Journal of Theoretical Biology 259 (2009) 820–827

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

On immunotherapies and cancer vaccination protocols: A mathematical modelling approach

Badal Joshi [a], Xueying Wang [a], Sayanti Banerjee [a], Haiyan Tian [b], Anastasios Matzavinos [c,*], Mark A.J. Chaplain [d]

[a] Department of Mathematics, The Ohio State University, Columbus, OH 43210, USA
[b] Department of Mathematics, The University of Southern Mississippi, Hattiesburg, MS 39406, USA
[c] Department of Mathematics, Iowa State University, Ames, IA 50011, USA
[d] Department of Mathematics, University of Dundee, Dundee DD1 4HN, UK

ARTICLE INFO

Article history:
Received 8 January 2009
Received in revised form
8 April 2009
Accepted 5 May 2009
Available online 14 May 2009

Keywords:
Cancer vaccination
Immunotherapy
Cancer dormancy
Cancer recurrence
Cytotoxic T-lymphocytes

ABSTRACT

In this paper we develop a new mathematical model of immunotherapy and cancer vaccination, focusing on the role of antigen presentation and co-stimulatory signaling pathways in cancer immunology. We investigate the effect of different cancer vaccination protocols on the well-documented phenomena of cancer dormancy and recurrence, and we provide a possible explanation of why adoptive (i.e. passive) immunotherapy protocols can sometimes actually promote tumour growth instead of inhibiting it (a phenomenon called immunostimulation), as opposed to active vaccination protocols based on tumour-antigen pulsed dendritic cells. Significantly, the results of our computational simulations suggest that elevated numbers of professional antigen presenting cells correlate well with prolonged time periods of cancer dormancy.

1. Introduction

Cancer still remains one of the most difficult diseases to treat clinically and is one of the main causes of mortality in developed western societies. For example, the mortality statistics for the United Kingdom for the year 2005 show that 153,491 people were registered as dying from a malignant neoplasm.[1] This figure represents 26% of all causes of death in the UK for 2005, and similar statistics hold for the United States (Ries et al., 2007).

Great effort and resources are devoted to cancer research and our understanding of cancer biology is constantly expanding. However, the overall efficiency of our current therapeutic approaches remains rather poor. Current patient therapies for the treatment of cancer include surgery (i.e. removal of the tumour), chemotherapy (administration of anti-cancer drugs) and radiotherapy (treatment with X-rays). Of course surgery is appropriate only for solid tumours. Although there have been great advances in patient care and treatment over the past few decades with refinement of anti-cancer drugs and medical equipment, unfortunately chemotherapy and radiotherapy both still carry major side-effects for individual patients. This is mainly due to the severe effects that these treatments have on normal, healthy proliferating cells in the patients. As a result, the treatment of cancers itself causes significant morbidity and mortality.

Given these facts any design of new therapeutic approaches is of great interest and one such new approach is to treat cancer using key components of the immune system, the body's natural defence mechanism (Abbas et al., 2007). In recent years there has been much biological, immunological and experimental interest in trying to develop what may be termed "immunotherapies" for cancers. One major advantage that some form of effective immunotherapy treatment would have over conventional anti-cancer treatment would be the fact that cells and other components of the immune system would be far more specific and localized in their actions, targeting cancer cells alone and leaving the vast majority of other healthy cells of the body untouched (Parmiani and Lotze, 2002).

As part of a deeper understanding of cancer therapy the role of quantitative and predictive mathematical modelling is becoming increasingly appreciated by experimentalists and clinicians, and in recent years several papers have begun to investigate the various aspects of the immune system response to cancer from a mathematical perspective. The development of mathematical models which reflect several spatial and temporal aspects of tumour immunology can be regarded as the first step towards an effective computational approach in investigating the conditions

* Corresponding author.
E-mail address: tasos@iastate.edu (A. Matzavinos).
[1] Source: Cancer Research, UK.

