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Dynamical Properties of a Stochastic Tumor-Immune Model with Pulsed Chemotherapeutic Dose Response*

N. Bajja[1,2,†,*] and D. Seghir[1,2]

Abstract Comprehensive pulsed chemotherapy and immunotherapy are widely employed in clinical tumor treatment. Given the periodically pulsed nature of this approach, we propose a stochastic tumor-immune dynamical model with a pulsed chemotherapeutic dose response. The model accounts for the combined effects of pulsed chemotherapy and pulsed immunotherapy, as well as the influence of environmental random disturbances. We prove the existence and uniqueness of a global positive solution to the proposed model. By using comparison theorems for impulsive differential equations, we show the boundedness of the solution's expectation. Furthermore, we derive sufficient conditions for the extinction and non-persistence in the mean of tumor cells, hunting T-cells, and helper T-cells, as well as for the weak persistence in the mean of tumor cells and helper T-cells, and the stochastic persistence of tumor cells. The results of our study, supported by numerical simulations, demonstrate that random disturbances can effectively inhibit tumor cell growth.

Keywords Tumor-immune model, chemotherapeutic dose response, random disturbances, Itô's formula, impulsive stochastic differential equation

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1. Introduction

Malignant tumors in cancer arise from the uncontrolled and abnormal proliferation of cells. Cancer continues to be a pervasive and aggressive global disease,with its treatment posing significant and persistent challenges. Traditional treatment methods, such as surgery, radiotherapy, and chemotherapy, are commonly employed. However, these approaches often fail to completely eradicate cancer cells and may result in numerous adverse side effects for patients. To address these challenges, which aim to enhance the immune system's response to target tumors, have been developed as promising cancer therapies [1, 2]. Preclinical data and staged clinical trials have demonstrated that immunotherapy has the potential not only to

†the corresponding author.
Email address: n.bajja@edu.umi.ac.ma. (N. Bajja), d.seghir@umi.ac.ma. (D. Seghir)
[1]Department of Mathematics,Faculty of Sciences, Moulay Ismail University, Zitoune, 11201 Meknes, Morocco.
[2]Laboratory of Mathematics and their Interactions, Faculty of Sciences, Moulay Ismail University, Zitoune, 11201 Meknes, Morocco.
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eradicate tumor cells but also to enhance the effectiveness of chemotherapy and radiotherapy [3–5].

Mathematical modeling has broad applications in ecological, epidemiological, and tumor fields [6–12, 17, 19, 38]. Samanta and co-authors established a system of impulsive ordinary differential equations to model the interactions between tumor, normal, and immune cells, incorporating the effects of periodically pulsed chemotherapy [15]. Their study identified the necessary parametric conditions to prevent relapse after tumor or metastasis removal. Additionally, the research explored the effects of resistant tumor sub-populations and proposed strategies to prevent recurrence. The authors developed and analyzed a nonlinear mathematical model for tumor-immune interactions with drug treatment [16]. They formulated an optimal control problem to reduce cancer cells, enhance the immune response, and minimize drug side effects. They conducted sensitivity and cost-effectiveness analyses, and the results confirmed the effectiveness of combination therapy in reducing the tumor. A bifurcation analysis of a tumor-immune model subjected to periodically pulsed immunotherapy revealed that when the immune response is weak, increasing its intensity can yield positive therapeutic effects [17]. However, if the immune response intensity exceeds a certain threshold, it may lead to treatment failure. Tang utilized a pulsed differential system to model the interactions between pulsed chemotherapy and immunotherapy, demonstrating the substantial benefits of combining low-dose chemotherapy with high-dose immunotherapy in treating solid tumors [18]. This study highlighted the hormetic effects of chemotherapy and immune response curves, affirming the synergistic advantages of this combined therapeutic approach in reducing side effects and enhancing tumor suppression. Similarly, Sharma developed a system of ordinary differential equations to examine the interactions among tumor cells, cytotoxic T lymphocytes (CTLs), and helper T-cells within the tumor-immune system under chemotherapy [19], further analyzing the dynamic behavior of this system.

Li and Cheng emphasized that in natural biochemical systems, the enzymatic activity of proteins is highly sensitive to environmental factors such as temperature, nutrition, oxygen, and pH levels [20]. Consequently, it is imperative to consider the effects of stochastic noise on cellular evolution.d'Onofrio argued that the complex interactions between tumor cells and immune effectors necessitate the inclusion of noise in deterministic models of the tumor-immune system [21]. The influence of noise on cancer dynamics has been extensively studied, including its role in stochastic fluctuations leading to extinction and recurrence, stochastic resonance [22], and the extinction and persistence of tumor cells [25, 28, 35]. These findings underscore the complexity of tumor behavior and the necessity of integrating stochastic elements into mathematical models to better reflect biological realities.

Yang developed a stochastic tumor-immune model under the influence of immunotherapy and chemotherapy [24], deriving sufficient conditions for the extinction and persistence of both tumor cells and effector cells. However, this model did not account for the role of helper T-cells, which are crucial for stimulating effector cells. In contrast, Wang analyzed a stochastic tumor-immune system using a system of stochastic differential equations [23]. Wang also derived sufficient conditions for the extinction and persistence of tumor cells. This study extends previous models by incorporating pulse treatment, which combines chemotherapy and immunotherapy, and by examining the effects of random disturbances in the internal environment on tumor cells and two types of immune cells. The mathematical modeling of com-