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Stability Analysis Tumour Growth Model with Interphase Delay: A Computational Study

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Abstract.

Purpose: In this manuscript, we study a mathematical model of the tumor cell cycle with delay to understand and improve patient quality of life, and design better treatment strategies.

Design/Methodology: This study investigates the system of differential equations to the represent the cell cycle progression in tumour growth model with interphase delay. This analysis seeks to determine the competition model of immune system react cell cycle progression of a specific drug of cycle phase. This theoretical analysis utilized to find impact of immune response, and the effects of specific drugs in cycle-phase and bifurcation analysis in biological process.

Findings: We demonstrate the influence of delay and the stability of the tumor growth with delay differential equation model. The tumor population is stable within 20 days without delay. But in the presence of delay, the tumor growth is stable around 120 days. Increased interphase duration enhanced the rate of cell death in mitosis, and potential drug resistance. Without drug and immune cells, tumor growth is unstable and reaching 10×10^6 cells around 160 days in interphase.

Originality/values: This study presents a novel investigation into the stability of delay differential equations for tumor population. We explore new territory in tumor growth model with interphase delay by considering cell cycle that have not been thoroughly examined in prior studies despite their obvious relevance.

1. Introduction

A single parent cell assists in the development of the new cell population, a process known as the cell cycle, which involves the duplication of DNA and the division of two daughter cells. The cell cycle has three stages, such as the quiescent phase, interphase, and mitosis. The quiescent phase

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is a G_0 phase when cells are active and dividing; they enter this phase mainly because of outside conditions and lack of nutrients, which are necessary for growth. The development program includes the most metabolically active cells, which have fully differentiated to the terminal G0 phase. Interphase division involves both cell growth and DNA replication. Mitosis, a nuclear division, occurs before other organelles through the process of cytokinesis. Mitosis is the process by which a eukaryotic cell divides its nuclear DNA and chromosomes into two distinct but identical sets of nuclei. The cell cycle process reacts to the interconnected immune system, playing a role in immune cell proliferation. The immune system can influence cell cycle immunity, including tolerance and autoimmunity. The immune system protects the body from diseases such as viruses, bacteria, and cancer cells. Such as viruses, bacteria, and cancer cells.

Delays influence key phenomena in the progression of cell cycle phases. Mathematical models using delay differential equations (DDEs) help accurately capture behaviors such as stability, oscillations, and uncontrolled proliferation. The biological process of tumor development involves complex cell proliferation and tightly regulated cell cycle control during growth and division. In cancer, this regulation is disrupted, leading to uncontrolled proliferation—a process that is not instantaneous due to delays in DNA replication and other cellular mechanisms. The slow response of the cell cycle to growth factors and treatment significantly affects how quickly tumors grow and how long they remain stable. Accurate modeling improves the prediction of tumor progression and enhances the timing of therapies such as chemotherapy and radiotherapy. Tumor growth is further complicated by the presence of a quiescent phase, where some cells temporarily exit the active cycle. These quiescent cells can re-enter the cycle, contributing to tumor regrowth after treatment. Transitions between quiescent and proliferating states are delayed, and thus, delay differential equations provide a natural framework for modeling these dynamics and describing the system's behavior over time.

Birkhead [5] developed to the resistance of chemotherapy via multiple mechanisms, which diminishes the efficacy of treatment and contributes to tumor recurrence. The tumor is categorized into populations of cells that are sensitive to pharmacological agents and those that exhibit resistance to such treatments. Cojocaru [7] focused to the drugs that are unique to certain stages of the cell cycle, such as the S-phase or M-phase, are designed to target tumor cells during those specific phases.

Incorporating important biological processes as cell cycle dynamics, medication resistance, and tumor heterogeneity, a nonlinear cell population model depicts the progression of cancer cells under periodic treatment in Webb [48]. Bifurcation analysis may detect situations that result in the complete removal of a tumor, its stable size, or its uncontrolled progression. Kuznetsov [25] investigated the immunogenic tumors through the lens of nonlinear dynamics entails the modeling of interactions between the immune system and tumor cells. These models frequently integrate essential biological processes, including tumor-immune interactions, mechanisms of immune evasion, and responses to immunotherapy.

Cycle-specific chemotherapeutic agents exert their effects during distinct stages of the cell cycle, rendering timing and scheduling essential for optimal treatment in Panetta [33] and Kirschner [23]. Based on the DNA makeup of the cells, Darzynkiewicz [8] examined the cells were spread out during the different stages of the cell cycle. It includes coloring cells with DNA-binding dye and measuring the strength of the light to find out DNA is in each cell. A clear peak is made by cells with a single DNA content. The DNA content of cells in the synthesis phase is in the middle, making a broad distribution. Cells that have copied their DNA (tetraploid) make a different peak with twice the light strength of the G1 phase.

Kozusko [24] developed a competitive framework to imitate the interactions between these groups, which would allow for the observation of tumor development, immune response, and the effects of treatment. The study presents novel chemotherapy procedures based on numerical simulations and optimum control mechanisms. These improved procedures are compared with typical pulsed periodic treatments, which shows that they may be more effective in treating patients. A delay differential equations model of tumor growth incorporating the immune response and drugs introduced by De [11], and Villasana [45, 46].

Liu [26] examined the prospective advantages of synchronizing cancer cells to concurrently enter the M-phase prior to the administration of M-phase specific medicines, with the objective of enhancing therapeutic efficacy. The activity of cells in the G_0-phase substantially affects overall cancer dynamics, indicating that targeting this phase may improve therapy success. Yafia [49] developed a model that emphasizes the eradication of tumors by effector T cells. This model highlights a number of immunosuppressive processes, such as the interactions between cytokines and the effect that tumor growth has on the infiltration of immune cells.