0022-5193/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2009.05.001

under which tumour recurrence takes place and in optimizing existing immunotherapy protocols. Key papers in this area include (Bellomo and Delitala, 2008; Bellomo et al., 1999, 2003, 2004; Delitala, 2002; Ambrosi et al., 2002; Arlotti et al., 2002; De Angelis et al., 2003; Bellomo and Preziosi, 2000), which focus on the modelling of tumour progression and immune competition by generalized kinetic (Boltzmann) models and (Owen and Sherratt, 1997, 1998, 1999; Sherratt et al., 1999), which focus on the development of tumour heterogeneities as a result of tumour cell and macrophage interactions. Moreover, Webb et al. (2002) is concerned with receptor–ligand (Fas–FasL) dynamics, Kelly et al. (2002) investigate the process of macrophage infiltration into avascular tumours, Matzavinos et al. (2004), Matzavinos and Chaplain (2004) and Chaplain and Matzavinos (2006) focus on the dynamics of cytotoxic T cell–tumour cell interactions, Arciero et al. (2004) study mechanisms of tumour–immune evasion and the effectiveness of siRNA treatments, de Pillis et al. (2006) develop mathematical models of mixed immunotherapy–chemotherapy therapeutic approaches and Kronik et al. (2008) focus on modelling specific cytotoxic T-lymphocyte (CTLs) immunotherapy protocols for malignant gliomas. Bodnar and Foryś (2007) perform a comparative analysis of delay differential equation models of tumour growth, and Foryś (2002) and Szymańska (2003) analyse various immune system and immunotherapy models in the context of cancer dynamics.

In this paper we develop a new mathematical model of immunotherapy, focusing on the role of antigen presentation and costimulatory signaling pathways in cancer immunology. We investigate the effect of different cancer vaccination protocols on the well-documented phenomena of cancer dormancy and recurrence, and we provide a possible explanation of why adoptive immunotherapy protocols can sometimes promote tumour growth instead of inhibiting it[2] (Zhang et al., 2007), as opposed to active vaccination protocols based on tumour-antigen pulsed dendritic cells (Banchereau and Palucka, 2005).

2. The mathematical model

2.1. Model formulation

Let us consider a simplified process of a small, growing, avascular tumour which elicits a response from the host immune system and attracts a population of lymphocytes and antigen presenting cells (APCs). The growing tumour is directly attacked by cytotoxic T-lymphocytes, which in the presence of tumour antigens undergo enhanced proliferation. Antigen presenting cells, such as dendritic cells or macrophages, internalize tumour cells through either phagocytosis or endocytosis, and display selected tumour antigenic peptides to the effector cells, i.e. the CTLs. In the following we only consider class I MHC pathway of antigen presentation (Abbas et al., 2007), where the antigenic peptides are presented to and activate CTLs directly (as opposed to class II MHC pathway that converges to the activation of helper T-cells that, in turn, activate the effector components of the host immune system).

The role of antigen presenting cells in the model is threefold: (a) they internalize tumour cells and present tumour antigens to the effector cells, (b) they kill the internalized tumour cells through the action of proteolytic enzymes and (c) they are subjected to programmed cell death as a result of their presenting of antigenic peptides to CTLs. The main effector functions of this system are performed by CTLs, which detect antigenic peptides either directly on tumour cells or through the presentation mechanism implemented by antigen presenting cells. Upon antigen recognition, CTLs bind to the target cell (which can be either a tumour cell or an antigen presenting cell with an internalized tumour cell). This binding event leads to the clustering of a large number of CTL receptors, triggering a cascade of events that converge to the delivery of an apoptotic signal and the killing of the target cell.

The kinetic interactions between the various cell types of the model are described by the kinetic scheme given in Fig. 1. The model consists of 10 time-dependent variables representing the total numbers of effector cells E, tumour cells T, naive antigen presenting cells A, tumour cell-loaded APCs L, CTL–tumour cell complexes C_T, CTL–APC complexes C_A, CTL–CTL complexes C_E, inactivated CTLs $\widetilde{E}$, lethally hit (or programmed-for-lysis) tumour cells $\widetilde{T}$ and programmed-for-lysis loaded APCs $\widetilde{L}$.

