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A deterministic and stochastic model for the system dynamics of tumor–immune responses to chemotherapy

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HIGHLIGHTS

- A deterministic and a stochastic tumor–immune model are constructed.
- The basic dynamical properties are investigated in the deterministic model.
- The CTMC model is harnessed to estimate the extinction probability of tumor cells.
- Numerical simulations are performed to confirm the obtained theoretical results.

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ABSTRACT

Modern medical studies show that chemotherapy can help most cancer patients, especially for those diagnosed early, to stabilize their disease conditions from months to years, which means the population of tumor cells remained nearly unchanged in quite a long time after fighting against immune system and drugs. In order to better understand the dynamics of tumor–immune responses under chemotherapy, deterministic and stochastic differential equation models are constructed to characterize the dynamical change of tumor cells and immune cells in this paper. The basic dynamical properties, such as boundedness, existence and stability of equilibrium points, are investigated in the deterministic model. Extended stochastic models include stochastic differential equations (SDEs) model and continuous-time Markov chain (CTMC) model, which accounts for the variability in cellular reproduction, growth and death, interspecific competitions, and immune response to chemotherapy. The CTMC model is harnessed to estimate the extinction probability of tumor cells. Numerical simulations are performed, which confirms the obtained theoretical results.

1. Introduction

Cancer treatment is a major public health problem in most parts of the world. It causes the highest mortality rate in economically developed countries and the second highest mortality rate in developing countries [1]. In 2012, there were about 14.1 million new cancer cases and 8.2 million deaths in the world based on the GLOBOCAN estimates. The occurrence of cancer is increasing as a result of population aging and growth, leading to an increasing prevalence of established risk factors such as smoking, overweight, physical inactivity, and changing reproductive patterns associated with urbanization and economic development [2].

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The interactions between the immune system and growing tumor are quite complicated. Generally speaking, the immune response to tumor mainly involves the division and coordination of several kinds of immune cells. Once a tumor occurs in one tissue, B-lymphocytes products and secrets antibodies into the blood or places them on the surface of the tumor. In the meantime, the effector cells (Cytotoxic-T-Lymphocytes, CTLs) destroy the antigens constantly. This leads to T helper-lymphocytes, the antigen-bearing cells, to secret interleukins, which stimulates both T and B cells to divide. Finally, the immune response is terminated by T-suppressor cells. The process of immune response to a tumor seems unassailable. Unfortunately, the tumor processes a rigorous defense system that could interrupt the occurrence of a fully efficient response by preventing themselves from contacting with lymphocytes through the surface expression of ligands which initiate the apoptotic signal in the cytotoxic T-lymphocytes [3].

Accounting for the complexity of immune responses to a tumor, various mathematical models were developed to understand its dynamical mechanism in the past few decades. Among these models, most of them are deterministic (e.g., [4–18] and references therein), and only a few of them are stochastic (e.g., [19–23] and references therein). In the investigation of deterministic models, some researchers focus on the estimation of parameters and the analysis of dynamical properties, such as stability, bifurcation and its stability and direction [4–11], while others further extend the applications of these models by exploring the optimal control of cancer treatment [12–18]. Stochastic models are introduced to characterize immune responses to a tumor, which improves understanding of the pathological process from a different perspective. Sarkar and Banerjee [19] constructed a stochastic system, consisting of tumor cells, hunting predator cells and resting predator cells, and investigated the stochastic stability properties of the model. Albano and Giorno [20] proposed a stochastic model for solid tumor growth based on deterministic Gompertz law, and studied the effects of a time-dependent therapy via a numerical approach. Bose and Trimper [21] analyzed a stochastic model for tumor cell growth with both multiplicative and additive colored noises as well as nonzero cross correlations in between. Xu et al. [22] discussed the stochastic bifurcation for a tumor–immune system in the presence of a symmetric non-Gaussian Lévy noise, and found that stochastic dynamics induced by Gaussian and non-Gaussian Lévy noises were quite different. Kim et al. [23] constructed deterministic and stochastic models of cancer-virus dynamics, and investigated virus characteristic parameter sensitivities using a reproduction ratio. Overall, mathematical modeling plays an essential role in designing and analyzing clinical trials to oncology, which offers a potentially powerful tool in the development of improved treatment regimens.

Actually, many factors influence the effect of cancer treatment, such as the strength of patient's own immune response, the severity of the disease, and the application of the treatment. From the perspective of tumor therapy, chemotherapy is a very important treatment method which maybe cure part of patients with non-metastatic cancer. Even for patients with advanced cancer, it is still possible to extend their life spans to some extent. Taking lung cancer for example, it leads to approximately one third of all cancer-related deaths, which is more than the aggregate proportion of breast, prostate, and colon cancer in each year. The median survival of patients with untreated metastatic non-small-cell lung cancer is only four to five months, with a survival rate at one year of only 10% [24]. However, many studies proved that chemotherapy, as a supportive care, slightly promotes the survival time for patients with advanced non-small-cell lung cancer [25–27]. Moreover, Cullen et al. [28] demonstrated that chemotherapy with the "best supportive care" reduced symptoms and improved the quality of life for lung cancer patients. Fortunately, a variety of new drugs have been found for treating metastatic non-small-cell lung cancer over the past two decades, such as the taxanes, gemcitabine, and vinorelbine. A number of phase II studies show that it has resulted in high response rates and prolonged survival at one year by combining one or more of these drugs with a platinum compound [29–31].

Inspired by the above researches, this paper attempts to explore the influence of chemotherapy on tumor–immune responses from a long-term perspective. Clinical medicine researches have shown that the stable period of a cancer patient with chemotherapy could remain for months or even a couple of years, which means that the population of tumor cells remained nearly unchanged in quite a long time after fighting against the immune system and drugs. Unfortunately, in most cases tumor cells eventually develop resistance to these chemicals and defeat immune system *in vivo*. However, it is still very significant to harness mathematical and statistical modeling to improve the understanding of the system dynamics of tumor–immune responses to chemotherapy, which should contribute to make some effective cancer treatment strategies. For this, we shall first construct a deterministic model by adding the terms of chemotherapy effect based on the immune responses system proposed in [32,33], and obtain asymptotically stable conditions of equilibriums. Moreover, considering much uncertainty in the process of treatment, such as the variability in cellular reproduction and death, the change of fight ability between immune system and tumor cell, and the fluctuation of chemotherapy effect, we extend the deterministic model to stochastic one, and further use a continuous-time Markov chain (CTMC) model to estimate the extinction probability of tumor cells.

The remaining sections are organized as follows. The deterministic ordinary differential equation (ODE) model that characterizes tumor–immune responses is constructed, and its basic dynamical properties are discussed in Section 2. In Section 3, a stochastic model is proposed based on the deterministic ODE model, and a continuous-time Markov chain model is employed to estimate the extinction probability of tumor cells. Some numerical simulations are performed to verify the theoretical results obtained in this paper. The paper ends with a brief conclusion.