Eisen [15] proposed a differential equation model that included immune system reactions and medication interactions. The research looks at equilibrium points, stability qualities, and how sensitive they are to chemotherapeutic factors. The importance of activating the immune system in the success of therapy is shown by numerical simulations. Sensitivity analysis shows that drug-induced tumor mortality and degradation rates have a major effect on therapy. Depillis [14], Awang [1], and Awang's [2] proposed a concept that separates the tumor cell population into interphase cells, mitosis cells, and quiescent cells. This model considers how the immune system targets and eliminates tumor cells, both growing and quiescent cells. Charlebois [6] determined mathematical modeling cell population dynamics, including simple models, complex models, the underscores the significance of population modeling in biology, accentuating its comprehending to the biological processes and occurrences.

The equilibrium point stability, and Hopf bifurcation situations that cause periodic solutions, and time delays affect tumor-immune system stability, perhaps causing oscillations in Dehingia [13]. Sardar [38] introduced a conceptual mathematical model consisting of three interrelated nonlinear mathematical model fot tumor cells. This model integrates discrete time delays to accommodate the duration necessary for the development of immune responses. Das [10], and Dehingia [12]

presented an altered prey-predator model that includes tumor cells. This work illustrating the temporal dynamics of immune responses, and offers a mathematical model for the immune system and tumor cells.

Khamidullina [22] and Das [9] studied biological processes involved in breast cancer development, including cell proliferation, immune response, and angiogenesis (formation of new blood vessels). The dynamics of cancer are intricate, encompassing not only the proliferation of the primary tumor but also its interactions with the encircling environment. Tumor development may often be represented by differential equations that consider the non-linear and frequently chaotic characteristics of cancer proliferation and dissemination, where fractal calculus provides more accurate methodologies Golmankhaneh [17]. Kar [21] developed a fractional order mathematical model to examine glioblastoma proliferation, emphasizing the prediction of tumor appearance in medical imaging and the evaluation of patient survival. The model employs fractional derivatives to more precisely depict the intricate, diverse characteristics of glioblastoma tumors.

Sardar [39] analyzed the intricate interactions between tumor cells and the immune system, combining three distinct time delays. These delays signify distinct biological processes, including the duration necessary for the immune system to identify tumor cells and initiate a reaction. The model seeks to elucidate the complex connections and feedback mechanisms intrinsic to tumor-immune dynamics. Guo [19] and Meng [29] concentrate an extensive assessment of diverse computational methodologies employed to ascertain cell cycle phases from single-cell RNA sequencing data. The efficacy of these methodologies is examined across various datasets by Wang [47].

Recently, Serizay [40] examined the unique cyclin switch changes the normal cell cycle to make it easier for multiciliated cells to differentiate. This type of cell cycle uses a cyclin-dependent kinase threshold that is lower than the S-phase threshold. This system lets the cell change the genetic program for the cell cycle by controlling only certain parts to change CDK activity from division to differentiation. Tubtimsri [43] shows that quercetin can cause death by creating reactive oxygen species and stopping the cell cycle in the S and G2/M stages. Park [34] constructed a mathematical model to elucidate the dynamic mechanism via which cancer cells attain a permanent state in response to pharmacological intervention. This model seeks to forecast the circumstances in which cancer cells endure therapeutic treatments by developing a drug-tolerant phenotype. Liu [27] developed a free boundary problem technique to simulate the tumor progression, integrating time delays to reflect the time frame necessary for cell multiplication. They undertake a linear stability analysis to these delays effect the tumor growth dynamics and stability.

2. Mathematical formulation

In this section, we consider the mathematical modeling and interactions between immune cells, drug, and tumor cells on the cell cycle. Goodman [18] studied the effects of dosing intervals in the proliferating and resting cells on the tumor populations. Their model approaches the cycling

tumor cell population into phases but they didn't discuss the quiescent phase combined with interphase delay. This study interact tumor cell cycle with interphase delay, immune system and drug responses. The cell cycle appear naturally and it is explained by Baker [3]. The cell cycle duration is approximately 24 hours for most typical normal cells with various exceptions. Tubiana [42] provided that the median duration of 30 solid human tumors phases is 2 days and distributed by 1 day for pre-synthetic G_1, 18 hours for synthetic S, 6 hours for post-synthetic G_2, and approximately 1 hour for mitosis M (see [11, 23, 25]). The cell cycle and mathematical model for tumor growth with interphase delay is shown in Figures 1, and 2. We assume that the concentration of drug (D) exponentially decreases with time and destroyed tumor cells in mitosis T_M.

