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Delay Differential Equations Modelling and Stability of Tumor Growth with Immune Responses

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Abstract

The development of tumors is a very complicated biological process, which is controlled by various interacting factors, such as the proliferation of cells, immune system, nutrients, and treatment. Mathematical and computational modelling is an efficient method to the comprehension of the mechanisms governing tumor dynamics. In the present paper, we construct a delayed differential equation model that is used to explain the interaction between tumor cells and the responses of immune system. Linearization techniques and analysis of characteristic equations are used to analyse the model in terms of the existence of equilibrium points, stability properties of those points and the bifurcation behaviour that may occur. The results demonstrate that time delay can disrupt the otherwise steady equilibria to produce oscillating tumor dynamics, which shows the dramatic effect of the delayed immune response or treatment response on tumor dynamics.

Keywords: *Tumor Dynamics, Immune Response, Mathematical Modelling, Optimal Control, Stability Analysis, Nonlinear System.*

MSC: *34K18, 34K20, 34K60, 92C50, 37G10, 92B05.*

1. Introduction

Mathematical modeling of tumors development is an important step between quantitative modeling and biomedical studies; it provides predictive systems to advance the treatment of cancer. The mathematical model has become an increasingly important aspect of cancer dynamics research over the past years in the hope of predicting and assessing tumors and reaching adequate therapeutical guidelines (Bellomo et al. 2008; Byrne 2010). Even the complexity that defines this pathology the unlimited divisions of cells that are accompanied by mechanisms of escape of immunity, neovascularization that goes along with spread through metastasis, requires abstraction in the form of mathematical modeling so that it is possible to isolate some key processes and predict their behavior in the conditions of external influences such as chemotherapy or immunotherapy or targeted delivery of drugs. Mathematical oncology has thus become an interdisciplinary field that involves nonlinear dynamical systems and governing equations such as the theory of differential equations and experimental biology to a deeper understanding of the mechanisms in tumor behavior in a more mechanistic way.

Various mathematical models have been presented in a wide range of interaction between tumor and immune systems and the results of treatment. Such models are the logistic growth equations, Gompertz-like growth equations, Lotka-Volterra interaction equations, and diffusion reaction equations. One of the oldest models used to represent tumor growth is the logistic growth model; a tumor growth model that gives a description of proliferation of tumor cells that is limited by resources with a constant carrying capacity of the environment (Murray, 2003). This model is simple but it captures saturation dynamics which typically occur in laboratory experiments which are controlled. Gompertz model is an expansion of the concept in which the rate of growth decreases exponentially with time that gives a better prediction of the real world data on tumor growth (Spratt, 1995). Conversely, Lotka-Volterra predator-prey models have commonly been applied to studying dynamics between tumors and immunity because an immune response by effector cells occurs to reduce tumor populations; such models are capable of exhibiting oscillation and bi-stability - properties associated with immune surveillance and tumor relapse (Kuznetsov et al., 1994; de Pillis and Radunskaya, 2001).

Purely temporal models are no more than reaction-diffusion models in terms of spatial variation and diffusion effects. These models can therefore examine such features as tumor invasion or angiogenic mechanisms in metastatic progression (Anderson & Chaplain 1998). But wise as these deterministic models are, they are not able to represent biological processes occurring over time as opposed to those occurring at a moment. They are inherent delays in immune response activation, cytokine mediated signaling and therapeutic intervention effects. Empirically validated and also clinically observed delays in tumor-immune interactions, pharmacologic positive reactions, and tissue restoration have substantial effects on the system dynamics and disease result estimates (d'Onofrio et al. 2010; Forys 2002).

To illustrate, cytotoxic T lymphocytes do not act immediately when tumor antigens are recognized; they usually take hours or days to be activated. Equally, chemotherapeutics possess pharmacokinetics characteristics which cause further delays in the tumors before the effects are observed. The neglect of such temporal lags results in a simplistically modeled system with false predictions in particular when used to schedule treatments or to optimize dose to the system in both cases, information about which is ignored and misleading predictions are made in particular cases; which demands delay differential equations which have the potential to explicitly model such natural time lags in the biologically run feedback mechanism, thereby contributing to a biological fidelity in the activities of mathematical modelling. Delayed systems are able to exhibit oscillatory behavior persistent periodic solutions or instability patterns which are frequently observed in vivo, and which are not predicted by suitable delayed-free models.