The parameters $k_T^{\pm}$, k_{C_T}, k_A, k_L, $k_L^{\pm}$, k_{C_A}, $k_E^{\pm}$ and k_{C_E} are non-negative kinetic constants. Parameters k_T^{+} and k_T^{-} describe the rate of binding of CTLs to tumour cells and detachment of CTLs from tumour cells *without* damaging cells; k_{C_T} is the rate of detachment of CTLs from tumour cells, resulting in an irreversible programming of the tumour cells for lysis (i.e. death) with probability p or inactivating/killing CTLs with probability $(1-p)$. Similarly, $k_L^{\pm}$ and $k_E^{\pm}$ are the corresponding kinetic constants for binding and detachment of CTLs to tumour cell-loaded antigen presenting cells and other CTLs without damaging cells. Parameters k_{C_A} and k_{C_E} are the rate constants for the CTL-mediated killing of (a) loaded antigen presenting cells and (b) CTLs, respectively, whereas k_A and k_L characterize the rate of tumour cell internalization by antigen presenting cells and the destruction/lysis of internalized tumour cells.

The kinetic step that corresponds to the constant $k_{C_T}(1-p)$ models a direct "counterattack" of the tumour cells against effector immune cells. O'Connell et al. (1999) have shown that such a mechanism might be realized through the Fas receptor (Fas, Apo-1/CD95) and its ligand (FasL, CD95L). Engagement of Fas on a target cell by FasL triggers a cascade of cellular events that results in programmed-cell-death. Both these transmembrane proteins (belonging to the tumour necrosis factor, TNF, family of receptors and ligands) are expressed on the surface of immune cells, including T-lymphocytes and NK-cells. However, many

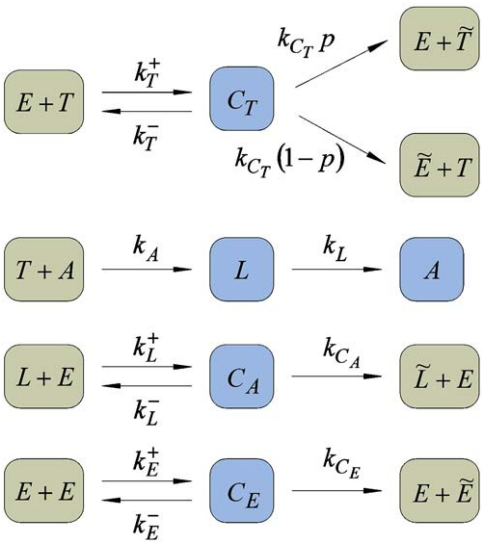

Fig. 1. Schematic diagram of the interactions between effector cells (CTLs), tumour cells and antigen presenting cells.

[2] A phenomenon that is usually referred to as immunostimulation.

non-lymphoid tumour cells also express FasL which can counter-attack and kill the Fas-sensitive CTLs. On the other hand, most cancer cells, unlike normal cells, are relatively resistent to Fas-mediated apoptosis by the immune cells. Resistance to programmed-cell-death (apoptosis) through the Fas receptor pathway coupled with expression of the Fas ligand might enable many cancer cells to deliver a "counterattack" against attached cytotoxic lymphocytes.

In the formulation of the model, and in addition to the kinetic mechanisms described in Fig. 1, we consider other kinetic interaction terms accounting for the host immune system homeostasis, the enhanced proliferation of lymphocytes in the presence of antigen, etc.

2.1.1. Cytotoxic T-lymphocytes

We assume that there is a source term modelling the underlying lymphocyte production by the host immune system, a linear decay (death) term and an additional CTL proliferation term in response to the presence of the tumour cells. Combining these assumptions with the kinetics derived from Fig. 1 we have the following ordinary differential equation[3] for CTLs:

$$\begin{aligned}\frac{dE}{dt} = {} & \overbrace{s_1}^{\text{supply}} - \overbrace{d_1 E}^{\text{linear decay}} + \overbrace{\frac{f(C_T + C_A)}{g + T}}^{\text{proliferation}} \\ & - \overbrace{k_T^+ ET + (k_T^- + k_{C_T} p) C_T - k_L^+ LE}^{\text{mass action kinetics, according to Fig. 1}} \\ & + \overbrace{k_L^- C_A + k_{C_A} C_A + 2k_E^- C_E}^{\text{mass action kinetics}} \\ & - \overbrace{2k_E^+ E^2 + k_{C_E} C_E}^{\text{Fas/FasL interactions}},\end{aligned} \tag{1}$$