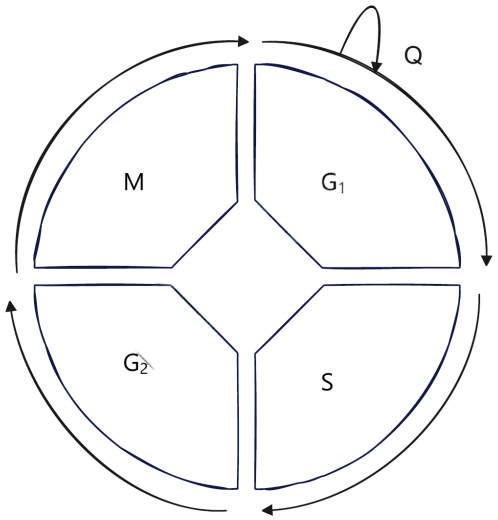

FIGURE 1. Schematic diagram of the cell cycle

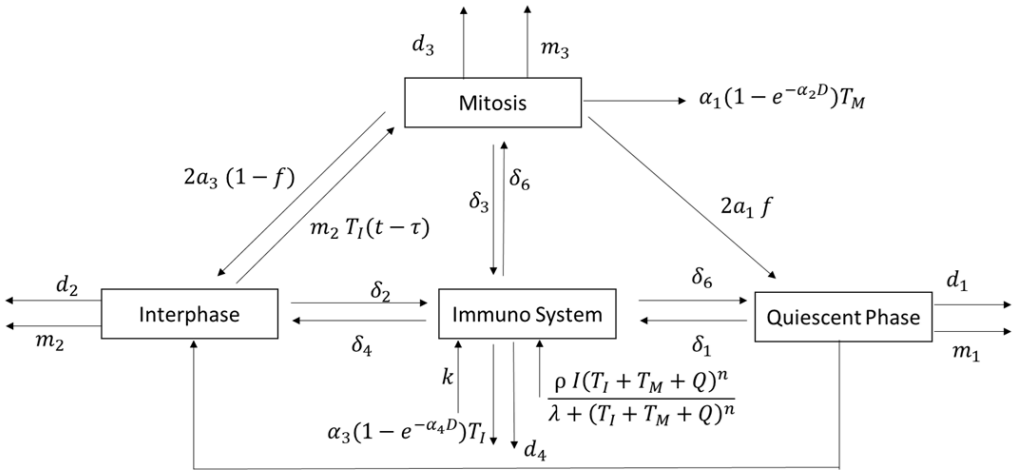

FIGURE 2. Mathematical model for tumor growth with interphase delay

The mathematical model of the system is characterized by [2,26,45,46]

$$\frac{dQ}{dt} = 2a_1 f T_M(t) - d_1 Q(t) - m_1 Q(t) - \delta_1 I(t) Q(t) \tag{2.1}$$

$$\frac{dT_I}{dt} = a_2 Q(t) + 2a_3(1-f)T_M(t) - d_2 T_I(t) - m_2 T_I(t-\tau) - \delta_2 I(t) T_I(t) \tag{2.2}$$

$$\frac{dT_M}{dt} = m_2 T_I(t-\tau) - d_3 T_M(t) - m_3 T_M(t) - \delta_3 I(t) T_I(t) - \alpha_1(1-\exp(-\alpha_2 D(t)))T_M(t) \tag{2.3}$$

$$\begin{aligned}\frac{dI}{dt} &= K + \frac{\rho I(t)(T_I(t)+T_M(t)+Q(t))^n}{\lambda + (T_I(t)+T_M(t)+Q(t))^n} - d_4 I(t) - \delta_4 I(t) T_I(t) - \delta_5 I(t) T_M(t) \\ &\quad - \delta_6 I(t) Q(t) - \alpha_3(1-\exp(-\alpha_4 D(t)))T_I(t)\end{aligned} \tag{2.4}$$

$$\frac{dD}{dt} = -\gamma D(t) \tag{2.5}$$

with initial conditions given by

$$\begin{aligned} Q(t) = \phi_1(t),\ \ T_I(t) = \phi_2(t),\ \ T_M(t) = \phi_3(t), \\ I(t) = \phi_4(t),\ \ D(t) = \phi_5(t),\ \ \text{for } t \in [-\tau,\ 0]. \end{aligned} \tag{2.6}$$

where the tumor cells population in the cell cycle at time is denoted by interphase $T_I(t)$ contains $G_1 + S + G_2$, mitosis $T_M(t)$, immune system $I(t)$, and drug $D(t)$ respectively, τ be the rate of time resident in interphase, $d_i,\ (i = 1,2,3,4)$ denotes the rate of natural death of cells, $a_i,\ (i = 1,2,3)$ is flow rate of cells add from another phase, f is flow rate of cells that enter in quiescent phase, $m_i,\ (i = 1,2,3)$ represent losses of tumor cells from the phase in cell cycle, $\delta_i,\ (i = 1,2,...,6)$ terms represent tumor cells destroyed by immune cells, α_i terms represent tumor cells destroyed by drug, K is constant growth of immune cells, ρ, and λ are growth of the immune due to stimulus and saturation level without stimulation, and γ is decay of drugs.

Tumor cells inside the interphase at a time t continue in the cycle, and assuming that the cells enter mitosis at time $t-\tau$. The population of the tumor cell obtained by mitosis T_M and τ that regulate the rate of cell division. This explains the terms $T_I(t-\tau)$ in system (2.1) to (2.5). (see references [20,30–32]). We assume that $u(0) = u_0 > 0$ at time $t = 0$ (see [45]). The values of the parameters are summarized in Table 1.

Consider the non-dimensional variables [46]

$$\begin{aligned} u(t) = \frac{Q}{Q(0)},\ v(t) = \frac{T_I}{T_I(0)},\ w(t) = \frac{T_M}{T_M(0)}, \\ x(t) = \frac{I}{I(0)},\ y(t) = \frac{D}{D(0)},\ s = \frac{Q(0)}{T_I(0)},\ T_I(0) = T_M(0). \end{aligned} \tag{2.7}$$

Using the non-dimensional change of variables 2.7, the system 2.1 to 2.5 has been rewritten in the form of dimensionless variables u, v, w, x, y

$$\frac{du}{dt} = \frac{2a_1 f}{s} w(t) - d_1 u(t) - m_1 u(t) - \delta_1 I(0) u(t) x(t) \tag{2.8}$$

$$\frac{dv}{dt} = a_2 s u(t) + 2a_3(1-f)w(t) - d_2 v(t) - m_2 v(t-\tau) - \delta_2 I(0) x(t) v(t) \tag{2.9}$$

$$\frac{dw}{dt} = m_2 v(t-\tau) - d_3 w(t) - m_3 w(t) - \delta_3 I(0) x(t) w(t) - \alpha_1 \left(1 - e^{-\alpha_2 D(0) y(t)}\right) w(t) \tag{2.10}$$

$$\frac{dx}{dt} = \frac{K}{I(0)} + \frac{\rho x(t) \left(su(t) + v(t) + w(t)\right)^n}{\lambda + \left(su(t) + v(t) + w(t)\right)^n} - d_4 x(t) - \delta_4 I(0) x(t) v(t) - \delta_5 T_M(0) x(t) w(t)$$
$$- \delta_6 Q(0) x(t) u(t) - \alpha_3 \left(1 - e^{-\alpha_4 D(0) y(t)}\right) x(t) \tag{2.11}$$