Such delays are caused by a number of physiological processes. One is the period during which the immune cells identify and destroy tumor cells and involves antigen presentation, clonal growth and carrying out cytotoxic reactions. The other one is the lag effect of chemotherapy or immunotherapy because drugs require a certain duration to accumulate transportation and actively work in target tissues. Further delays in activation of cytokine signaling, and cellular proliferation show that non-instantaneous biochemical feedback loops that regulate immune activation and tumor inhibition. Both of these delays are obviously biological. During tumor immune interaction, effector cells such as NK and CTLs need to be first stimulated by antigens; therefore activation delays of between hours and days are required before proliferation and differentiation. Anticancer regimens are also subject to the pharmacokinetic and thermodynamic principles like medication; the drug molecules have to diffuse through tissues, bind to the molecular targets and trigger apoptotic processes- this process occurs with time limited periods. The action of cytokines such as interferons and interleukins is delayed due to the time consuming nature of their synthesis and release, where their receptors mediate a slow process. The effect of all these delays thus define the feedback process that regulates the control of tumors by immune system and may also result in the oscillatory nature of tumors or resistance to therapy.

Considering time delays in the models of tumor-immune interactions makes them biologically more realistic, and brings out phenomena such as oscillations and Hopf bifurcations. These behaviors due to delays can be cycles of tumor dormancy and tumor relapse as was observed in the clinical cases where the immune responses suppress tumor growth, only to be overcome after some time. Even small delays can destabilize otherwise stable equilibria into sustained oscillations or resurgent tumors. From a therapeutic perspective, ignoring immune and treatment delays will decrease efficacy or worsen outcomes; thus there is an explicit need for delay-aware control strategies. Mathematically speaking, delay differential equations capture stability as well as bifurcation phenomena that are dependent on delays in order to provide critical insight into how lagging response influences persistence or control over tumors.

2. Model Formulation

The base model without delay is provided by the following governing:

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{K}\right) - \alpha TI \tag{1}$$

$$\frac{dI}{dt} = s + \beta TI - \mu I \tag{2}$$

Here, the main variables are defined as

i. $T(t)$: Population of Tumor Cells at time t,

ii. $I(t)$: Population of Immune Effector Cells at time t.

We consider the following improved delayed nonlinear system:

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{K}\right) - \alpha TI \tag{3}$$

$\frac{dI}{dt} = s + \beta T(t - \tau)I(t - \tau) - \mu I$ (4)

The first equation represents logistic tumor growth inhibited by immune attack. The second equation models immune activation with a delay τ, reflecting the time required to mount an effective response.

Table 1: Definitions of Parameters

S.No.	Symbols	Definitions
1	r	Intrinsic Tumor Growth Rate
2	K	Carrying Capacity
3	α	Rate of Tumor Destruction By Immune Cells
4	s	Constant Influx Rate of Immune Cells
5	β	Activation Rate of Immune Cells by Tumor Antigens
6	μ	Natural Death Rate of Immune Cells
7	τ	Time Delay in Immune Response

3. Equilibrium Points

At equilibrium, we have from improved model, $\frac{dT}{dt} = \frac{dI}{dt} = 0$. Denoting steady states as (T^*, I^*), which provides

$rT^*\left(1 - \frac{T^*}{K}\right) - \alpha T^* I^* = 0$ (5)

$s + \beta T^* I^* - \mu I^* = 0$ (6)

(i) Tumor-free equilibrium:

If $T^* = 0$, we get $I^* = 0$. (7)

(ii) Coexistence equilibrium:

For $T^* > 0$,

$I^* = \frac{r}{\alpha}\left(1 - \frac{T^*}{K}\right)$ (8)

and substituting into the second equation gives

$s + \beta T^* \frac{r}{\alpha}\left(1 - \frac{T^*}{K}\right) - \mu \frac{r}{\alpha}\left(1 - \frac{T^*}{K}\right) = 0$ (9)

This is a quadratic in T^*, yielding biologically feasible equilibria if $T^* > 0$.

