Applied Mathematics and Computation 232 (2014) 606–623

Contents lists available at ScienceDirect

Applied Mathematics and Computation

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

A time delay model of tumour–immune system interactions: Global dynamics, parameter estimation, sensitivity analysis

F.A. Rihan [a,*], D.H. Abdel Rahman [a], S. Lakshmanan [a], A.S. Alkhajeh [b]

[a] Department of Mathematical Sciences, College of Science, UAE University, 15551 Al Ain, United Arab Emirates
[b] Department of Biology, College of Science, UAE University, 15551 Al Ain, United Arab Emirates

ARTICLE INFO

Keywords:
DDEs
Hopf bifurcation
Immune cells
Parameter estimation
Sensitivity
Stability
Tumour cells

ABSTRACT

Recently, a large number of mathematical models that are described by delay differential equations (DDEs) have appeared in the life sciences. In this paper, we present a delay differential model to describe the interactions between the effector and tumour cells. The existence of the possible steady states and their local stability and change of stability via Hopf bifurcation are theoretically and numerically investigated. Parameter estimation problem for given real observations, using least squares approach, is studied. The global stability and sensitivity analysis are also numerically proved for the model. The stability and periodicity of the solutions may depend on the time-lag parameter. The model is qualitatively consistent with the experimental observations of immune-induced tumour dormancy. The model also predicts dormancy as a transient period of growth which necessarily results in either tumour elimination or tumour escape.

1. Introduction

The immune system (IS) is a complex network of cells and signals that have evolved to respond to the presence of pathogens (such as bacteria, virus and fungi) and protect the body from cancer cells. IS basically works by keeping track of all substances normally found in the body. Any new substance in the body that the IS does not recognize raises an alarm, causing the IS to attack it. Substances that cause an IS response are called ‘‘antigens’’. The IS can lead to destruction of anything containing antigens, such as pathogens or cancer cells. Pathogens have substances on their outer surfaces such as certain proteins that are not normally found in the human body. The IS sees these foreign substances as antigens. Cancer cells are also different from normal cells in the body and they have unusual substances on their outer surfaces. However, the IS is such better recognizing and attacking pathogens (harmful germs) than cancer cells. This is due to the fact that pathogens are very different from normal human cells and are often easily seen as foreign, but cancer cells and normal cells have fewer clear differences. This leads us to the fact that the IS may not always recognize cancer cells as foreign (see [18]). We should also mention here that the immunity has basically two categories: innate (natural or non specific) immunity and adaptive (acquired or specific) immunity, which are generally carrying out mutual and collaborative functions to eliminate pathogens (see [19,25,26]). The innate immune system recognizes molecules produced by foreign invaders, or pathogens. Adaptive immunity is very specific and does lead to an increase in response with repeated exposures. Exposure to a particular antigen will lead to a faster, more effective response to that particular antigen in the future, but not to any other antigens. It will lead

* Corresponding author.
E-mail address: frihan@uaeu.ac.ae (F.A. Rihan).

http://dx.doi.org/10.1016/j.amc.2014.01.111
0096-3003/

to the creation of memory T lymphocytes and memory B cells that will then be available to "remember" a particular species of pathogen or other antigenic substance, so that the response will be more effective and rapid on subsequent exposure; See [16,27].

Mathematical models of tumour-immune dynamics have added to our understanding of how host immune cells and cancerous cells evolve and interact (see e.g. [1,4,5,7–9,20,21,24,28,35,40]). Kuznetsov et al. [22] model the interactions of cytotoxic T lymphocyte (CTL) response and the growth of an immunogenic tumour. In recent contributions of [11,12,33,34], the authors take into account the penetration of the tumour cells by the effector cells, which simultaneously causes the inactivation of effector cells. The authors in [6] consider the effects of time delay on the two-dimensional system which represents the basic model of the immune response. They study variations of the stability of the fixed points due to time delay and the possibility for the occurrence of the chaotic solutions. Foryś and Kolev [13] propose and study the role of time delay in solid avascular tumour growth. They study a delay model in terms of a reaction–diffusion equation and mass conservation law. Two main processes are taken into account i.e. proliferation and apoptosis. In [15], Galach provides a simplified version of the Kuznetsov–Taylor model where immune reactions are described by a bilinear term with time delay. Yafia [39] analyzed an interaction between the proliferating and quiescent cells tumour with a single delay. He showed the occurrence of Hopf bifurcation as the delay crosses some critical value; See [41].