$$\frac{dy}{dt} = -\gamma y(t). \tag{2.12}$$

TABLE 1. Parameter values

Source	Estimated value of the parameters
[25,32,41]	$\tau = 2$ hr (≈ 0.9167 days) $a_3 = 0.9159$ day^{-1} $d_2 = 0.1145$ day^{-1} $m_2 = 0.8470$ day^{-1} $\delta_2 = \delta_3 = 2.16 \times 10^{-7}$ cell^{-1} day^{-1} $d_3 = 0.6641$ day^{-1} $m_3 = 0.9159$ day^{-1}
[25,28,37,46]	$a_1 = a_2 = 0 - 1$ day^{-1} $d_1 = 0 - 1$ day^{-1} $m_1 = 0 - 0.056$ day^{-1} $\delta_1 = 0.1 \times 10^{-8} - 1 \times 10^{-8}$ cell^{-1} day^{-1}
[32,46]	$\alpha_1 = \alpha_3 = 0 - 1$ day^{-1} $\alpha_2 = \alpha_4 = 0.01 \times 10^{-2} - 1 \times 10^{-2}$ mg^{-1}
[25]	$k = 1.3 \times 10^4$ cell day^{-1} $\rho = 0.2$ day^{-1} $\lambda = (0.3 \times 10^6 \text{ cell})^3$ $d_4 = 0.04$ day^{-1}, where $\frac{dI}{dt} = k - d_1 I$ $\delta_4 = \delta_5 = 3.422 \times 10^{-10}$ cell^{-1} day^{-1} day^{-1}
[4,25,46]	$\delta_6 = 0.01 \times 10^{-6} - 1 \times 10^{-6}$ cell^{-1} day^{-1} $\gamma = 0.1 \times 10^{-2} - 1 \times 10^{-2}$ day^{-1}
[16,35,36,44]	$n = 3$
[26,46]	$I(0) = 3.5 \times 10^5$ $T_I(0) = T_m(0) = 0.1 \times 10^6$ $Q(0) = 0.1 \times 10^6$ $D(0) = 8$

3. Result and discussion

In this section, we examine the dynamics of tumor cell populations under a range of experimental conditions. The dimensionless equations (2.8) to (2.12) with the initial conditions (2.7) are solved using the dde23 procedure in matlab, and the their results are graphically illustrated.

We first analyze the population with and without delay to observe the impact of timing on cell proliferation. Specifically, we compare scenarios where a delay is introduced in the interphase and mitosis phases, and assess how this delay affects tumor growth. Next, we explore the effect of drug treatment, both with and without delay. This allows us to investigate how therapeutic intervention alters tumor progression under different time constraints.

Additionally, we consider a scenario in which both immune response and drug treatment are absent. This condition serves as a baseline to understand the natural growth and equilibrium of the tumor population in the absence of external factors. Finally, we study the effects of increasing delay in the absence of drug treatment, providing insight into the role of timing in tumor cell regulation and how a prolonged delay might influence the overall population dynamics. By comparing these various scenarios, we aim to gain a comprehensive understanding of the factors influencing tumor cell behavior and potential therapeutic strategies.

3.1. **Tumor population without delay ($\tau = 0$).** Figure 3, we illustrate the dynamics of the tumor population in the absence of delay in the growth cycle. Without delay, the proliferation of tumor cells occurs rapidly, leading to a stabilization of the tumor cell population within a span of 20 days. This rapid growth phase is critical as it highlights the aggressive nature of tumor cells, which can quickly adapt and proliferate in a conducive environment.

We observe that the drug cells completely vanish after 175 days. This decline occurs under the assumption that the rate of drug cell depletion is linear, specifically at a rate of 0.1×10^{-2} cells per day. The linear decrease suggests a consistent and predictable reduction in the effectiveness of the drug over time, which may be attributed to factors such as drug resistance. In parallel, the behavior of immune cells in response to the tumor environment. Initially, the immune cell population experiences a significant increase, reaching up to 4.3×10^6 cells within the first 60 days. This rapid expansion indicates a robust immune response aimed at combating the tumor. However, after this initial growth phase, the rate of immune cell proliferation begins to slow down. By the end of the 175-day observation period, the immune cell population stabilizes at approximately 4.5×10^6 cells. This slight increase beyond the 60-day mark suggests that while the immune system is initially effective in mobilizing resources against the tumor, it may face challenges in maintaining this heightened state of activity over time.

3.2. **Impacts of delay ($\tau = 0.9167$) on tumor population with and without drug.** From figure 4 and 5, we illustrate the tumor population with drug and without drug. The impact of delay in the interphase cell cycle is significant, as it directly influences the progression of cells through mitosis and the quiescent phase. When the drug is administered, the tumor population initially shows

an unstable and declining trend, indicating the drug's effectiveness in reducing tumor growth. This reduction occurs approximately in a linear, suggesting that the drug consistently targets proliferating tumor cells over time. After around 120 days, the tumor population reaches a stable state, indicating that the drug has achieved control over the tumor dynamics, maintaining a lower tumor burden. Eventually, the system stabilizes after approximately 160 days. This delayed stabilization compared to the drug-treated scenario highlights the crucial role of therapeutic intervention in achieving earlier and controlled tumor suppression.

In the quiescent phase, where cells primarily prepare for division, tumor cell growth is effectively stable after a duration of 120 days (approximately). This regulation implies that the rate of cellular proliferation is moderated, preventing uncontrolled growth in Figures 4(a) and 5(a). With the drug, the cell growth in this phase is 0.004×10^6 cells (60 days), while without the drug, it is significantly lower at 0.0009×10^6 cells (60 days). This difference suggests that the drug has a cytostatic effect, encouraging more cells to enter or remain in the quiescent state rather than undergoing active division. By pushing cells into a dormant state, the drug may reduce the overall proliferation of tumor cells, indirectly controlling tumor growth.

