Journal of Theoretical Biology 334 (2013) 130–140

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Periodic and chaotic dynamics in a map-based model of tumor–immune interaction

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HIGHLIGHTS

- A discrete model of the complex interactions between tumor and immune populations.
- Explain many biologically observed and some potential tumor states and dynamics.
- Providing insight into the future behaviors of the tumor.
- Even an avascular tumor could become invasive under certain conditions.

ARTICLE INFO

Article history:
Received 24 December 2012
Received in revised form
18 May 2013
Accepted 28 May 2013
Available online 11 June 2013

Keywords:
Tumor growth model
Discrete map
Delay difference equation system
Chaos
Limit cycle

ABSTRACT

Clinicians and oncologists believe that tumor growth has unpredictable dynamics. For this reason they encounter many difficulties in the treatment of cancer. Mathematical modeling is a great tool to improve our better understanding of the complicated biological system of tumor growth. Also, it can help to identify states of the disease and as a result help to predict later behaviors of the tumor. Having an insight into the future behaviors of the tumor can be very useful for the oncologists and clinicians to decide on the treatment method and dosage of the administered drug. This paper suggests that a suitable model for the tumor growth system should be a discrete model capable of exhibiting periodic and complex chaotic dynamics. This is the key feature of the proposed model. The model is validated here through experimental data and its potential dynamics are analyzed. The model can explain many biologically observed tumor states and dynamics, such as exponential growth, and periodic and chaotic behaviors in the steady states. The model shows that even an avascular tumor could become invasive under certain conditions.

1. Introduction

Cancer is becoming the leading cause of death around the world but our overall knowledge of its causes, methods of prevention and cure is still in its infancy. One great tool that has shown its potential in our better understanding of such a complicated biological system is mathematical modeling (Cristini and Lowengrub, 2010; Preziosi, 2003; Tan and Hanin, 2008; Moghtadaei et al., 2012). Mathematical models provide realistic and quantitative representations of important biological phenomena, and biological interpretation of their results can give insight to make realistic predictions of the state of disease under different conditions (Swanson et al., 2003).

The idea of using mathematical models for cancer was introduced in 1955 by Thomlinson and Gray (1955). After that, many mathematical models for tumor growth have been developed and the application of these models has been increased recently (Bonate, 2011; Hwang et al., 2009; Moghaddasi et al., 2012; Rejniak and Anderson, 2011; Moreira and Deutsch, 2002). What makes mathematical models of tumor growth interesting is that they can be simple but indeed still indicate the complicated interactions involved (Sachs et al., 2001). The tumor growth dynamics and the antitumor immune response dynamics in vivo are very complex (Galach, 2003), and not well understood mainly because in most of states, the measurements are impossible in vivo. Models are not only able to explain many phenomena observed in vivo, but they could also provide a good insight about the phenomena that are unobservable in vivo.

Major causes of the complexity in the tumor system are the diversity of levels of the tumor system (gene, molecular, cellular,

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0022-5193/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jtbi.2013.05.031

tissue, organ, body and population), different time scales of each level, self-organization of the system, multitude of signaling pathways and tumor–immune and tumor–environment interactions (d'Onofrio et al., 2010; Robertson-Tessi et al., 2012; Bellomo and Preziosi, 2000; Kiyoshi et al., 1988). In theory, this complexity can lead to an emergence of different types of attractors (fixed point, limit cycle, and even strange attractor) (Liu et al., 2009; Kuznetsov et al., 1994; Ahmed, 1992). In fact, one can also experimentally demonstrate the existence of these limit cycles and strange attractors as a result of the complex dynamics of the tumor system (Ivancevic et al., 2008a; El-Gohary, 2008; Rew, 1999). These strange behavior of tumors can be addressed based on the inherent properties of chaos (Lorenz, 1963), such as sensitive dependence on initial conditions. Sensitive dependence on initial conditions makes the tumor growth patterns case specific, i.e. evolution of cancer for any patient is different from another patient, due to the different initial conditions for any individual. While this is a challenging issue for the oncologists, this is a very interesting topic in the field of tumor modeling. For these reasons, chaos theory could allow a better understanding of this complex system (Denis and Letellier, 2012a, 2012b; Letellier et al., 2013; Obcemea, 2006). The main connecting points between chaos and carcinogenesis have been described by Denis and Letellier recently (Denis and Letellier, 2012a).

On the other hand, the cell cycles with characteristic doubling times in the mitosis stage, makes the tumor growth system a discrete time system (Obcemea, 2006). This is a good reason to say that cancer models should be discrete maps and not some continuous differential equations. In addition, as mentioned above, it is also known that the tumor can grow, regress, and re-grow in an oscillatory manner (Ivancevic et al., 2008a; Obcemea, 2006; Siu et al., 1986). Discretizing a continuous model can recover oscillations in tumor dynamics that might have been smoothened in the continuous counterparts.

