T_0) = \frac{K_{\max} T_0}{K_{\max} e^{-at} + aT_0 \sum_{n=0}^{\infty} (b^n/(a - n\delta))(e^{-n\delta t} - e^{-at})}, \quad \forall t \geq 0. \tag{4}$$

Notice that in practical applications, the previous series solution (4) must be truncated. It is well known that Eq (3) represents a wide range of restrictions and applications and suggests the use of techniques from differential inequalities; see [7]. For example, if $g(t)$ is also p-periodic, then it can be proven that there are only two nontrivial p-periodic solutions: one locally asymptotically stable and the other unstable.

Let us see this conclusion in a particular case of the tumor cell model considered by Panetta in [1], where the author considered the following equation:

$$\frac{dT(t)}{dt} = g(t)T(t)\left(1 - \frac{T(t)}{g(t)}\right), \tag{5}$$

where $g(t)$ is a periodic function that represents the *chemotherapeutic effects* on a tumor cell mass. In this case, Eq (5) can be explicitly solved as a Bernoulli-type equation.

Lemma 2. *The solution of Eq* (5) *that satisfies* $T(0) = T_0$ *is given by:*

$$T(t, T_0) = \frac{T_0 \exp\left(\int_0^t g(s)ds\right)}{1 + T_0 \int_0^t \exp\left(\int_0^s g(\sigma)d\sigma\right)ds}. \tag{6}$$

Equation (6) describes the growth of the tumor tissue during each period, where, again, T_0 is the initial mass of tumor cells of the period. There are exactly two initials of T_0 that provide periodic solutions, namely

$$T_0 = 0 \quad \text{and} \qquad T_0^* = \frac{\exp\left(\int_0^T g(s)ds\right) - 1}{\int_0^T \exp\left(\int_0^s g(\sigma)d\sigma\right)ds}.$$

Denote the mean value of $g(t)$ with period p by the following:

$$\langle g \rangle_p = \frac{1}{p} \int_0^p g(t)dt.$$

If $0 < \langle g \rangle_p \leq 1$,then the nonnegative periodic solution $T(t, T_0^*)$ is stable and the trivial solution $T(t, 0) = 0$ is unstable. Meanwhile, if $\langle g \rangle_p < 0$, then the stability shifts, where $T(t, T_0^*)$ is now unstable and $T(t, 0) = 0$ is stable. To the best of our knowledge, Panetta's work is one of the first papers to consider chemotherapeutic effects on tumor cell growth.

Compartimental models. Let us consider an insightful growth type model with multiple compartments. This model framework provides a foundation to understand complex tumor dynamics

while remaining mathematically tractable for analysis and parameter estimation from experimental data:

$$\begin{aligned} \frac{dT_1(t)}{dt} &= f_1(t, T_1(t), T_2(t)), \\ \frac{dT_2(t)}{dt} &= f_2(t, T_1(t), T_2(t)). \end{aligned} \tag{7}$$

In general, in model (7), the variable $T_1 = T_1(t)$ refers to the proliferating population, thereby representing actively dividing cells in both the tumor core and periphery, although nutrient limitations and the availability of growth factors restrict its growth. In contrast, the $T_2 = T_2(t)$ population may embody therapy-resistant quiescent cells, thus highlighting the differential drug sensitivities between proliferating and dormant cells and underscoring the need for combination therapies that target both compartments. This type of model elucidates tumor dormancy states, where minimal growth reflects an equilibrium between T_1 and T_2, with implications for metastatic disease and recurrence patterns. The treatment timing is critical: early intervention is more effective when T_2 remains small, while antiangiogenic therapies could modulate the expansion of the dynamic carrying capacity K. Established tumors require combined strategies to address both populations, as their balance dictates the overall tumor activity and therapeutic resistance.

Table 1. Description of parameters at (8).

Variables/Parameters	Interpretation
$T_1(t)$	Proliferating population of tumor cells at time t
$T_2(t)$	Population of quiescent or non-proliferating tumor cells at time t
$K(t)$	Carrying capacity function
α	Maximum growth rate of T_1 cells
β	Rate of transition from proliferating cells to quiescent cells
γ	Death rate of quiescent cells
δ	Rate of expansion of the carrying capacity function
$K_{\max}$	Maximum saturation of the carrying capacity function

To give a precise idea of the situation described by the model (7), let us consider the Gompertz growth dynamics for the function $f_1(t, T_1(t), T_2(t))$ and a typical linear outflow of first-order kinetics for $f_2(t, T_1(t), T_2(t))$. With this, we obtain the following system:

$$\begin{aligned} \frac{dT_1(t)}{dt} &= \alpha T_1(t) \ln\left(\frac{K(t)}{T_1(t)}\right) - \beta T_1(t), \\ \frac{dT_2(t)}{dt} &= \beta T_1(t) - \gamma T_2(t), \end{aligned} \tag{8}$$

where $K(t)$ is given as in Lemma 1. Notice that system (8) implies the following:

$$T_1(t) = T_1(0)e^{H(t)} \quad \text{and} \quad T_2(t) = e^{-\gamma t}\Big(T_2(0) + \beta \int_0^t T_1(s)e^{\gamma s} ds\Big),$$

where $H(t)$ is given by

$$H(t) := \int_0^t \left(\alpha \ln\left(\frac{K(s)}{T_1(s)}\right) - \beta\right) ds.$$

We should emphasize that $T_1(t)$ represents the proliferating tumor cell population, which is comprised of dividing cells in both the core and periphery of the tumor. Its growth is constrained by the limitations of nutrients and the availability of growth factors and exhibits contact inhibition effects, as captured by the Gompertz term. Furthermore, T_2 represents the population of quiescent (non-proliferating) tumor cells, including cells from hypoxic regions, dormant cancer stem cells, and differentiated cells. These cells can exhibit different drug sensitivity profiles. In model (8), the logarithmic growth term reflects how tumor growth slows as it approaches its environmental limits, that is, the term $\ln\left(K(t)/T_1(t)\right)$ creates a logarithmic growth limitation. In fact, if $T_1(t) \approx K(t)$, then $\ln\left(K(t)/T_1(t)\right) \approx 0$ leads to near-exponential growth $T_1 \approx T_1(0)e^{-\beta t}$. More precisely, as $|T_1(t) - K(t)| \to 0$ uniformly, then $\ln\left(K(t)T_1(t)\right) \to 0$; consequently, the growth rate is density-dependent and self-limiting. Meanwhile, the carrying capacity function remains as $K(t) = K_{\max}(1 - (1 - b)e^{-\delta t})$, (see Lemma 1) where $t_0 = \ln(2b)/\delta$ determines the half saturation speed. We observe that the dynamic $K(t)$ creates a non-autonomous system where the carrying capacity evolves independently of immediate cell population changes. From the implications of the growth pattern, we observe that in the early growth phase, rapid exponential growth occurs when $T_1 \ll K(t)$, characterized by high proliferation rates and a minimal quiescent population, which corresponds to the vascular growth phase in tumor development. During the intermediate growth phase, the growth rate slows as T_1 approaches $K(t)$, which is accompanied by an increase in cell transitions to the quiescent state, marking the shift to vascular growth. In the late growth phase, growth plateaus as the carrying capacity $K(t)$ is reached, leading to a large quiescent population, which models an established tumor with a necrotic core. Finally, with respect to system (8), in the case $K(t) = K_{\max}$, there exists a unique equilibrium solution $X_* = (T_1^*, T_2^*)$ with $T_1^* = K_{\max}e^{-\beta/\alpha}$ and $T_2^* = \frac{\beta}{\gamma}T_1^*$. The ratio $T_2^*/T_1^* = \beta/\gamma$ in a steady state represents the balance between the transition cell states.