During the interphase, where cells prepare for division by undergoing growth and DNA replication, the effect of the drug is more pronounced in Figures 4(b) and 5(b). With the drug, the growth of cells in this phase reaches 0.03×10^6, which is five times higher than the value observed without the drug (0.006×10^6). This substantial increase suggests that the drug may enhance cell survival during interphase, possibly by improving DNA repair mechanisms or slowing the transition to mitosis. Conversely, without the drug, fewer cells survive this phase, likely due to the absence of drug-induced stabilization.

The mitotic phase, where cells actively divide, demonstrates a different effect in Figures 4(c) and 5(c). With the drug, the growth rate is -0.02×10^6, indicating a net loss of cells. This negative value suggests that the drug is highly effective at inducing cell death during division, a characteristic of many cytotoxic drugs that target rapidly dividing cells. In contrast, without the drug, the cell loss in mitosis is reduced to -0.008×10^6, reflecting a lower rate of cell death. The higher cell death rate in the presence of the drug indicates its effectiveness in disrupting mitosis and reducing the proliferative capacity of the tumor.

This accelerated tumor growth necessitates a more robust immune response to maintain homeostasis. This effect is clearly illustrated when comparing Figures 4(d) and 5(d). With the drug, the immune cell count is 6.1×10^6, while without the drug, it is slightly higher at 6.5×10^6. This marginal reduction with the drug could be due to mild immunosuppression, a common side effect of some anti-tumor drugs. Alternatively, it may indicate that the drug reduces the need for a strong immune response by directly targeting tumor cells.

Finally, from Figures 4(f) and 5(e) the growth of tumor cells provides critical insight into the overall effectiveness of the drug. With the drug, tumor cell growth is 0.01×10^6 cells, whereas without the drug, it is 0.002×10^6 cells. This counterintuitive result indicates that the drug may

inadvertently support a higher rate of tumor cell survival. This can occur if the drug drives cells into less active states (such as the quiescent or interphase phases), where they are not directly targeted by cytotoxic effects. The higher growth rate with the drug may also suggest the development of drug resistance, where surviving tumor cells adapt to the treatment.

3.3. **Tumor population in the absence of immune response and drug.** From Figure 6, in the absence of immune cells and drug, tumor cells experience unchecked proliferation, reaching a peak growth rate around day 45. Without immune regulation, the balance between cell division leading to accelerated tumor expansion is unstable. On day 160, approximately 10×10^6 cells transition from the interphase stage, indicating a high proliferation potential. However, only 5×10^6 of these cells successfully progress from interphase to mitosis, where they actively divide. Meanwhile, a smaller fraction, around 0.8×10^6 cells, are recycled back into the quiescent phase, where they enter a non-dividing, resting state. The remaining cells that do not advance to mitosis or enter the quiescent phase are lost due to natural cell death. This natural cell attrition is a critical factor in maintaining cellular homeostasis under normal conditions. However, in the absence of immune intervention, this balance is tilted in favor of tumor growth. Consequently, despite the initial 10×10^6 cells leaving interphase, the effective growth rate of the tumor on day 160 is approximately 5×10^6 cells. This value represents the net increase in dividing tumor cells after accounting for the losses due to recycling and natural death. The inability to eliminate excess tumor cells due to the absence of an immune response further exacerbates tumor progression, highlighting the critical role of immune cells in maintaining cellular balance and controlling tumor growth.

As shown in Figure 7, prolonging the delay time from 2 to 12 hours in the interphase and mitosis phases markedly alters the steady-state distribution of the tumor cell population. Specifically, as the delay time increases, the transition of cells from interphase to mitosis is slowed, disrupting the natural progression of the cell cycle. This disruption affects the overall balance of cell distribution across the different phases. One of the most notable consequences of this increased delay is a reduction in the number of cells that transition from the quiescent phase to the active phases of reproduction. In a normal cycle, a portion of quiescent cells re-enter the cell cycle, contributing to tumor growth. However, with extended delay in interphase, fewer cells successfully complete the transition to mitosis, which means fewer cells are available for subsequent divisions. This imbalance ultimately leads to an increase in the overall growth of tumor cells. As a result, the delay in interphase allowing the tumor cells to accumulate without effective control.

