Chapter 23
Antimonotonicity, Crisis, and Route to Chaos in a Tumor Growth Model

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ABSTRACT

In this chapter, a new model of a tumor growth is dynamically investigated. The model is presented in a form of a system of three ordinary differential equations, which describe the avascular, vascular, and metastasis tumor growth, respectively. For the investigation of system's dynamics and especially of the population of the immune cells in system's behavior, some of the most well-known tools from nonlinear theory, such as the phase portrait, the Poincaré map, the bifurcation diagram the Kaplan-Yorke dimension, and the Lyapunov exponents have been used. Interesting phenomena related with chaos theory, such as a period-doubling route to chaos, crisis phenomena, and antimonotonicity, have been revealed for the first time in this model.

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1. INTRODUCTION

Cancer is a group of diseases, defined by an abnormal, uncontrolled proliferation of cells in a part of the body (Tiwari, 2012). It is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018, according to World Health Organization (WHO, 2020). In spite of the advances of molecular biology and genomics, humanity's understanding of cancerous cell growth is still vague. As a result, it poses a daunting task to detect it early with the goal of taking appropriate measures to hinder its growth and reduce the victims' suffering, let alone find a cure. Developed countries are heavily investing into cancer research and many scientific disciplines are involved, including physics and mathematics, and this is where this chapter will focus.

In many cases, mathematical models have vastly contributed to comprehending carcinogenesis and cancer progression (Adam & Bellomo, 2012; Deisboeck *et al*., 2011; Dominic *et al*., 2005; Frank, 2007; Majhi, 2018; Nikulin, 2007; Tan, 2020; Voiculetz *et al*., 1991). Consequently, that renders the need for formulating newer and more accurate models depicting cancer growth in all its stages more compelling. It is important to highlight the fact that cancer has three distinct stages: *avascular*, *vascular* and *metastatic* (Hogea *et al*., 2005). During the avascular phase, the tumor obtains nutrients and "feeds" itself via diffusion processes alone, with nutrients already existing in the environment (Breward *et al*., 2002; Byrne, & Chaplain, 1998; Chaplain, 1996; Izquierdo-Kulich *et al*., 2013; Knighton *et al*., 1977; Ward & King, 1997). In the vascular phase, when the tumor grows faster through angiogenesis (the process by which new blood vessels form), malignant tumor cells secrete chemicals that can diffuse into the surrounding healthy tissues and stimulate the growth of new capillary blood vessels (Ribatti *et al*., 1999; Huang *et al*., 2009; Keogan *et al*., 1997; Verstovsek *et al*., 2002; Yao *et al*., 2008). The newly born blood vessels penetrate into the tumor mass providing it with nutrients and resulting in rapid growth of the tumor. Tumor growth occurs basically via the following mechanism. When tumor is supplied with a sufficient amount of nutrient, malignant cells are divided (cellular mitosis). So, when the density of malignant cells in a specific volume becomes too high, the cells are compressed by their neighbors, so they tend to move to less compressed areas, where they are allowed to continue the division process, and this process is repeated. In the third phase, metastasis, malignant cell migrate through the blood vessels and/or the lymphatic system towards other parts of the body, giving rise to secondary tumors (Chaffer & Weinberg, 2011; Gupta & Massagué, 2006; Nguyen & Massagué, 2007; Pani *et al*., 2010; Poste & Fidler, 1980). This process is the primary cause for the host death.

Due to the fact of the existence of these distinct phases, researchers often attempt to answer specific questions for each of those stages separately. In many attempts these questions have been attempted to be answered by using dynamical system analysis. The reason of this is because growth of malignant tumors can be described as ordinary differential equation (ODE) models including two main populations: effector cells and tumor cells. Especially, dynamical systems with chaotic behavior have been used widely for this purpose (Ahmed, 1993; Brinkley, 2001; Dirks, 2008; Duarte *et al*., 2013; Duesberg, 2007; Saleem & Agrawal, 2012). Chaotic dynamical systems have the feature of the sensitive dependence to initial conditions, which is a key component of chaos theory (Strogatz, 2015). Furthermore, dynamical systems are systems in which a function describes the time dependence of a point in a geometrical space (Verhulst, 1996), and they can be divided into discrete and continuous systems. A discrete dynamical system is a dynamical system, which state evolves over state space in discrete time steps according to a fixed rule (Moysis & Azar, 2017a). A continuous dynamical system is a dynamical system, which state evolves over state space continuously over according to a fixed rule.