The model identifies several critical parameters that govern tumor dynamics: the ratio α/β determines the equilibrium fraction of proliferating cells T_1, while the ratio β/γ controls the accumulation of quiescent cells T_2. Furthermore, δ governs the speed of microenvironmental adaptation and $K_{\max}$ sets the ultimate tumor size limit. These parameters reveal different therapeutic targets: a reduction of α through antiproliferative drugs can suppress tumor growth, while an increase in γ through pro-apoptotic therapies can eliminate quiescent cells. Antiangiogenic strategies can slow microenvironmental adaptation by decreasing δ, and targeting $K_{\max}$ can restrict tumor expansion by modulating nutrient or spatial constraints. Together, these levers suggest a multipronged approach, thereby combining proliferation inhibition, quiescent cell elimination, and microenvironment modulation for optimal tumor control. We conclude this section by mentioning that the typical parameter values in (8) can be found in several papers; for example [18, 19] and the references therein.

3. A walk through delayed models

In mathematical modeling of tumor-immune interactions, time-delay differential equation models emerge almost naturally. DDEs provide a more biologically realistic framework to model tumor-immune interactions than traditional ODEs by explicitly incorporating time delays inherent to immune processes. Unlike ODEs, which assume instantaneous responses, DDEs account for the 24–48 hours needed for T-cell activation, the days required for clonal expansion, and the lag in cytokine signaling. This allows the system to "remember" past tumor states, meaning that a high

historical antigen exposure drives the current immune response, even if the tumor has since shrunk, thus capturing the biological reality of immune memory based on historical patterns. Consequently, DDEs naturally produce complex dynamics such as sustained oscillations, which mirror clinically observed cycles of tumor regression and progression, whereas ODEs typically converge to unrealistic steady states. Additionally, this approach also accurately models critical temporal phenomena such as the early "blind period" where a tumor establishes itself before the adaptive response is mounted, and the gradual onset of T-cell exhaustion from prolonged antigen exposure, both of which ODEs fail to capture without artificial forcing.

Within any tumor growth model, the possibilities to consider one or multiple types of delay are numerous. Therefore, to illustrate these diverse possibilities, in the following, we present an executive summary of a select set of tumor growth models that include some component that accounts for delay. We will focus on soley discussing the delay; readers interested in delving into the details of each case can refer to the cited reference to gain a better understanding of the different nuances of the models.

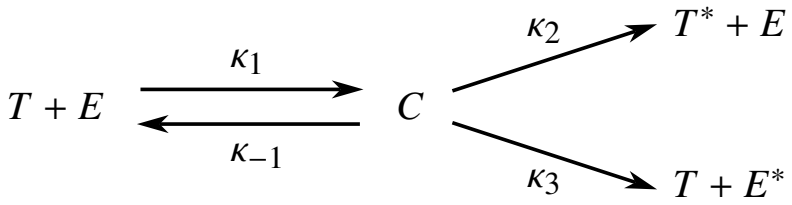

Figure 1. Kinetic diagram of the interaction (*in vitro*) between tumor cells T, effector cells E, effector-tumor cells complexes C, inactive effector cells E^*, and *lethally hit* T^* modeled by (9).

For future purposes, our starting point will be a mathematical model (with no time delay effects) proposed in 1994 by Kuznetsov et al. [20], where the authors analyzed the interactions between effector cells and tumor cells *in vitro* and presented the following autonomous system (see Figure 1):

$$\begin{aligned}
\frac{dE(t)}{dt} &= s + F(E(t), T(t)) - d_1 E(t) + \kappa_1 E(t)T(t) + (\kappa_{-1} + \kappa_3)C(t),\\
\frac{dT(t)}{dt} &= aT(t)(1 - b(T(t) + E(t))) - \kappa_1 E(t)T(t) + (\kappa_{-1} + \kappa_2)C(t),\\
\frac{dC(t)}{dt} &= \kappa_1 E(t)T(t) - (\kappa_{-1} + \kappa_2 + \kappa_3)C(t),\\
\frac{dT^*(t)}{dt} &= \kappa_3 C(t) - d_2 T^*(t),\\
\frac{dE^*(t)}{dt} &= \kappa_2 C(t) - d_3 E^*(t),
\end{aligned} \tag{9}$$

where $T(t)$, $E(t)$, $C(t)$, $T^*(t)$, and $E^*(t)$ are the concentrations of tumor cells, effector cells, effector-tumor cell complexes, terminally damaged tumor cells, and inactive effector cells at time t, respectively. A study from Kuznetsov et al. (see reference in [20]) suggested the next two major claims,

$$C \approx \frac{\kappa_1 ET}{\kappa_1 + \kappa_2 + \kappa_3} \quad \text{and} \quad F(C,T) = F(E,T) = \frac{\nu_1 ET}{\nu_2 + T} \quad \nu_1, \nu_2 > 0.$$

Table 2. Description of parameters at (9).

Variables/Parameters	Interpretation
$E(t)$	Concentration of effector cells (E-cells) at time t
$E^*(t)$	Concentraction of inactived effector cells at the time t
$T(t)$	Concentration of tumor cells (T-cells) at time t
$T^*(t)$	Concentraction of terminally damaged tumor cells at the time t
$C(t)$	Concentraction of E-T cell complexes at the time t
$F(C,T)$	Accumulation of effector cells at the tumor site due to its presence
s	Rate of the flow of adult effector cells into the tumor zone
d_1, d_2, d_3	Destruction/migration coefficients for effector, effector-tumor and tumor cell complexes and tumor cells, respectively
κ_1, κ_{-1}	Rates of binding of E-cells to T-cells and detachment of effector cells from tumor cells without damaging cells
κ_2	Rate at which effector-tumor cell interactions irreversibly program tumor cells for lysis.
κ_3	Rate at which effector cell activity is suppressed by their interactions with tumor cells
a	Intrinsic growth rate of tumor cells
b^{-1}	Carring capacity of tumor cells

Moreover, based on the experimental data given in [21, 22], a simplified model of (9) is given by the following:

$$\begin{aligned} \frac{dE(t)}{dt} &= s + \frac{pE(t)T(t)}{\nu_2 + T(t)} - mE(t)T(t) - dE(t), \\ \frac{dT(t)}{dt} &= aT(t)(1 - bT(t)) - nE(t)T(t), \end{aligned} \tag{10}$$

where $p = \nu_1\mathcal{K}$, $m = \mathcal{K}\kappa_3$, $n = \mathcal{K}\kappa_2$, $d = d_1$, and $\mathcal{K} = \kappa_1/(\kappa_2 + \kappa_3 + \kappa_{-1})$, thus allowing for the study of local stability properties of the equilibra and the characterization of critical parameters for the existence of local and global saddle-node bifurcations of transcritical bifurcations.