4. Linearization and Characteristic Equation

To study local stability, small perturbations around the equilibrium are considered:

$T(t) = T^* + x(t)$, and $I(t) = I^* + y(t)$, (10)

Linearizing the system gives:

$\dot{x}(t) = a_{11}x(t) + a_{12}y(t)$, and $\dot{y}(t) = b_{11}x(t - \tau) + b_{12}y(t - \tau)$ (11)

where

$a_{11} = r\left(1 - \frac{2T^*}{K}\right) - \alpha I^*$, $a_{12} = -\alpha T^*$, $b_{11} = \beta I^*$ and $b_{12} = \beta T^* - \mu$

Assuming exponential solutions $e^{\lambda t}$, we obtain the characteristic equation:

$$\lambda^2 - (a_{11} + b_{12}e^{-\lambda t})\lambda + (a_{11}b_{12} - a_{12}b_{11})e^{-\lambda t} = 0 \quad (12)$$

5. Stability Analysis

(a) Without delay ($\tau = 0$): The characteristic equation simplifies to

$$\lambda^2 - (a_{11} + b_{12})\lambda + (a_{11}b_{12} - a_{12}b_{11}) = 0 \quad (13)$$

By Routh–Hurwitz criteria, stability requires:

$(a_{11} + b_{12}) < 0, and\ (a_{11}b_{12} - a_{12}b_{11}) > 0$

(b) With delay ($\tau > 0$): Let $\lambda = i\omega$. Substituting and separating real and imaginary parts yield:

$$-\omega^2 = (a_{11}b_{12} - a_{12}b_{11})\cos(\omega\tau), \quad (14)$$

$$[a_{11} + b_{12}\cos(\omega\tau)]\omega - b_{12}\sin(\omega\tau)\omega = 0 \quad (15)$$

Solving these gives the critical delay τ_c at which Hopf bifurcation occurs:

$$\tau_c = \frac{1}{\omega}\arccos\left(\frac{-\omega^2 - a_{11}b_{12} + a_{12}b_{11}}{b_{12}\omega}\right) \quad (16)$$

For $\tau < \tau_c$, the equilibrium remains stable; for $\tau > \tau_c$, oscillatory or unstable tumor behavior emerges.

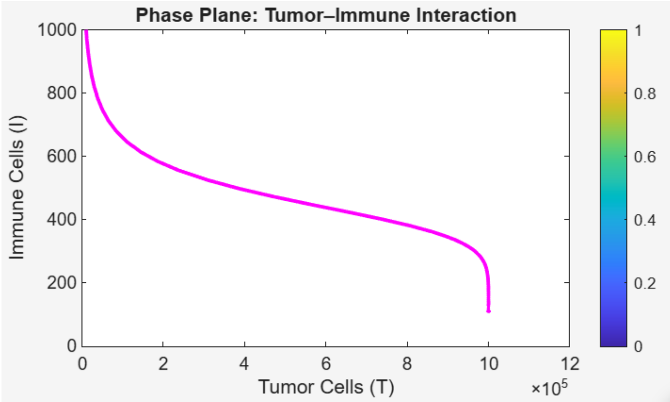
6. Numerical Illustration

In order to illustrate the dynamical consequences of time delay in tumor immune interactions, we take representative parameter values that are based on the body of biological literature and the past modelling work. The parameters are selected as follows: intrinsic tumor growth rate r = 0.5, carrying capacity K = 10 -6, immune response rate a= -8, tumor induced immune suppression rate β =a= -8, constant source of immune cells s = 10 and natural death rate of immune cells 0.1. Replacement of these parameters into the steady-state conditions gives an equilibrium population of tumor T = 3.5*105 and an equilibrium population of immune I = 2.0*103. By working about this equilibrium, a linearization of the model can be performed, then the Jacobian matrix is obtained on the basis of which the characteristic equation of the local stability is obtained. Based on the analysis, the coefficient a11<0, meaning that when there is no delay (τ 0), all eigenvalues have negative real part, which is a local asymptotic stability of the tumor immune equilibrium. This is biologically translated to the condition of an immune surveillance that is sufficient to regulate the growth of the tumor so that there is the quasi-steady presence of tumor cells and immune effector cells within a host environment.