where s_1, d_1, f, g, $k_E^{\pm}$, $k_T^{\pm}$, $k_L^{\pm}$, k_{C_E}, k_{C_T} and k_{C_A} are all positive constants. Parameter s_1 represents the "normal" rate of flow of mature lymphocytes into the tissue (non-enhanced by the presence of tumour cells).

The proliferation term $f(C_T + C_A)/(g + T)$ represents the experimentally observed enhanced proliferation of CTLs in response to the tumour. Similar functional forms for this term have been derived through data fitting and used by Kuznetsov et al. (1994), Chaplain et al. (1998) and Matzavinos et al. (2004). This functional form is also consistent with a model in which one assumes that the enhanced proliferation of CTLs is due to signals, such as released interleukins, generated by effector cells in target cell–CTL complexes (where a target cell is either a tumour cell or a antigen presenting cell with an internalized tumour cell). We note that the growth factors that are secreted by lymphocytes in complexes (e.g. IL-2) act mainly in an autocrine fashion. That is to say they act on the cell from which they have been secreted. We assume that the growth factors are produced when lymphocytes are activated by target cell–CTL interactions. Thus we define effector cell proliferation to be proportional to target cell–CTL complex density $C_T + C_A$. The kinetic interaction terms related to the rate constants k_E^+, k_E^- and k_{C_E} correspond to Fas/FasL interactions between effector cells (Marsden and Strasser, 2003).

2.1.2. Tumour cells

The growth dynamics of pre-angiogenic tumours, in the absence of an immune system response, may be described adequately by the logistic equation:

$$\frac{dT}{dt} = b_1 T(1 - b_2 T), \tag{2}$$

which takes into account a density limitation of growth (Prigogine and Lefever, 1980; Durand and Sutherland, 1984). The maximal growth rate of the tumour cell population is b_1, which incorporates both cell multiplication (mitosis) and death, and the maximum density of the tumour cells is represented by the parameter b_2^{-1}.

An alternative approach is to modify the logistic growth kinetics by incorporating terms modelling competition for space between various cell types (Gatenby, 1995, 1996). However, in the framework of our model, we will assume that the CTLs do not compete with the tumour cells for space. This is a reasonable assumption since according to observations (Kyle et al., 1999) the volume of extracellular space in tumours is typically in the range 25–65% of the total volume of cells and hence there is enough space for the migration of lymphocytes within a tumour. Also, tumour cells lack the contact inhibition properties of normal cells and destroy the extracellular matrix. This allows the lymphocytes to migrate into the tumour tissue faster than in normal tissue, which has regular extracellular matrix. Therefore, we do not explicitly include a term for space competition between the tumour cells and the lymphocytes and thus a logistic growth term is, we believe, a good first modelling approximation to the tumour growth kinetics.

In the presence of CTLs and antigen presenting cells, the ODE governing the tumour growth dynamics in conjunction with the interactions dictated by the kinetic scheme in Fig. 1 is

$$\begin{aligned}\frac{dT}{dt} = {} & - \overbrace{k_T^+ ET + (k_T^- + k_{C_T}(1 - p)) C_T}^{\text{mass action kinetics, according to Fig. 1}} \\ & - \overbrace{k_A TA}^{\text{mass action kinetics}} + \overbrace{b_1 T(1 - b_2 T)}^{\text{logistic growth}},\end{aligned} \tag{3}$$

where b_1, b_2, p, $k_T^{\pm}$, k_{C_T} and k_A are positive parameters.

2.1.3. Antigen presenting cells

The antigen presenting cell population is represented by two variables, distinguishing between those antigen presenting cells that are associated with an internalized tumour cell and those that are not. The former population is denoted by L (loaded cell population), whereas the latter is denoted by A.