System (10) can be rescaled by letting

$$\begin{aligned} &x = E/E_0, \quad y = T/T_0 \quad \sigma = s/nE_0T_0, \quad \rho = p/nT_0, \\ &\eta = \nu_2/T_0, \quad \mu = m/n \quad \delta = d/nT_0, \quad \alpha = a/nT_0, \quad \text{and} \quad \beta = bT_0, \end{aligned} \tag{11}$$

with E_0, respectively,T_0 representing the initial concentrations of effector and tumor cells ($E_0, T_0 = 10^6$cells), respectively, and the time scale $t \to nT_0t$ leads to the dimensionless system

$$\begin{aligned} \frac{dx(t)}{dt} &= \sigma + \frac{\rho x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t), \\ \frac{dy(t)}{dt} &= \alpha y(t)(1 - \beta y(t)) - x(t)y(t). \end{aligned} \tag{12}$$

At this point, it is worth mentioning that d'onofrio in [23], provides a general framework for the tumor-

immune dynamics given by the following:

$$\begin{aligned} \frac{dx}{dt} &= \beta(y)x - \mu(y)x + \sigma q(y) + \theta(t), \\ \frac{dy}{dt} &= y(\alpha f(y) - \Phi(y)x), \end{aligned} \tag{13}$$

where

a. $\beta(y)$ is a differentiable and non-negative function, such that $\beta(0) = 0$, meanwhile $\mu(y)$ is differentiable, increasing and positive function.
b. $q(y)$ is a continuous function that satisfies $q(0) = 1$. Moreover, it might be non-increasing, or it could first increase and subsequently decrease. In other words, we can hypothesize that tumor growth curtails the influx of immune cells or, in contrast, provides an initial boost to it.
c. $\theta(t)$ is a non-negative periodic function that models the effects of immunotherapy.
d. $f(y)$ is a differentiable function that represents the intrinsic growth function of tumor cells, which satisfy
$$0 \leq f(0) \leq \infty, \quad \text{and} \quad \lim_{y\to\infty} yf(y) = 0.$$
and in some important cases, the existence of $0 \leq \hat{y} < \infty$ can be assumed such that $f(\hat{y}) = 0$.
e. $\Phi(y)$ is a differentiable, non-increasing, and positive function such that
$$\Phi(0) = 1 \quad \text{and} \quad \lim_{y\to\infty} y\Phi(y) \leq \infty.$$

In model (13), the influx of effector cells may be a function of the number of tumor cells (i.e., $\sigma \to \sigma q(y)$). In addition, constant, periodic, or even impulsive therapies are analytically investigated for this general class of models. We emphasize that part of the conclusions in [23] point out that the shape type of $\theta(t)$ is only a crucial factor for very high values of the therapy period T, while for realistic values of T, the elimination of tumor cells depends on the mean values of the therapy term, thus allowing the author to propose some clinical strategies to combat the progression of tumor cells.

Remark 1. *In the remainder of this section, we will adhere to the original notation found in the reference for each model. It should be noted that authors often prefer to use dimensionless variables, defined by the various parameters involved, resulting in a dimensionless model with a time delay. We will focus on discussing the implications of the delay; for a detailed description of the set of parameters in each model, the interested reader is referred to the original article.*

Model (23) is reexamined in [24, 25] when the immune response ω is negative and positive, respectively. In both papers, using τ as the bifurcation parameter, the existence of periodic solutions is proven to emerge from the appearance of a Hopf bifurcation for suitable values of τ.

Remark 2. *In the family of models (13), the mortality rate is determined by a linear function. To improve this issue, a more general non-linear functional pattern was introduced in [26], and with this, the authors evaluated how the inclusion of a delay affects the proliferation rate $\beta(x)$and may influence the behavior of the $T - IS$ interplay. Moreover, in [27], Han et al. introduce a time delay effect in the following special case:*

$$\sigma q(y(t-\tau)) = \hat{\beta} + \frac{\hat{\alpha}y(t-\tau)}{\hat{\kappa} + y(t-\tau)^2},$$

with the novelty in its immune response term being non-monotonic. With this in mind, the authors aim to investigate the novel dynamics introduced by the time-delay effects, thereby focusing on the possible existence of oscillatory solutions that potentially model recurring episodes of cancer growth.

Why is it so important to look for a Hopf bifurcation? Almost all mathematical models devoted to analyzing the dynamics between tumor cells and the immune system show a particular interest in the potential existence of stable equilibrium solutions and periodic oscillations. This dynamic often arises from what is known as a Hopf bifurcation. This type of transition, where the system moves from a stable state to limit-cycle oscillations, offers a plausible mechanism to account for periodic fluctuations in the tumor cell counts. This theoretical link is strongly supported by the biological literature, thus providing valuable insights into phenomena such as tumor evasion and relapse [28, 29], the development and treatment strategies of immunotherapies [30, 31], and long-term balance in which the tumor is never fully eradicated but also never grows uncontrollably [30, 32]. In [33], it was documented that tumors under active immune surveillance can exhibit a dynamic transition from dormancy to escape, which leads to a cyclical recurrence rather than monotonic growth. Furthermore, numerical evidence presented in [34] confirmed that the oscillatory behavior within the tumor-immune system can indeed originate from a Hopf bifurcation, thus underscoring the dynamic equilibrium between tumor latency and recurrence. Based on a special case of the Beretta-Kuang model [35, 36], Tóbiás et al. in [37] illustrated the potential role of a Hopf bifurcation in driving tumor recurrence. In addition, the identification of the parameters that induce a Hopf bifurcation provides crucial information on the conditions under which a tumor may escape immune surveillance. This information is instrumental in the development and optimization of therapeutic strategies. For example, a model may demonstrate that adjusting the therapeutic dosage or reducing a specific time delay can steer the system away from a recurrent oscillatory state, thus facilitating the return to a stable, tumor-free state; for example, see [32] and the references therein. Moreover, analyzing the direction and stability of the resulting limit cycle offers a predictive measure of whether the oscillations will grow in amplitude, which leads to disease progression, or shrink, which ultimately results in tumor regression.

For a more detailed analysis of the linear analysis of the model with delays in the possible equilibria (i.e., the tumor-free and positive equilibria and the existence of a Hopf bifurcation in these equilibria), see [15]. Other types of bifurcations, such as the Bogdanov-Takens bifurcation and the steady-state bifurcation, and for details of numerical simulations used to illustrate the theoretical analysis and results, see [24, 38, 39].

