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An immune system–tumour interactions model with discrete time delay: Model analysis and validation

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ABSTRACT

In this article a generalised mathematical model describing the interactions between malignant tumour and immune system with discrete time delay incorporated into the system is considered. Time delay represents the time required to generate an immune response due to the immune system activation by cancer cells. The basic mathematical properties of the considered model, including the global existence, uniqueness, non-negativity of the solutions, the stability of steady sates and the possibility of the existence of the stability switches, are investigated when time delay is treated as a bifurcation parameter. The model is validated with the sets of the experimental data and additional numerical simulations are performed to illustrate, extend, interpret and discuss the analytical results in the context of the tumour progression.

1. Introduction

Cancer immunology is a new trend in immunology that focuses on the variety of interactions between the immune system and cancer cells. The aim of cancer immunology is to discover new cancer immunotherapies to fully cure or at least to retard the progression of the disease. According to recent reports [1] lymphocytes sensitive to tumour antigens are often present in the patient's body, providing a potentially natural way to prevent tumour growth. On the other hand, it is also observed that the full immune response usually does not occur and so the natural protection afforded by the immune system is ineffective.

In general the interactions between tumour cells and immune system are very complex and involve a number of different kinds of molecules, immune cells and events [2]. The immune response against tumour antigens involves different kinds of immune cells: B-Lymphocytes producing and secreting antibodies into the blood or placing them on their surfaces, cytotoxic T-Lymphocytes – the effector cells that destroy the antigens and thus the antigen-bearing cells, T helper-lymphocytes secreting interleukins, hence stimulate both T and B cells to divide and finally T-suppressor cells that end the immune response. All these cells are produced in the body from a small fraction of the precursor cells. Whenever antigens are presented to the precursor cells they are activated, start to proliferate and then differentiate into effector or memory cells. Unfortunately, these mechanism do not guarantee the fully efficient response of the immune system due mainly to the tumour's own defence system. Tumour cells protect themselves from contact with lymphocytes by, amongst other methods, surface expression of ligands which initiate the apoptotic signal in the cytotoxic T-Lymphocytes, thus killing off the cytotoxic T-Lymphocytes before the necessary cell-contact with the tumour cells can be initiated.

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Clearly, due to the complexity of the considered problem systems describing most of the tumour–immune system interactions would involve a large number of variables and thus equations, as in [3], where a model of 12 equations is proposed and numerically analysed or in [4], where a system of 5 equations describing the response of the effector cells to the growth of tumour cells is studied. More recently, systems of four or more equations investigating the immunotherapy and its improvement for high grade gliomas [5,6], predicting outcomes of prostate cancer personalised immunotherapy [7] or humoral mediated immune response [08] were proposed. Also well known immune system Marchuk's model [9–11], describing the immune system dynamics which was applied to the description of the tumour growth phenomenon, see e.g. [12]. However, to better understand the main underlying mechanism of immune response to the presence of the tumour cells complex models were simplified and thus reduced into two- or three-equation and less detailed ones, see e.g. [13–19] or [20–26].

In this article the influence of a particular modification to the generalisation of the two-equation model proposed in [19] is studied. The proposed generalisation concerns the form of the stimulus function, namely only some essential assumptions regarding the shape and regularity of this function are assumed for the theoretical part of the paper. The proposed modification reflects the fact that the immune system requires some time before the presence of a tumour (actually, tumour antigens) in the body is detected and the immune system is able to respond. This assumption leads to the incorporation of a discrete time delay in the function describing the immune system stimulation by presence of the tumour cells. For the obtained system the basic mathematical properties of the model, the possible asymptotic behaviour of the system depending on the delay and the role of the native background immunity and the immune stimulation strength are investigated. For the particular form of the stimulus function the considered model is validated with two sets of the experimental data for particular tumour cell line and further studied in the context of the model dynamics within the framework of the other experimental data. It is shown that model can reflect different patterns, including periodic, reported in the experimental literature. For the estimated parameter values it is shown that an increase of the background immunity or the stimulation strength of the tumour cells on the immune system enlarge the stability region for the positive dormant steady state. Moreover, the increase of the background immunity might stabilise the unrestricted tumour growth observed for the control experiment.

The paper is organised as follows: in Section 2 the model without delay and summary of the existence and stability of the non-negative steady states are presented; in Section 3 the model with discrete delay is described and analysed. Next, in Section 4 model is validated with the experimental data. The numerical simulations confirming and extending the analytical results are shown in Section 5. Finally, in Section 6 above results are summarised and discussed.

2. Presentation of the base model

In [19] a simple model for tumour–immune system interaction, that takes into account the two most important variables: the size of specific anti-tumour immunity at time s ($X(s)$) and the size of tumour ($Y(s)$), is studied. To describe the size of the overall specific immunity against the tumour Foryś et al. [19], make the following assumptions. First, in the absence of tumour antigens one observes a constant (with rate w) production of precursor cells that are able to respond to the tumour antigens and the natural death of the cells, which is expressed by a linear term uX. Thus, as a consequence of the tumour absence within the body a constant immunity level (so-called background immunity) is kept. Second, the presence of tumour antigens stimulate an increase of the immunity level. Moreover, it is assumed that immunity response is proportional to the current size of the immunity X with the proportionality coefficient (aF), which is assumed to be a bounded function of both immunity size and tumour antigens or tumour antigens only. It is also assumed that the creation of the tumour cell–T-cytotoxic lymphocyte conjugates lead to the death of the immune cells and it is modelled by a bilinear term XY with constant coefficient b. Clearly, if for particular tumours this process is not observed, then $b = 0$. Finally, the destructive influence of immune system on the tumour development is described by the bilinear term XY with the constant rate c, similarly as it was assumed in [16]. In addition, it is assumed that the tumour grows according to the exponential law, as e.g. in [14,18,20], with growth rate equal to r. The system proposed in [19] has the following form

$$\dot{X}(s) = w - uX(s) + aF(X(s), Y(s))X(s) - bX(s)Y(s), \tag{2.1a}$$

$$\dot{Y}(s) = Y(s)(r - cX(s)), \tag{2.1b}$$

where the presence of tumour antigens that stimulate the immune system response (F) is defined by

$$F_1(X, Y) = \frac{Y^\alpha}{k_1^\alpha X^\alpha + Y^\alpha}, \quad \text{or} \quad F_2(X, Y) = \frac{Y^\alpha}{k_2^\alpha + Y^\alpha}. \tag{2.2}$$

Different forms of F_1 and F_2 reflect different assumptions on tumour–immunity interactions, and both of them were earlier considered in the literature in the context of the immune system response. For $F = F_2$ it is assumed that the number of stimulated cells does not depend on the size of the immune system itself, hence stimulation is tumour dependent. Such a form of the stimulus function in the context of immune response was considered for example in [4,27–29] and more recently in [19,21,25]. In case of $F = F_1$ a number of tumour cells needs to be reached before faster production of immune cells is activated (after which, the size of anti-tumour immunity increases) hence such a function is often called a ratio-dependent stimulation function and it was considered in the immune system–tumour interactions context in [3].

Due to the biological interpretation of constants, it is assumed that all parameters are non-negative and in particular parameters a, c, u, r, w and k_i, $i = 1, 2$ are strictly positive. Moreover, it is assumed that α, which describes the switching characteristics of the stimulus functions, is greater or equal to 1.