As in the case of CTLs, the model incorporates a source term modelling the underlying cell production by the host immune system and a linear decay (death) term. Combining these processes with the kinetic scheme in Fig. 1, we get the following equation for the non-tumour-bearing population:

$$\frac{dA}{dt} = \overbrace{s_2}^{\text{supply}} - \overbrace{d_2 A}^{\text{linear decay}} - \overbrace{k_A TA + k_L L}^{\text{mass action kinetics}}, \tag{4}$$

where the parameters s_2 and d_2 correspond to the flow of antigen presenting cells into the tissue and the decay constant due to cell death, respectively.

The dynamics of the loaded cell population are governed by the kinetic scheme in Fig. 1, and the corresponding equation for L is

$$\frac{dL}{dt} = k_A TA - k_L L - k_L^+ LE + k_L^- C_A. \tag{5}$$

2.1.4. Cell complexes

The dynamics of cell-complexes are governed by the kinetics derived from Fig. 1. Therefore, the equations for the complexes are

[3] In what follows, we neglect spatial heterogeneity and focus on ordinary differential equations modelling the evolution of cell populations. For an alternative approach based on partial differential equations see Matzavinos et al. (2004).

Table 1
Estimated kinetic rate constants.

Symbol	Value	Symbol	Value	Symbol	Value
g	2.02×10^7 cells	b_2	2.0×10^{-9} cells^{-1}	k_T^-	24 day^{-1}
k_T^+	1.3×10^{-7} day^{-1} cells^{-1}	k_{C_T}	7.2 day^{-1}	p	0.9997
d_1	0.0412 day^{-1}	f	0.2988×10^8 day^{-1} cells	b_1	0.18 day^{-1}
s_1	1.36×10^4 day^{-1} cells	k_A	0.5×10^{-6} day^{-1} cells^{-1}	k_L	10.0 day^{-1}
k_L^+	1.3×10^{-7} day^{-1} cells^{-1}	k_L^-	24 day^{-1}	k_{C_A}	7.2 day^{-1}
k_E^+	1.3×10^{-7} day^{-1} cells^{-1}	k_E^-	24 day^{-1}	k_{C_E}	7.2 day^{-1}
s_2	1.36×10^4 day^{-1} cells	d_2	0.0412 day^{-1}		

given by

$$\frac{dC_T}{dt} = k_T^+ ET - (k_T^- + k_{C_T})C_T, \tag{6}$$

$$\frac{dC_A}{dt} = k_L^+ LE - (k_L^- + k_{C_A})C_A, \tag{7}$$

$$\frac{dC_E}{dt} = k_E^+ E^2 - (k_E^- + k_{C_E})C_E. \tag{8}$$

2.1.5. Cells programmed for lysis

The time-dependent variables corresponding to the tumour cells and APCs that have been programmed for lysis are "slave variables" of the system and do not provide any feedback to the equations for the other cell types. Hence, in the following we focus on the system of Eqs. (1)–(8).

2.2. Estimation of parameters

In order to carry out an analysis of the model by numerical methods it is useful to estimate values for the parameters obtained from experimental data and work with a non-dimensionalized system of equations.

The murine B cell lymphoma (BCL_1) is used as an experimental model of tumour dormancy in mouse (Siu et al., 1986; Uhr and Marches, 2001). It has been demonstrated that $CD8^+$ T-cells (CTLs) are required for inducing and maintaining dormancy in BCL_1. In these experiments $CD8^+$ T cells are enhanced with anti-Id antibodies into inducing dormancy by secreting INF-γ. A description of the growth kinetics of a BCL_1 lymphoma in the spleen of recipient mice, chimeric with respect to the major histocompatibility complex (Siu et al., 1986), was provided by the model of Matzavinos et al. (2004).

The kinetic constants that correspond to the interactions of CTLs with tumour cells in the model developed in this paper have been obtained from Matzavinos et al. (2004). The remaining of the kinetic constants have been chosen on the basis of generic order of magnitude estimates. The latter were obtained by comparison of the associated time scales with those corresponding to the fitted kinetic constants of Matzavinos et al. (2004). Table 1 presents the values of the kinetic constants used in the numerical simulations of the following section.