In search of a better biological reality, Yu et al. in [40] considered that the immune system requires considerable time to mount an effective response after identifying non-self cells. Therefore, they modeled the proliferation of effector cells stimulated by Helper T-cells, thus necessitating the incorporation of temporal delay effects. There exist two primary approaches to integrate delays into ODE systems: direct delay terms, which introduce explicit delay components; and kernel function approach, which implements a memory kernel as an additional model compartment. In this article, the authors employ a distributed delay represented by the following integral expression:

$$G(t) = \int_{-\infty}^{t} be^{-b(t-s)}z(s)ds, \tag{14}$$

where b is a positive constant that expresses the intensity of the delay, and $z(t)$ denotes the

dimensionless density of the Helper T cell population, which captures the delayed immune activation dynamics in the following model.

$$\begin{aligned}\frac{dx(t)}{dt} =&\alpha x(t)(1-\beta x(t)) - x(t)y(t),\\ \frac{dy(t)}{dt} =&\sigma_1 - \delta_1 y(t) + \rho y(t)G(t),\\ \frac{dz(t)}{dt} =&\sigma_2 - \delta_2 z(t) + \omega x(t)z(t),\\ \frac{dG(t)}{dt} =&bz(t) - bG(t).\end{aligned} \tag{15}$$

In [41], Sadar et al. proposed and analyzed a system of three coupled nonlinear ordinary differential equations, namely tumor cells, effector cells, and cytokine interleukin-2 (IL-2) as follows:

$$\begin{aligned}\frac{dx(t)}{dt} &= \alpha x(t)(1-\beta x(t)) - d_1 x(t)y(t),\\ \frac{dy(t)}{dt} &= c_2 + p_2 y(t-\tau)z(t-\tau) - d_2 y(t),\\ \frac{dz(t)}{dt} &= c_3 + p_3 x(t)y(t) - d_3 z(t),\end{aligned} \tag{16}$$

respectively. Using transversality conditions, they analyzed the Hopf bifurcation by using the time delay as a bifurcation parameter. The authors also estimated the length of the time delay parameter by applying the Laplace transformation to preserve the stability of the periodic limit cycle, which provides insight into the mode of action in controlling oscillations in the growth of tumor cells.

In [42], it was the authors considered that effector $\mathcal{T}$ cells ($\mathcal{T}$-lymphocytes) play a key role in the immune surveillance of tumors, thereby participating in kinetic processes that can eliminate malignant cells. The main challenges to the immune efficacy of the tumor microenvironment that they consider are as follows:

1) Tumor cells actively compete with $\mathcal{T}$- lymphocytes, inducing functional anergy in these immune cells;
2) Malignant cells secrete proliferative cytokines that promote tumor growth and survival; and
3) The resulting biological interactions create a significant time delay in tumor cell clearance by $\mathcal{T}$-lymphocytes.

This temporal delay, which we denote as τ, represents the cumulative effect of the following:

1) Immune recognition and activation latency;
2) Tumor-immune interaction dynamics; and
3) Functional suppression of cytotoxic $\mathcal{T}$-cells.

Mathematically, we can express this delayed tumor-immune interaction as follows:

$$\frac{dT(t)}{dt} = \underbrace{rT(t)}_{\text{growth}} - \underbrace{\delta T(t-\tau)E(t-\tau)}_{\text{delayed killing}} + \underbrace{\alpha T(t)E(t)}_{\text{immune suppression}}, \tag{17}$$

where $T(t)$ represents the tumor cell population, $E(t)$ denotes the concentration of effector $\mathcal{T}$ cells, τ is the cumulative time delay, and the parameters r, δ, and α represent the growth, death, and suppression rates, respectively. With this in mind and the use of non-dimensional variables and parameters, they studied the following model:

$$\begin{aligned}\frac{dx}{dt} &= -x(t) + \frac{y(t-\Delta)z(t-\Delta)}{1+z(t-\Delta)},\\ \frac{dy}{dt} &= a_1x(t) - a_2y(t) + a_3,\\ \frac{dz}{dt} &= a_4z(t) - y(t-\Delta)z(t-\Delta),\end{aligned} \tag{18}$$

where Δ represents the discrete-time delay factor added for the interaction and stimulation delay of the tumor-immune system. In [43], a model was proposed that studied the effect of a glucose risk factor on breast cancer, thereby considering the interaction between cancer and immune cells as instantaneous, though this undergoes some biological process before such an interaction can manifest itself. Therefore, in this study, a time delay is incorporated to depict the biological process that causes the delay caused by the interaction in the suppression of immune cells and the derivation of cytokines by tumor cells, as well as to investigate how the resulting dynamics are affected by the time delay. The proposed model, which includes three equations–normal cells, $N(t)$, tumor cells, $T(t)$, and immune cells, $M(t)$ – is presented by the following delay differential system:

$$\begin{aligned}\frac{dN(t)}{dt} &= N(t)(\alpha_1 - \mu_1N(t)) - \phi_1N(t)T(t),\\ \frac{dT(t)}{dt} &= T(t)(\alpha_2 - \mu_2T(t)) + gT(t) - \gamma_1M(t-\tau)T(t-\tau) + \phi_2N(t)T(t),\\ \frac{dM(t)}{dt} &= s + \frac{\rho M(t)T(t)}{\omega + T(t)} - \gamma_2M(t-\tau)T(t-\tau) - \mu_3M(t) - gM(t),\end{aligned} \tag{19}$$

with initial conditions.

$$\begin{aligned}&N(s) = \Upsilon_1(s), \quad C(s) = \Upsilon_2(s), \quad \text{and} \quad M(s) = \Upsilon_3(s)\\ &\Upsilon_1(s), \Upsilon_2(s), \Upsilon_3(s) \geq 0,\ s \in [-\tau, 0], \quad \Upsilon_1(0), \Upsilon_2(0), \Upsilon_3(0) > 0,\end{aligned}$$

where $\Upsilon(s) := (\Upsilon_1(s), \Upsilon_1(s), \Upsilon_3(s)) \in C([-\tau, 0], \mathbb{R}^3_+)$ is the Banach space of continuous functions mapping $[-\tau, 0]$ into $\mathbb{R}^3_+$. Here, τ is used to describe the time it takes tumor cells to secrete immunosuppressive cytokines to evade immune surveillance and the time it takes immune cells to recognize and attack tumor cells. $\gamma M(t-\tau)T(t-\tau)$ represents the delay in the clearance of cancer cells by immune cells, and $\gamma M(t-\tau)T(t-\tau)$ describes the delay in the clearance of immune cells by tumor cells.