Considering these mentioned properties, an optimum model for the tumor growth system is a discrete model that can exhibit different behaviors of the tumor system, i.e. exponential growth approaching to an asymptotic value, periodic and chaotic behaviors, and to have different attractors, i.e. fixed point, limit cycle and strange attractor for different parameter values.

In this article we propose a discrete model of tumor growth in a macroscopic scale which includes the tissue level growth phenomena, keeping in mind the mesoscopic interaction of tumor and immune cells. This model is a discrete map that is developed using different time lags in its continuous counterpart. The model is validated using experimental data. The dynamics of the model is analyzed using some numerical simulations by means of computing Lyapunov Exponents spectrum, bifurcation diagram, phase portraits, and first return maps to the Poincare section.

In the following sections, first the formulation of the continuous and its discrete form is described, and then the stability of the fixed points of the model is analyzed. Next, the requirements of chaos in a discrete map and our methods to measure them are briefly explained. Subsequently, the results of our analysis on the behavior of this map are reported, and finally, in the conclusion and discussion section, the importance and probable usage of this model are explained.

2. Tumor–immune model

The continuous model used in this study is the two dimensional Kuznetsov model (Kuznetsov et al., 1994). This model includes two types of cells, i.e. tumor and immune cells. The prototype of the model is described with a system of differential equations:

$$\begin{cases} \dot{X} = s - dX + g(X,Y) - h_1(X,Y) \\ \dot{Y} = f(Y) - h_2(X,Y) \end{cases} \tag{1}$$

where, the variables X and Y are used to model the number of immune cells and tumor cells respectively. The function $f(Y)$, in the second equation is the tumor growth function. It involves the mechanisms that control the growth. The iterated map of the tumor growth time series is proved to be bell shaped (Galach, 2003; Kuznetsov et al., 1994; Ahmed, 1992; Voitikova, 1997). In the Kuznetsov model, it is assumed to be the logistic function as below

$$f(Y) = aY(1-bY) \tag{2}$$

In which the parameter a models the tumor growth rate, and the parameter b determines the carrying capacity of the tumor in the model.

In this model, the immune system in assumed to be composed of two types of cells, i.e. NK and CTL cells. The NK cells, which are always present, have a constant source of production which is included by the constant term, s, in the model. The fraction of the NK cells that die off is modeled by the term dX. The function $g(X,Y)$ models the production of tumor specific immune cells, i.e. CTLs. It should be an increasing function with respect to the tumor cells, i.e. Y. It is assumed to be (Kuznetsov et al., 1994)

$$g(X,Y) = \frac{pXY}{g+Y} \tag{3}$$

where the parameter p models the maximum immune response rate and the parameter g determines the steepness of immune response in the model.

The functions $h_1(X,Y)$ and $h_2(X,Y)$ model the competitive interaction of the tumor and immune cells. This interaction can be modeled from different aspects. In this model, only the tumor–immune conjugate pairs are considered. The conjugates are quiescent and do not reproduce, and only contribute in the crowding effects. This crowding effect caused by conjugate pairs is modeled as (Kuznetsov et al., 1994)

$$h(X,Y) = \xi XY \tag{4}$$

where, the parameter ξ represents the fraction of immune or tumor cells that are inactivated or killed in the conjugate pairs in the model. Later in the model, ξ is replaced by parameters m, for the fraction of inactivated immune cells, and n, for the fraction of killed tumor cells due to interaction of cells

– Finally, the Model described by (eq. 1) can be written as:

$$f1: \begin{cases} \dot{X} = s - dX + \frac{pXY}{g+Y} - mXY \\ \dot{Y} = aY(1-bY) - nXY \end{cases} \tag{5}$$

The parameters of the ODE model (Eq. (5)) are estimated by minimizing the difference between the model output and the data points for BCL_1 lymphoma in the spleen of chimeric mice for three different groups of mice (Siu et al., 1986). Different initial numbers of BCL_1 cells were inoculated i.v. into each group of chimeric mice. The initial number of BCL_1 cells for groups one to three was 5×10^5, 5×10^6 and 5×10^7 respectively. The mice were followed up for 70 to 110 days (Siu et al., 1986). At various intervals after injection of BCL_1 cells, animals were sacrificed, their spleens were removed, and the tumor cells were counted (Siu et al., 1986). The average number of tumor cells for mice in each group during the follow up period (as shown in Fig. 1) is used to estimate the parameters of the model. The initial number of effector cells is assumed to be 3.2×10^5.