The system of Eqs. (1)–(8) is closed by applying appropriate initial conditions. The initial cell counts of effector and tumour cells are those used by Matzavinos et al. (2004) and are given by

$$E_0 = \frac{s_1}{d_1} \quad \text{and} \quad T_0 = \frac{1}{b_2}. \tag{9}$$

Under physiological conditions, in the absence of a tumour and assuming that the Fas/FasL apoptotic pathway is inactive, the steady-state value of E is s_1/d_1 and therefore this is the value we have taken for the initial cell count E_0. Similarly, in the absence of an immune response, the steady-state tumour cell count is $1/b_2$ and this is what we take as the initial tumour cell count T_0. It is assumed that there are no cell complexes or tumour cell-loaded APCs initially. Finally, the initial CTL to APC ratio is assumed to be 1 : 10.[4]

The closed system has been non-dimensionalized by choosing order-of-magnitude scales according to the initial conditions, and the numerical results in the next section are given in terms of the non-dimensionalized system.

3. Results

The non-dimensionalized system was solved numerically under different experimental settings using the stiff solver of the XPP numerical package (Ermentrout, 2002). A stiff solver is needed for solving numerically the ODE model developed in this paper due to the wide range of parameter values in Table 1.

The main focus of the numerical experiments was: (a) to investigate the relative importance of CTLs and antigen presenting cells on tumour dormancy and tumour recurrence, and (b) to quantify the effectiveness of different cancer vaccination protocols. The vaccination protocols considered were based on the administration of antigen presenting cell vaccines (Banchereau and Palucka, 2005), and the effectiveness of the latter was compared to that of an adoptive (i.e. passive) immunotherapy approach based on the administration of CTLs (Gattinoni et al., 2006). An excellent review of the current cancer immunotherapy approaches is given by Gilboa (2004).

Figs. 2(a) and (b) show the results of a computational experiment that quantifies how different numbers of CTLs and antigen presenting cells affect the time period between tumour regression and recurrence. All parameter values for these simulations were set according to Section 2.2. The initial conditions for variables A in Fig. 2(a) and E in Fig. 2(b) were varied in a biologically relevant range around the values adopted in Section 2.2.

For all parameter values investigated, in both Figs. 2(a) and (b), the tumour cell population initially decreases in number before subsequently settling to some stationary value for a finite period of time. For visualization purposes, the transient decrease in the number of tumour cells is not shown. The reduced tumour bulk attained in the simulations after tumour regression persists until the tumour recurs at a time that depends on the initial CTL and antigen presenting cell counts. As shown in Fig. 2(a), the initial antigen presenting cell count correlates well with the tumour

[4] Estimates of the CTL to APC ratio in the literature vary from 10 : 1 to 1 : 30 (in tumour infiltrates).