Biological systems inherently exhibit stochastic variability, particularly in the expression levels of neoantigens that initiate immune responses and the molecular signals required for T cell activation. The complex tumor-immune interplay requires consideration of random fluctuations, which is especially significant when dealing with small cell populations. To incorporate stochasticity into deterministic frameworks, there are two principal methodologies:

1) Parameter substitution approach

a) Replace deterministic parameters with stochastic counterparts
b) Introduce white or colored noise perturbations

2) Direct forcing approach
   a) Add stochastic driving forces to the system equations
   b) Maintain original parameter values

In [44], Alsakaji et al. implemented the second methodology through

$$dX(t) = f(X)dt + \sigma(X)dW(t), \tag{20}$$

where $X(t) = (E(t), T(t), I(t))^{tr}$ are the variables in the system, with $f(X)$ provides the deterministic dynamics, $\sigma(X)$ is the noise intensity matrix, and $dW(t)$ represents a Wiener process increase. In this setting, the stochastic differential system is given by the following:

$$\begin{aligned} dE(t) &= \left[\alpha E(t-\tau_1)T(t-\tau_1) - \eta_1 E(t) + \mu_1 E(t)I(t) + e_1\right]dt + \gamma_1 H_1 dW_1, \\ dT(t) &= \left[rT(1-\beta T) - \xi E(t)T(t)\right]dt + \gamma_2 H_2 dW_2, \\ dI(t) &= \left[\eta_2 E(t-\tau_2)T(t-\tau_2) - \mu_2 I(t) + e_2\right]dt + \gamma_3 H_3 dW_3, \end{aligned} \tag{21}$$

with initial conditions

$$\begin{aligned} &E(s) = \Phi_1(s), \quad T(s) = \Phi_2(s), \quad \text{and} \quad I(s) = \Phi_3(s). \\ &\Phi_1(s), \Phi_2(s), \Phi_3(s) \geq 0, \ s \in [-\tau, 0], \end{aligned}$$

where $\Phi(s) := (\Phi_1(s), \Phi_2(s), \Phi_3(s)) \in C([-\tau, 0], \mathbb{R}^3_+)$ is the Banach space of continuous functions mapped $[-\tau, 0]$ to $\mathbb{R}^3_+$. where $\tau = \max\{\tau_1, \tau_2\}$. The stochastic components W_i $(i = 1, 2, 3)$ represent independent Brownian motions defined in a complete probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P})$ with filtration $\{\mathcal{F}_t\}_{t\geq 0}$ that satisfies the following:

1) Usual conditions:
   ‡) Right-continuity: $\mathcal{F}_t = \bigcap_{s>t} \mathcal{F}_s$
   ‡) Completeness: $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets
2) Independence:
$$\mathbb{E}[W_i(t)W_j(s)] = \delta_{ij} \min(t, s),$$
   where $\mathbb{E}$ represents the usual mathematical expectation value, and δ_{ij} is the Kronecker delta.
3) The probability space satisfies:
$$\mathbb{P}(\omega \in \Omega : W_i(0) = 0) = 1.$$
4) $H_i = H_i(E, I, T)$, $(i = 1, 2, 3)$ are locally Lipschitz-continuous functions of certain form.

The combined effects of multiple time delays and stochastic perturbations on the dynamics of the tumor-immune system and control optimization are examined. Their detailed mathematical framework incorporates the following:

I. Two distinct time delays representing:

- Immune response activation latency
- Tumor-immune interaction duration

II. Multiplicative white noise processes modeling:

- Biological fluctuations in cell populations
- Environmental stochasticity

4. On two-dimensional immune-tumor delayed models

In the following lines, we will show some recent and well-known planar differential equation systems that model, simulate, and analyze the dynamics between effector cells $E = E(t)$ and tumor cells $T = T(t)$, both analytically and numerically. In Section 3, we already introduced some of these models through a simplification of the seminal model (9) proposed by Kuznetsov et al. The following models are not necessarily presented chronologically, but follow a certain structure of complexity.

Let us begin with the system analyzed by Li et al. in [45], which is given by the following:

$$\begin{aligned} \frac{dE}{dt} &= \sigma + \hat{\mu}T(t-\tau)E(t) - \eta E(t), \\ \frac{dT}{dt} &= aT(t)(1 - bT(t)) - nE(t)T(t). \end{aligned} \tag{22}$$

Table 3. Description of parameters at (22).

Variables/Parameters	Interpretation
$E(t)$	Concentrations of effector cells at time t
$T(t)$	Concentrations of tumor cells at time t
σ	Constant input of effector cells
$\hat{\mu}$	Rate of action of the tumor cells to the effector cells
η	Natural elimination (death) rate of effector cells
a	Intrinsic growth rate of tumor cells
b^{-1}	Carring capacity of tumor cells
n	Rate at which effector cells damage (kill) the tumor cells

In system (22), the parameter $\tau \geq 0$ represents the time progress of the tumor cells; in this sense, at time t, the effector cells $E(t)$ react to the tumor cells that arise at time $t-\tau$. Consequently, $\hat{\mu}T(t-\tau)E(t)$ gives the total effects of tumor cells $T(t-\tau)$ on effector cells $E(t)$. It is worth mentioning that all parameters in (22) are nonnegative except for $\hat{\mu}$. When $\hat{\mu} > 0$, it indicates that the immune system's ability to stimulate the production or activity of effector cells is enhanced due to the presence of tumor cells. Instead, if $\hat{\mu} < 0$, then the inhibitory and neutralizing effects of the tumor cells over the effector cells are favored. In [45], Li et al. provided sufficient conditions for the global stability and bistability properties of tumor-free equilibria via the Fluctuation Lemma [46] and the appearance of a stable periodic solution through the Hopf bifurcation.

The model proposed by Li et. al. was based on perhaps one of the first time delay models for studying the dynamic behavior of a tumor-immune system, written by Galach in [47], where the author changed the Michaelis-Menten form of $F(E,T)$ in (10) by $F(E,T) = \hat{p}ET$ and performed the same

scaling given in (11) to obtain the time delay model (with a slight abuse of notation $x \to E$ and $y \to T$) as follows:

$$\begin{aligned} \frac{dE(t)}{dt} &= \sigma + \omega E(t-s)T(t-s) - \delta E(t), \\ \frac{dT(t)}{dt} &= \alpha T(t)(1-\beta T(t)) - E(t)T(t), \end{aligned} \tag{23}$$

where the parameter $\omega := \hat{p} - \mu$ describes the immune response to the presence of tumor cells. Consequently, model (23) can be viewed as a time-delayed version of the simplified model (12) given in [20], which describes the response of effector cells of a dimensionless density $E(t)$ to the dimensionless growth density of tumor cells $T(t)$. For system (23), the parameter $s \geq 0$ is the time delay of the immune system to produce suitable effector cells after the recognition of a nonself cell, that is, the immune system needs some time s to develop a suitable response after recognition of a nonself cell. In [47], Galach presented an analytical and numerical study of the stability properties of the corresponding equilibrium points and the appearance of oscillations.

Model (23) is reexamined in [24] and [25] when the immune response ω is negative and positive, respectively. In both papers, using s as the bifurcation parameter, the existence of periodic solutions is proven to emerge from the appearance of a Hopf bifurcation for suitable values of s.