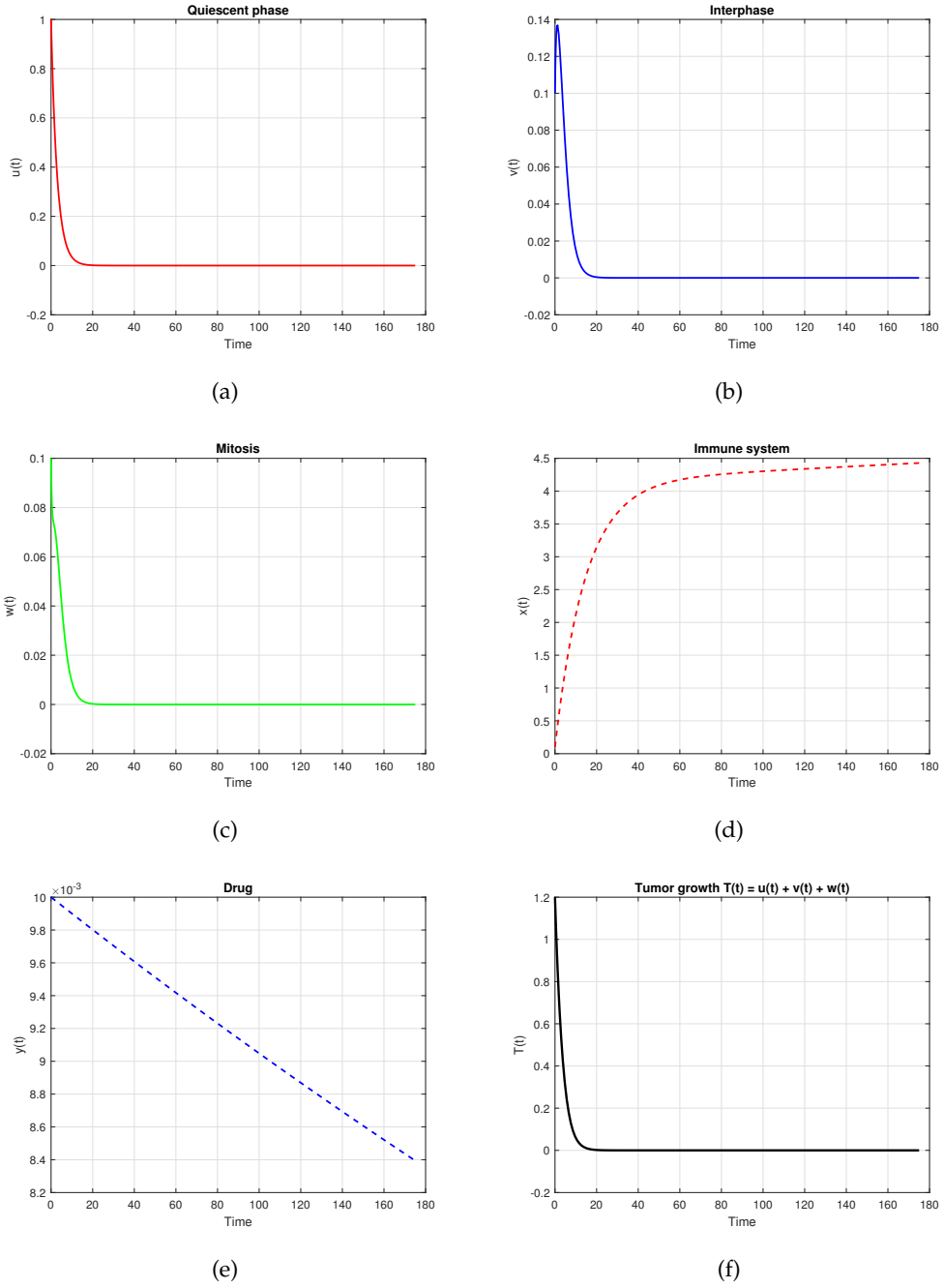

FIGURE 3. Solution of the tumor growth model without delay

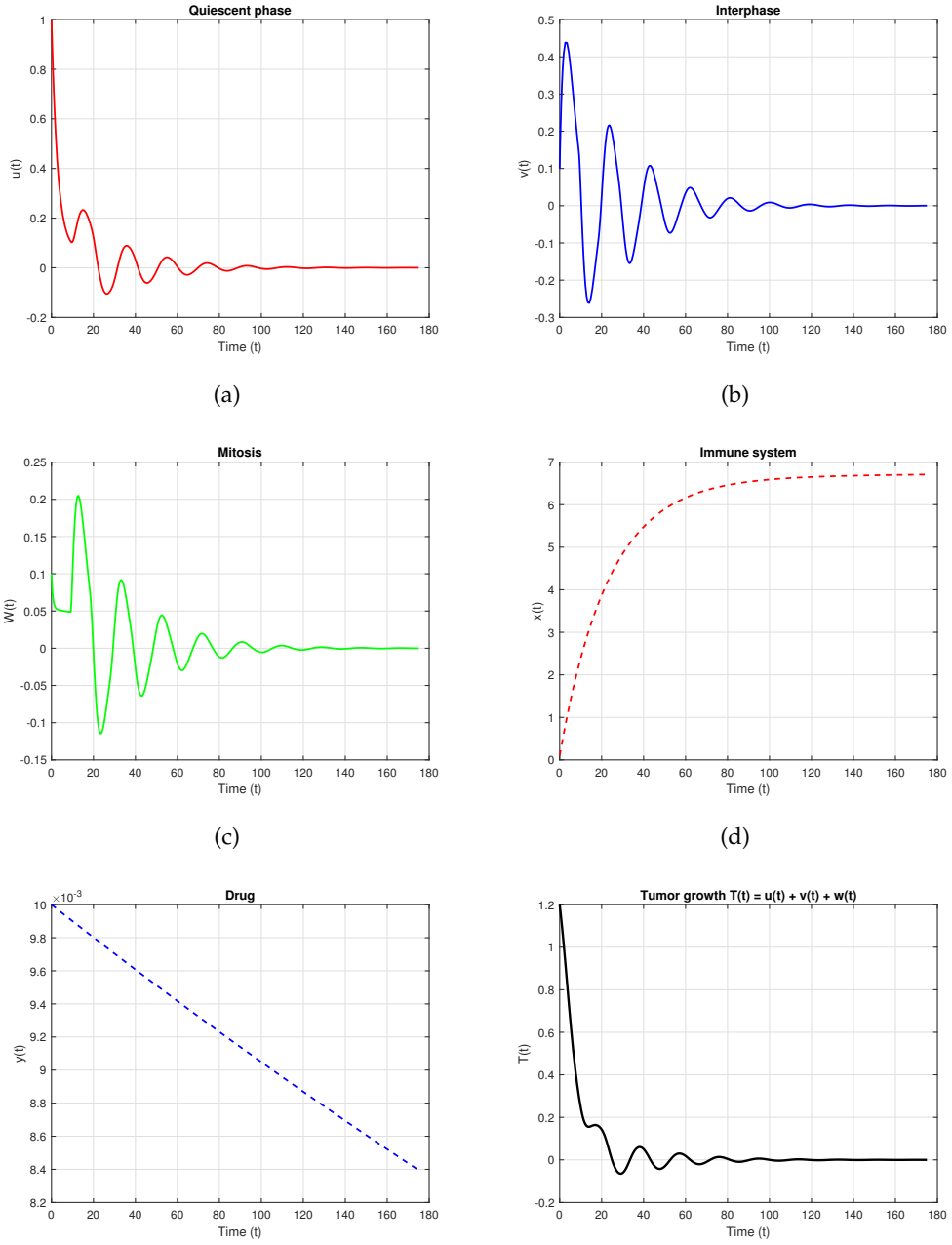

FIGURE 4. Solution of the tumor growth model with delay ($\tau = 0.91$)