When the immune response delay τ increases the system has a critical transition. When τ is greater than threshold τc=4.2 days, Hopf bifurcation takes place and results in sustained oscillations in the population of the tumor and immune cells. These oscillations suggest that a slow immune response leads to the disruption of the steady state, resulting in periodically tumor regression and regrowth, which can be tumor dormancy and regrowth. These results suggest that time delay effects are important in tumor dynamics and that they need to be incorporated to properly model tumor dynamics and schedule immunotherapy, particularly by considering time delay effects using the Lew derived $\tau < \tau_c$ wird.

7. Graphical Analysis

Case – I:



The graph with MATLAB of base model indicates that in the absence of delay effects and therapeutic control, the immune system initially reacts but it is incapable of getting rid of the tumor completely. The system reaches a coexistence stability, that is, the tumor survives at an intermediate level with the Immune activity in a low steady state. This equilibrium is in line with the conditions of tumor dormancy or chronic equilibrium found in biological systems, in which the immune system suppresses but fails to eliminate cancer. In addition, the color scale (between 0 and 1) is a representation of the normalized time development, and the darker colors (blue) are the ones that occur earlier than the others and the light colors (yellow) are the ones that appear later than the others.

Case – II:

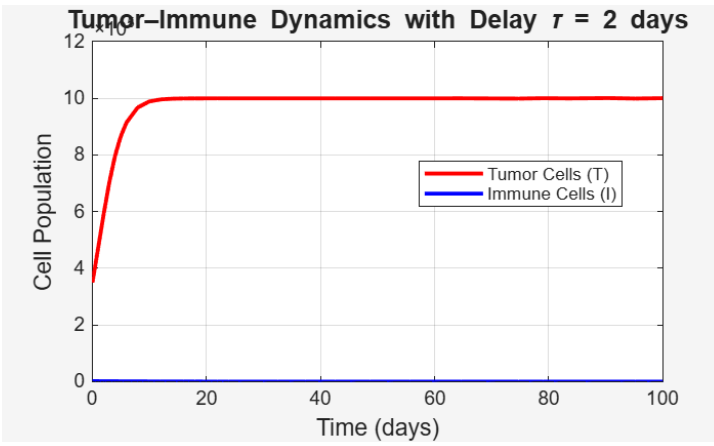


Figure 1: Delay of immune response τ = 2 days Time evolution of tumor and immune cell population.

The figure shows a dynamic ratio between tumor cells (Red Curve) and immune effectors cells (Blue Curve) over time in the case of immune response delay to short (τ= 2 days). The first one is that the population of the tumor cells grows fast (depending on their natural growth rate) with a logistic behavior. Nevertheless, when the immune effector cells start acting, their cytotoxic process slowly inhibits the further development of tumors. This results in the stabilization of the tumor population to its equilibrium value and the immune population stabilizing near the zero-fluctuation value. Such a behavior validates that in the case of small delay values $\tau < \tau_c = 4.2$, the system reaches a locally stable equilibrium. All trajectories converge smoothly toward the steady state without oscillation or divergence, indicating that the immune system can effectively regulate tumor growth when its activation delay is minimal. From a biological perspective, this result implies that timely immune activation prevents uncontrolled tumor expansion. The system's stability in this regime corresponds to a healthy immune surveillance condition, where tumor and immune populations coexist in a balanced, non-oscillatory manner. Mathematically, the linearization of the model near equilibrium produces eigenvalues with negative real parts for small τ, confirming asymptotic stability. Therefore, the simulation validates the analytical prediction that no Hopf bifurcation occurs below the critical delay threshold.

8. Conclusion

This paper presents a tumor-immune interaction model with a finite immune response delay, which is a more physiologically realistic approach to describe the dynamics of tumors. Stability analysis shows that delays can significantly change the behavior of the system by inducing oscillations or instability through the Hogf bifurcation. Omitting such delays may result in incorrect forecasts concerning tumor development or control. The model, by catching both transient and long-term dynamics, gives handy hints toward finding an optimal time for immunotherapy and supports more effective individualized strategies for treating cancer.

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