System (23) can be viewed as a simplified version of the model.

$$\begin{aligned} \frac{dE(t)}{dt} &= \sigma + \frac{pE(t-s)T(t-s)}{g + T(t-s)} - mE(t)T(t) - \eta E(t), \\ \frac{dT(t)}{dt} &= aT(t)(1-bT(t)) - nE(t)T(t), \end{aligned} \tag{24}$$

given by Khajanchi and Banerjee in [16]. System (24) is a modified version of Kuznetsov's model for the dynamics between effector cells found in [20]. The modification involves adding a time delay to the corresponding recruitment term in the equation for effector cells. In that paper, the discrete time delay referred to the time lag between the stimulated accumulation of effector cells close to tumor cells and the interaction with the tumor cells themselves. As in [10], Khajanchi et al. in [16] established sufficient conditions for a Hopf bifurcation at critical values s, thereby showing the existence of periodic orbits.

Table 4. Description of parameters at (24).

Variables/Parameters	Interpretation
$pET/(g+T)$	Recruiment term of effector cells
p	Maximum value of the Michaelis-Menten function $pT/(g+T)$
g	Half saturation rate of tumor cells
m	Rate at which tumor cells damage (neutralize) the effector cells
$\sigma, \eta, a, b^{-1}, n$	As is Table 3

Finally, in a recent article [48], the authors of that paper considered a model of chimeric antigen receptor therapy (CAR-$\mathcal{T}$ cells) with a population size $C(t)$ that interacted with Glioblastoma (the tumor $T = T(t)$-cells). This model included a time delay in the term that described interactions between

Glioblastoma cells and CAR cells, which are responsible for the appearance of new CAR cells:

$$\begin{aligned} \frac{dC(t)}{dt} &= \frac{aT(t-\theta)C(t-\theta)}{1+T(t-\theta)} - \left(\frac{bT(t)}{1+C(t)} + 1\right)C(t), \\ \frac{dT(t)}{dt} &= (\rho_T f(T(t)) - \alpha_T C(t))T(t), \end{aligned} \tag{25}$$

where the parameter θ reflects the time needed to trigger the production of CAR cells in the organism, ρ_T denotes the rate at which CAR-$\mathcal{T}$ cell proliferation is triggered by interactions with tumor cells, and the hypothesis is held that tumor cells are eliminated using an efficiency parameter α_T. In general, the authors assume that f is at least in the $\mathbf{C}^1$ class and is a decreasing function with $f(0) = 1$ and $f(K) = 0$, which leads the consideration of a logistic-type growth, and K reflects the tumor carrying capacity, that is, the maximum tumor size. The classic logistic growth with $f(T) = 1 - T/K$ satisfies these assumptions, thus making it a suitable choice for our calculations and numerical analysis, in particular. Another example of a logistic-type function corresponds to the Richard growth function, with $f(T) = 1 - (T/K)^\nu$ for $\nu > 0$, which was used in the Greenspan model with $\nu = 2/3$. This assumption analysis does not cover the Gompertz growth (with f being unbounded for $T \to 0$) as assumption $f(0) = 1$ is crucial for the obtained results.

Tumor-system interaction with two time delays. Until now, previous delay models on the dynamics between effector cells and tumor cells considered positive effects on the growth of effector cells due to "stimulation in the immune system" due to the presence of tumor cells. However, it should be reasonably expected that tumor cells also have negative effects on effector cell growth. This interaction was first pointed out in [23, 49] and subsequently taken into account in [16]. The previous observation was revisited by Li et al. in [50], who presented the following modified version of (22):

$$\begin{aligned} \frac{dE}{dt} &= \sigma + \mu T(t-\tau)E(t) - \beta T(t-\omega)E(t) - \eta E(t), \\ \frac{dT}{dt} &= aT(t)(1 - bT(t)) - nE(t)T(t), \end{aligned} \tag{26}$$

Table 5. Description of parameters at (26).

Variables/Parameters	Interpretation
μ	Coefficient of action of the tumor cells to the effector cells
β	Decline rate of effector cells neutralized by the tumor cells
$\sigma, \eta, a, b^{-1}, n$	As is Table 3

with $\mu, \beta > 0$. The parameter τ has the same interpretation as in model (22) and ω is the neutralization delay parameter (i.e., tumor cells that developed at the time $t-\omega$ negatively affect the growth of effector cells at time t). Concerning the dynamics of (26) we point out two interesting results. First, in the case where the model exhibits only tumor-present equilibrium, it undergoes multiple stability switches as the neutralization delay ω increases; this contrasts with the scenario where $\omega = 0$, in which its stability can change at most once as the stimulation delay τ increases. Second, under appropriate assumptions, when two tumor-present equilibria emerge, numerical simulations indicate the clinical effect known as either the burst of effector cells or the cytokine storm [51, 52].

Up to this point, the effect of the time delay is considered only in the immune response across all the models presented. However, a delayed effect can also appear in the binding of tumor cells and effector cells, which decreases the tumor cell growth. An interesting model that considers this scenario can be found in [15], where the authors introduced another time delay s in (23) and presented the following system:

$$\begin{aligned} \frac{dE(t)}{dt} &= \sigma + \mu E(t-\tau)T(t-\tau) - mE(t)T(t) - \eta E(t), \\ \frac{dT(t)}{dt} &= aT(t)(1-bT(t)) - nE(t-\tau)T(t-s). \end{aligned} \tag{27}$$

Regarding the dynamics of system (27), [15] only considered the case $\tau = s$, for which the authors proved the existence and stability of periodic solutions via the Hopf bifurcation theory, in addition to Bogdanov-Takens bifurcations at the tumor-free equilibrium point.

We conclude this section by mentioning a recent model that combines both chemotherapeutic effects on the tumor cell mass and time-delayed effects of the immune system. In [53], the following non-autonomous time-delay differential system was considered:

$$\begin{aligned} \frac{dE(t)}{dt} &= \sigma + \frac{pE(t-\tau)T(t-\tau)}{g + rT(t-\tau)} - mE(t)T(t-\omega) - \eta E(t), \\ \frac{dT(t)}{dt} &= T(t)G_\nu(t, T(t)) - nE(t-\tau)T(t), \end{aligned} \tag{28}$$

where $G_\nu(t, T)$ is the relative growth rate of tumor cells that corresponds to a generalized logistic growth function [54], in particular, given by

$$G_\nu(t, T) = a\Big[\frac{(1-T^\nu)}{\nu} - b(t)\Big],$$

with $r \in [0, 1]$, $\nu \in (0, 1]$ and $b(t) \in C(\mathbb{R}/p\mathbb{Z})$ (continuous and p-periodic function). As before, $\tau \in \mathbb{R}_{\geq 0}$ and $\omega \in \mathbb{R}_{\geq 0}$ are the response time delay of the immune system to an invasion of tumor cells, and the time delay of tumor cells in response to the appearance of effector cells, respectively. In particular, for $\nu = 1$ and $\nu \searrow 0$, we obtain the following:

$$G_1(r, T) = a[(1-T) - b(t)] \quad \text{and} \quad G_0(r, T) = a[\ln \frac{1}{T} - b(t)],$$

which corresponds to the time-periodic logistic relative and the Gompertz relative growth rate, respectively. Although it is still under development in [53], its authors have already provided a detailed stability analysis of the equilibria and demonstrated the existence of critical delay values where Hopf bifurcations emerge. In addition, they used an analytic continuation technique (based on an appropriate formulation of the Implicit Function Theorem in Banach spaces) to prove the existence of periodic solutions that arise from the autonomous and delay-free case (i.e., for $b(t) = b$ and $\tau = \omega = 0$). It should be noted that system (28) synthesizes several time-delayed models shown in this document.