In the present paper, we adopt a predator–prey formulation of the tumour immunity problem as a battle between immune cells and tumour cells (predators and prey, respectively). The model has a simple formulation in terms of delay-differential equations (DDEs). The critical time-delay, for which a destabilising Hopf bifurcation of the relevant fixed point occurs, and the conditions on the parameters for such bifurcation are found. Furthermore, delay-dependent global stability conditions for the proposed model are derived by constructing Lyapunov–Krasovskii functional and applying Linear Matrix Inequality (LMI) approach [14]. We then calculate the maximum allowable upper bound of the time delay τ of the linearized system.

We take into account the time delay to describe the time needed by the immune system to launch a suitable response after recognizing the non-self cells or foreign bodies. We fit the proposed model to experimental data of tumour cells that developed in the spleen of the laboratory mice to identify the appropriate parameters dedicated to study the dynamics of the model. We also investigate the sensitivity analysis of the model to determine the most sensitive parameters and informative subintervals. The paper is organized as follows: In Section 2, we present a time delay differential model for tumour-immune system dynamics. In Sections 3, we determine the existence of possible steady states of the model. In Section 4, we study local and global stability of the steady states and changes in the stability though the Hopf bifurcation analysis. In Section 5, we study the identification of the parameters occur in the model when given real observations. We also use the sensitivity functions to evaluate the sensitivity of the number of tumour cells with respect to the normal rate of the effector cells, death rate of the effector cells and small changes in the time-lag parameter (see Section 6). In Section 7, we carry out some numerical simulations and provide some biological interpretations. Summary and conclusions are then presented in Section 8.

2. The model

We first recall Kuznetsov et al.'s model [22] that describes the dynamics of tumour immune system interactions by incorporating a system of five ordinary differential equations (ODEs) model, then we reduce it into two equations but with time delays. The model proposed in [22] describes the response of the Effector Cells (ECs) to the growth of Tumour Cells (TCs). In this model, it has been taken into account the penetration of TCs by ECs, which simultaneously causes the inactivation of ECs. It is assumed that interactions between ECs and TCs are *in vitro* such that $\bar{E}(t), \bar{T}(t), \bar{C}(t), \bar{E}^*(t)$ and $\bar{T}^*(t)$ denote the local concentrations of ECs, TCs, EC–TC conjugates, inactivated ECs and 'lethally hit' TCs, respectively. The total population of unattacked TCs is $\bar{T}_{tot}(t) = \bar{T}(t) + \bar{C}(t)$. The rate of binding of ECs to TCs and the rate of separation of ECs from TCs without damaging them are denoted by k_1 and k_{-1}, respectively. The rate at which EC–TC integrations program for lysis is denoted by k_2 while the rate at which EC–TC interaction inactivate ECs is denoted by k_3. The model takes the form:

$$\begin{aligned}
\frac{d\bar{E}(t)}{dt} &= \bar{\sigma} + F(\bar{C}(t), \bar{T}(t)) - d_1\bar{E}(t) - k_1\bar{E}(t)\bar{T}(t) + (k_{-1} + k_2)\bar{C}(t),\\
\frac{d\bar{T}(t)}{dt} &= \bar{\alpha}\bar{T}(t)(1 - \bar{\beta}\bar{T}_{tot}(t)) - k_1\bar{E}(t)\bar{T}(t) + (k_{-1} + k_3)\bar{C}(t),\\
\frac{d\bar{C}(t)}{dt} &= k_1\bar{E}(t)\bar{T}(t) - (k_{-1} + k_2 + k_3)\bar{C}(t),\\
\frac{d\bar{E}^*(t)}{dt} &= k_3\bar{C}(t) - d_2\bar{E}^*(t),\\
\frac{d\bar{T}^*(t)}{dt} &= k_2\bar{C}(t) - d_3\bar{T}^*(t).
\end{aligned} \tag{1}$$

Here, the parameter $\bar{\sigma}$ represents the normal rate (not increased by the presence of the tumour) of the flow of adult ECs into the tumour side (region), $F(\bar{C}(t), \bar{T}(t)) = F(\bar{E}(t), \bar{T}(t)) > 0$ (when $\bar{T}(t) > 0$) describes the accumulation of ECs in the tumour side due to the presence of the tumour. While, d_1, d_2 and d_3 are the coefficients of the processes of destruction and migration of $\bar{E}, \bar{E}^*$ and $\bar{T}^*$, respectively. The maximal growth of tumour is represented by the coefficient $\bar{\alpha}$, and $\bar{\beta}^{-1}$ is the environment