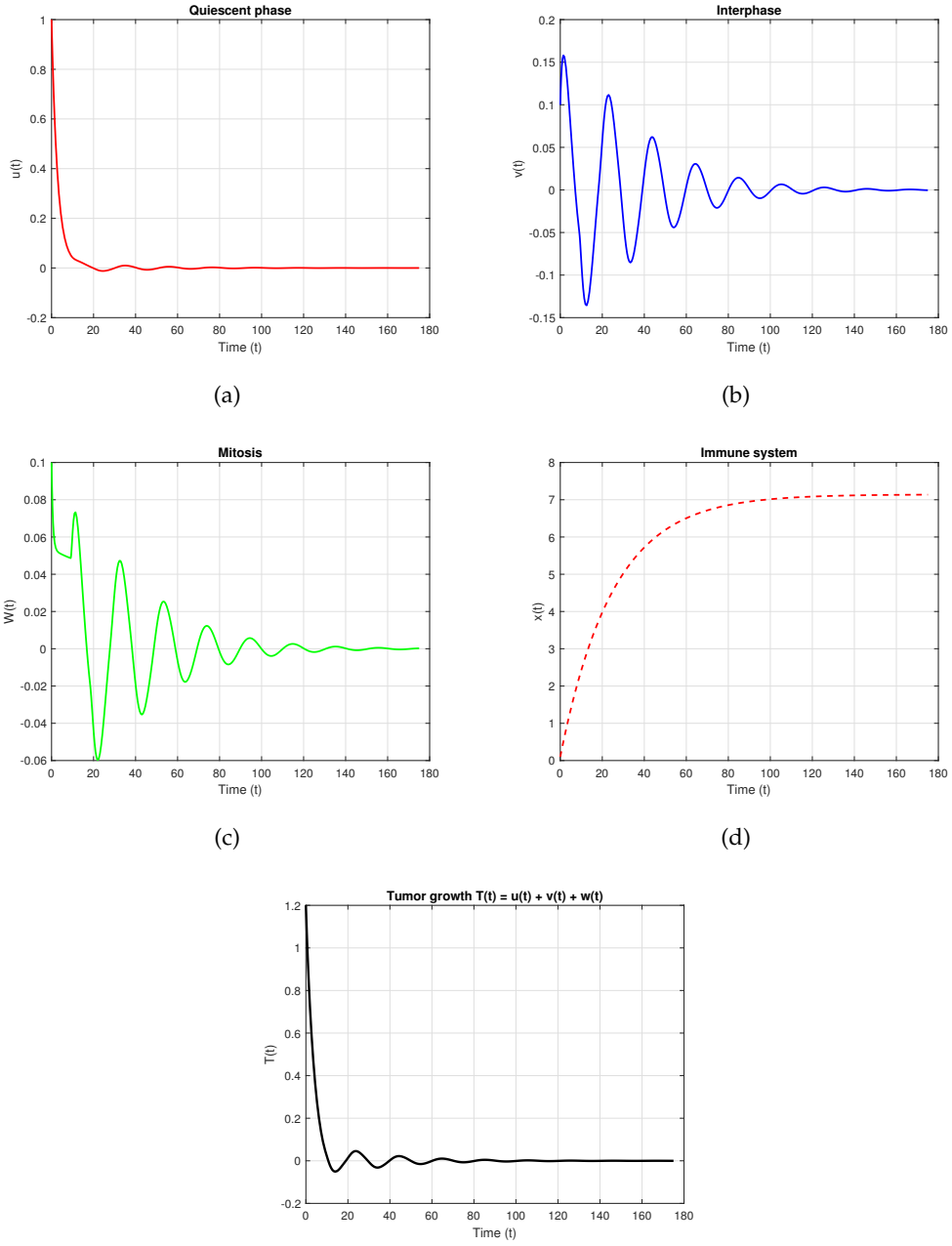

FIGURE 5. Solution of the tumor growth model with delay ($\tau = 0.91$), without drug