An emerging field of research. Oncolytic virotherapy is a promising clinically emerging approach for cancer treatment. Unlike traditional therapies such as chemotherapy, this approach not only directly

eliminates cancer cells (the oncolytic effect), but also triggers a systemic immune response against the tumor. Oncolytic viruses are designed to selectively infect and replicate in tumor cells, thus leaving the healthy tissue unharmed. This significantly reduces side effects and improves the patient's quality of life.

Virotherapy works in two primary ways:

1) *Immune system activation.* When infected cells break open, they release tumor antigens and viral particles that act as an "in situ vaccine". This teaches the immune system to recognize and attack any remaining malignant cells throughout the body, thus creating a powerful and lasting immune response.
2) *Direct cell death.* The viruses directly kill cancer cells, that is, they recognize and eliminate malignant cells, even in locations far from the original tumor. This is known as the oncolytic effect.

Another advantage of this therapy is that it can be used in combination with conventional treatments such as chemotherapy, radiation therapy, and other immunotherapies. This combination often produces synergistic effects, which means that the combined effect is greater than the sum of the individual effects. This can help overcome tumor resistance to other treatments. Given the rapid tumor growth, it is crucial to account for the infection delays inherent to oncolytic viruses in the mathematical models of this therapy.

In 2020, Li et al. [28] addressed this by introducing a delay differential equation model based on the work of Dingli et al. [55] and Kim et al. [56], and incorporated two key delays. The model improved upon several previous models conceived to describe the dynamics among cancer cells, immune cells, and oncolytic viruses. The four-dimensional model is given by the following:

$$\begin{aligned}
\frac{dE(t)}{dt} &= \rho_1 T(t)E(t) + \rho_2 T_i(t)E(t) - \delta_1 E(t),\\
\frac{dV(t)}{dt} &= \rho_3 T_i(t) - \delta_2 V(t),\\
\frac{dT_i(t)}{dt} &= (1-\eta_a)\beta e^{m\tau_1} T(t-\tau_1)V(t-\tau_1) - \varepsilon_1 E(t)T_i(t) - \delta_3 T_i(t),\\
\frac{dT(t)}{dt} &= \rho_4 T(t)(1 - b(T(t) + T_i(t)) - e^{m\tau_0}(1-\eta_a)\beta V(t-\tau_0)T(t-\tau_0) - \varepsilon_2 E(t)T(t).
\end{aligned} \tag{29}$$

In system (29), the first delay parameters τ_0 (with $0 \le \tau_0 \le \tau_1$) represent the time from a virus entering a tumor cell to the start of genome replication in the viral life cycle. However, virus genome replication can be stopped by specific chemicals secreted by tumor cells. Therefore, only a fraction $(1 - \eta_a)$ of viruses is considered effectively infected.

The second delay τ_1 stands for the total intracellular time delay, which covers the entire viral life cycle, from initial entry into a tumor cell to the release of new virions from that infected cell. The study conducted by Li et al. [28] provided an analytical and numerical study of the stability and bifurcation of the equilibria at (29) for three different scenarios depending on the specific values of the two delays, i.e., $\tau_0 = \tau_1 = 0$, $\tau_0 = 0 < \tau_1$, and $0 < \tau_0 < \tau_1$. By doing so, the authors provided a more realistic mathematical framework to study tumor virotherapy, showing the impact of these delays on the system's dynamics, stability, and existence of Hopf bifurcations. In addition, the theoretical findings

of the paper were supported by numerical simulations, where the parameter values refer to [55, 56], which are obtained as data from several clinical trials.

The previous and more important questions about oncolytic virotherapy can be found in [28,55–58] and the references therein.

Table 6. Description of parameters at (29).

Variables/Parameters	Interpretation
$E(t)$	Concentration of Cytotoxic T-Lymphocytes (CTLs-cells) at time t
$V(t)$	Concentration of virus cells (V-cells) at time t
$T_i(t)$	Concentration of tumor cells (T_i-cells) infected by the virus at time t
$T(t)$	Concentration of uninfected tumor cells (T-cells) at the time t
$\delta_1^{-1}, \delta_2^{-1}, \delta_3^{-1}$	Natural lifespan coefficients on an average $1/\delta_j$ days for CTLs-cells, V-cells and virus-infected T_i-cells respectively
ρ_1, ρ_2	Rates of binding of CTLs-cells with the T-cells and T_i-cells respectively
ρ_3, ρ_4	Rate at which T_i-cells produce V-cells and maximal growth rate of the tumor cells respectively
$\varepsilon_1, \varepsilon_2$	Rate at which T_i-cells and T-cells activity are suppressed by their interactions with CTLs-cells respectively
η_a	Proportion of virus cells whose genome replication may be inhibited by specific chemicals secreted by tumor cells
β	Rate at which tumor cells are infected after contacting with virus cells
b^{-1}	Carring capacity of tumor cells
m^{-1}	Average lifetime of an infected tumor cell
$e^{-m\tau}$	Survival probability of an infected tumor cell in the interval $[0, \tau]$

5. Conclusions and some open problems on delayed models

Analyzing how effector and tumor cells interact presents numerous challenges that continue to confront many scientists. DDEs offer a biologically realistic framework to model tumor growth by accounting for the inherent time lags in cellular processes. These delays reflect phenomena such as cell-cycle progression, immune system activation, drug absorption and distribution, and gene expression dynamics. Although substantial advances have been made, many critical questions in this field remain unresolved. To our knowledge, a major challenge is the precise quantification of time delays. These delays can originate from a variety of biological sources, including the following:

1) *Effector cell activation time*: The period of time required for immune cells to recognize and activate after contact with tumor cells.
2) *Tumor cell proliferation time*: The duration in which tumor cells divide and expand their population.
3) *Treatment response time:* If treatments are incorporated, this refers to the delay in the manifestation of their effects. Often, these delays are assumed to be constant or estimated based on data *in vitro* or *ex vivo*, which may not accurately reflect the complexity observed in vivo. Therefore, identifying robust methods to directly estimate these delays from clinical or preclinical data remains an open problem.

To sum up, DDEs offer a powerful tool for to understand effector-tumor cell interactions and open problems which revolve around integrating biological complexity (heterogeneity, escape mechanisms, spatiality) with high mathematical barriers (delay quantification, local and stability analysis of equilibria, optimization problems). Addressing these challenges is essential for mathematical modeling to have a more significant impact on cancer understanding and treatment.

Three key points are given in this document.

1) *Purpose of modeling*: The goal of these models is to simulate and predict the immune system's response to the proliferation of tumor cells. This allows for an improved evaluation and better decision-making regarding clinical and therapeutic strategies before they are implemented in practice.
2) *Recognition of limitations*: The document also highlights that these models, while useful, have inherent limitations. They significantly simplify the complex biological behavior of tumors. Therefore, their precision and usefulness depend a lot on the realistic formulation of the delay, the validation of the parameters, and the alignment of the models with clinical data.
3) *Connection between theory and practice*: The article emphasizes that, while these theoretical models are a powerful tool, they still present considerable challenges in bridging the gap between theoretical and applied oncology.

We would like to emphasize that this paper suits the presentation of some current mathematical models to maintain the dynamics between tumor cells and the immune system, not their biological or clinical relevance and application. The differential equation models of tumor growth integrate experimental or clinical data to validate their predictions; for example, reference [59] described how some researchers used time-resolved microscopy data to systematically calibrate apoptosis, proliferation, and necrosis rates, as well as the mobility parameters within mathematical models, with a careful quantitative characterization of uncertainties in both the experimental data and the modeling process; and reference [60] presented a sophisticated hybrid tool that combined computational modeling with experimental data to accurately simulate and predict the complex evolving behavior of diverse cancer cells. It captured how these cells variably grow, spread, and respond both spatially and temporally, thus providing high-accuracy forecasts of tumor progression before and after chemotherapy treatment.

We conclude this document with a brief list of associated mathematical problems.

Open problem 1: Consider the generalized Gompertz model with multiple time-dependent delays:

$$\frac{dT(t)}{dt} = r(t)T(t-\tau_1(t))\ln\left(\frac{K(t-\tau_2(t))}{T(t-\tau_3(t))}\right), \tag{30}$$

where $\tau_i(t)$ are time-dependent delay functions.

1) Under what conditions on $\tau_i(t)$ does the system remain stable? The current theory is limited to constant delays.
2) How do time-dependent delays affect Hopf bifurcations and the oscillatory behavior?
3) What biological mechanisms justify specific forms of $\tau_i(t)$?.
4) How can we reliably estimate time-dependent delay functions from experimental data?

Open problem 2: Consider a stochastic DDE with multiplicative noise:

$$dT(t) = \left(T(t-\tau)\left(1 - \frac{T(t-\tau)}{K}\right) - \delta T(t)\right)dt + \sigma T(t-\tau)dW(t), \tag{31}$$

where $W(t)$ is a Wiener process.

1) Under what conditions do strong solutions exist for nonlinear stochastic DDEs with state-dependent noise?
2) What are the conditions for extinction vs. persistence in stochastic delay models?
3) Can delayed stochastic terms induce transitions between different growth regimes?
4) What are the optimal numerical schemes for stochastic DDEs with high-dimensional noise?

Open Problem 3: Consider the integro-differential system:

$$\frac{dT(t)}{dt} = rT(t)\left(1 - \frac{T(t)}{K}\right) - \int_0^\infty k_1(\tau)I(t-\tau)T(t-\tau)d\tau, \tag{32}$$

$$\frac{dI(t)}{dt} = \int_0^\infty k_2(\tau)T(t-\tau)d\tau - \mu I(t) - \int_0^\infty k_3(\tau)I(t-\tau)T(t-\tau)d\tau, \tag{33}$$

where $T(t)$ and $I(t)$ represent tumor and immune cell populations, respectively.

1) What are the appropriate mathematical forms for delay kernels $k_i(\tau)$ based on biological mechanisms?
2) How do distributed delays affect the stability of equilibria in immune-tumor systems?
3) Under what conditions do distributed delays induce sustained oscillations?
4) How do different memory kernels influence long-term tumor-immune dynamics?

Open Problem 4: Consider a model of treatment response with pharmacokinetic delays:

$$\frac{dT(t)}{dt} = rT(t)\left(1 - \frac{T(t)}{K}\right) - \int_{-\infty}^t k(t-s)u(s)T(s)ds, \tag{34}$$

$$\frac{du(t)}{dt} = -\lambda u(t) + \sum_i \delta(t-t_i)D_i, \tag{35}$$

where $u(t)$ represents the drug concentration, and $k(t-s)$ is the pharmacokinetic delay kernel.

1) What is the optimal dosing strategy for delay differential equation models with pharmacokinetic delays?
2) How do treatment delays affect the evolution of drug resistance?
3) How should multiple drugs with different delay profiles be optimally combined?
4) How can patient-specific delay parameters be incorporated into treatment optimization?

Remark 3. *Beyond the models in differential equations, there are an endless number of other types of models represented in the same type of mathematical schemes. With the aim of mentioning some of these examples, we have the following:*

1) *Heterogeneous Population Dynamics are given by*

$$\mathcal{T}(t) = \sum_{i=1}^{n} \mathcal{T}_i(t), \tag{36}$$

represent subpopulations with distinct proliferative behaviors, such as proliferating cells, quiescent cells, cells undergoing differentiation, and cells experiencing apoptosis, among others.

2) *Stochastic variations that incorporate random fluctuations into the model, for example, genetic heterogeneity, microenvironmental variability, and uncertainties in cell interactions. A well-known stochastic model is the continuous-time branching process, specifically, the birth-and-death process.*

$$P(\mathcal{T}(t+\Delta t) = n | \mathcal{T}(t) = m) = \sum_{k=0}^{m} \binom{m}{k} [p_b(t)]^k [1 - p_b(t)]^{m-k} [p_d(t)]^{n-m+k}. \tag{37}$$

3) *Models involving partial differential equations are abundant; the seminal Chaplain-Anderson model is one of the most cited and influential models in mathematical oncology:*

$$\begin{aligned} \frac{\partial n}{\partial t} &= D_n \nabla^2 n + \rho n(1-n) - \mu n, \\ \frac{\partial c}{\partial t} &= D_c \nabla^2 c - \lambda n c + S, \\ \frac{\partial f}{\partial t} &= D_f \nabla^2 f + \alpha n - \beta f, \\ \frac{\partial e}{\partial t} &= D_e \nabla^2 e + \chi \nabla \cdot (e \nabla f) + \gamma e(1-e) - \delta e, \end{aligned} \tag{38}$$

where $n(\mathbf{x}, t)$ is the tumor cell density at position $\mathbf{x}$ and time t, $c(\mathbf{x}, t)$ is the nutrient (oxygen) concentration, $f(\mathbf{x}, t)$ is the tumor angiogenic factor concentration, and $e(\mathbf{x}, t)$ is the endothelial cell density.

4) *Models involving any type of differential equation or stochastic process have started to be treated by the new setting of physics-informed neural networks and the Machine Learning techniques applied there.*

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there is no conflict of interest.

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