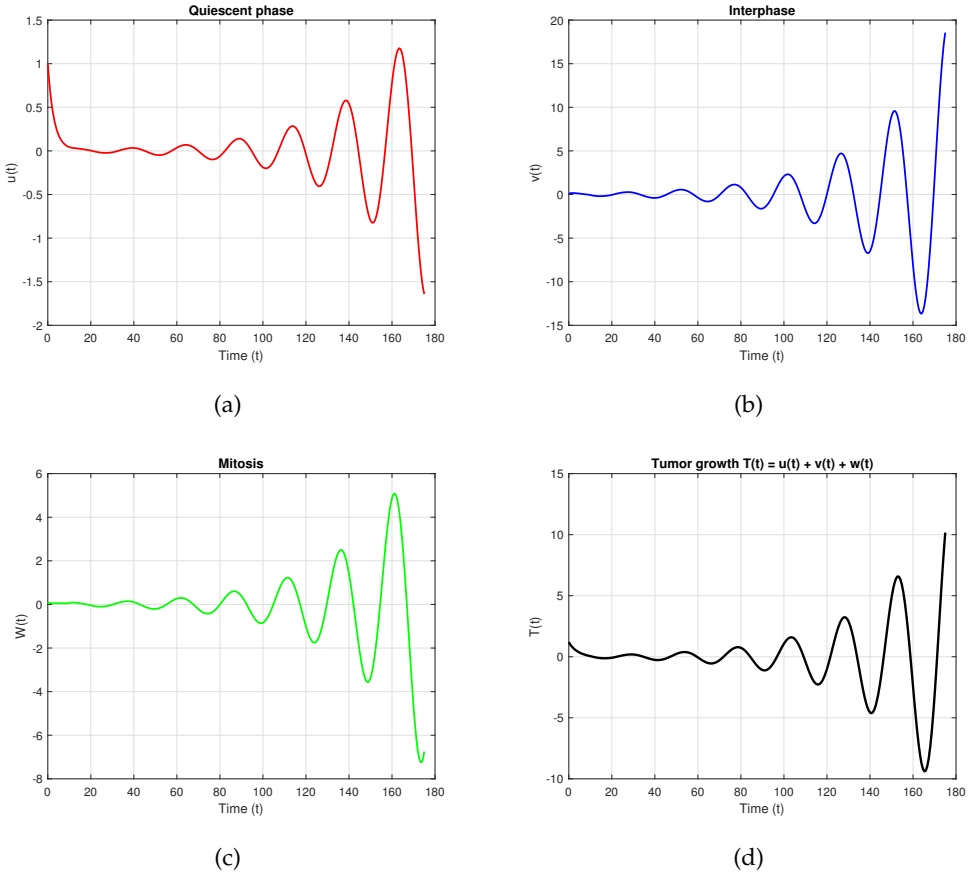

FIGURE 6. Solution of the tumor growth model with delay ($\tau = 0.91$), without immune and drug

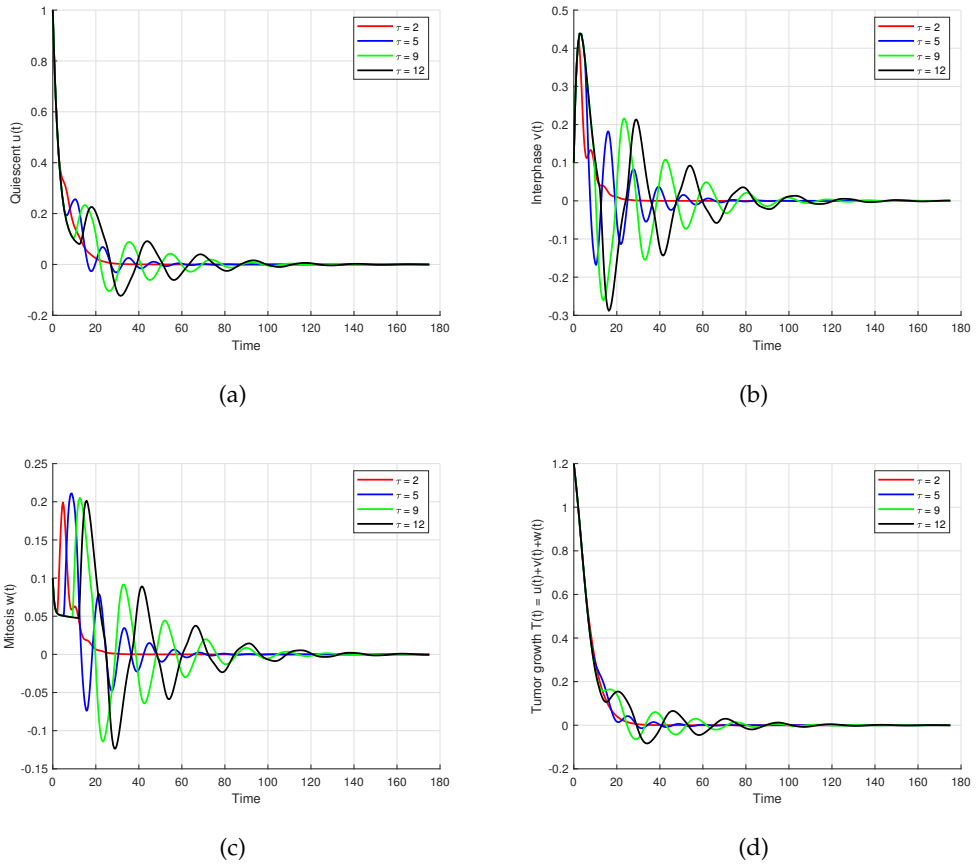

FIGURE 7. Solution of the tumor growth model with immune and drug responses vs delay

4. CONCLUSION

In this manuscript, we investigated the stability analysis of delay differential equation for tumour growth model with interphase delay. The findings of the manuscript are listed as follows:

- In the absence of delay, the tumor population rapidly stabilizes within 20 days, and the drug cells deplete linearly over 175 days, reflecting a predictable decline in drug effectiveness. Consequently, immune cells exhibit an initial rapid increase, reaching approximately 4.3×10^6 cells within 60 days before stabilizing around 4.5×10^6 cells, indicating an early strong immune response that gradually weakens over time.
- In the presence of delay, the tumor growth is stabilizing around 120 days with drug, and takes around 160 days to stabilize without the drug. The drug also significantly impacts cell cycle states such as increasing interphase, and enhancing cell death up to 0.008×10^6 in mitosis, while immune response is stable. A higher tumor cell growth rate with the drug suggests a potential for drug resistance and the complexity of treatment outcomes.
- Without immune cells and drug, the growth of tumor cells reaches approximately 10×10^6 around 160 days from interphase but only 5×10^6 progressing to mitosis, reflecting high

proliferation. Increasing the delay in interphase and mitosis disrupts cell cycle progression, reducing the transition of quiescent cells into active phases and creating an imbalance that promotes tumor expansion. This highlights the immune cells and precise cell cycle controlling tumor growth.

Future directions

The limitations of this study include interphase delay with immune and drug responses. However, we did not consider cells from quiescent phase destroyed by drug and delay in drug cells. Therefore, our future study will focus on these aspects.

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