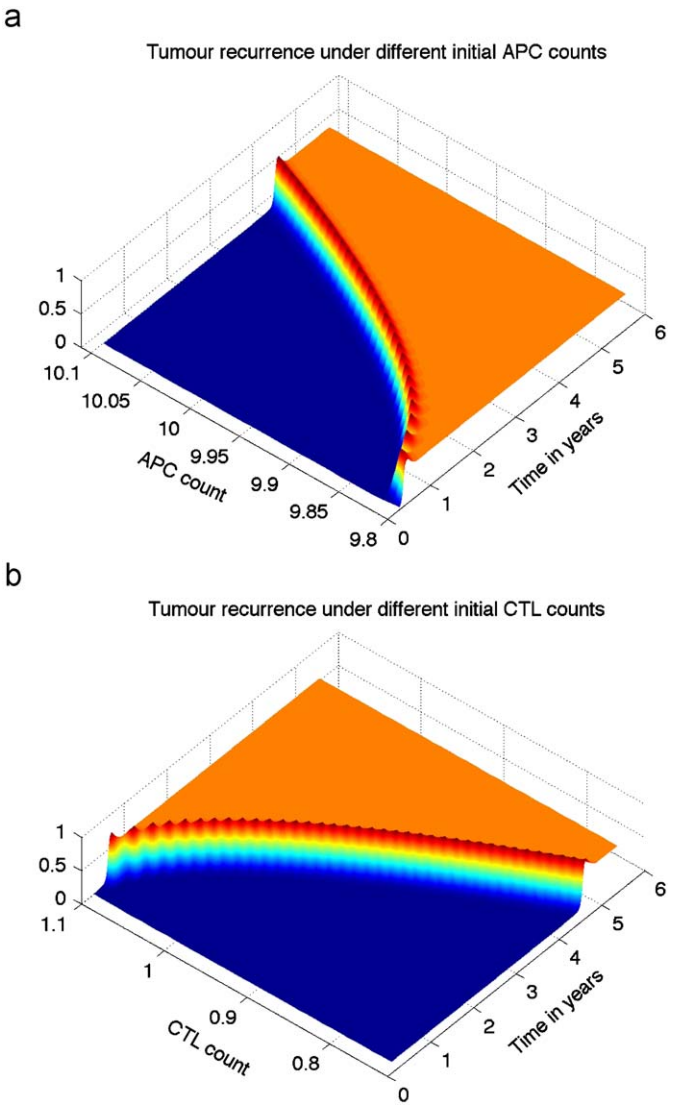

Fig. 2. Evolution in time of (non-dimensionalized) tumour cell counts under different initial numbers of: (a) antigen presenting cells and (b) cytotoxic T-lymphocytes.

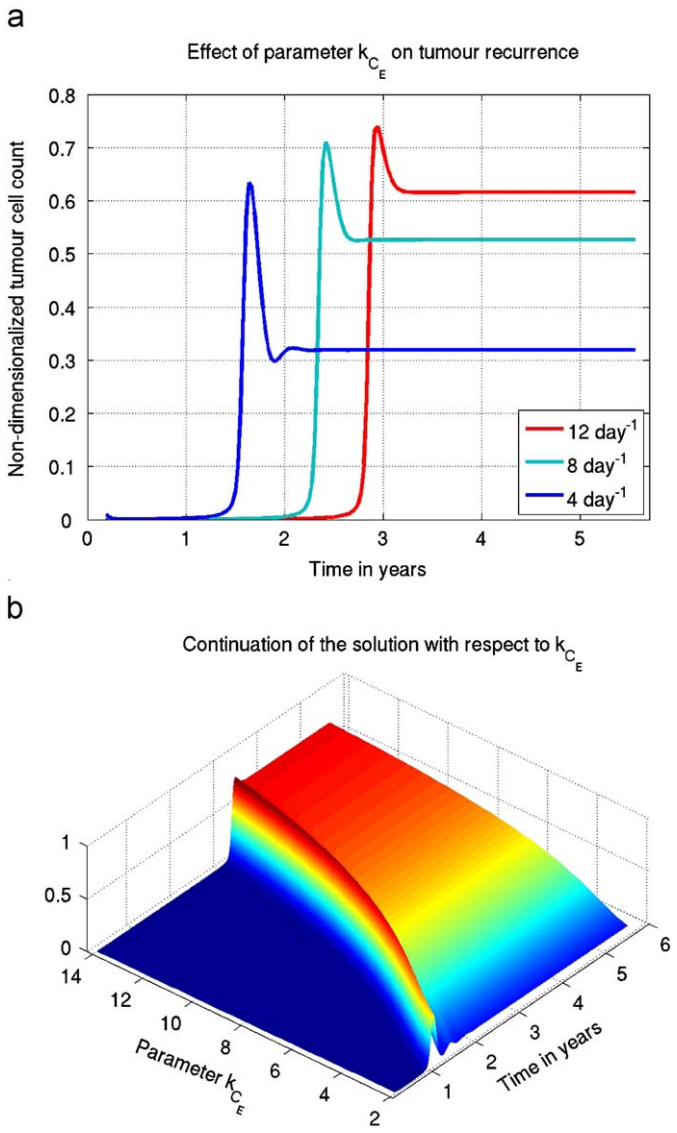

Fig. 3. (a) Effect of parameter k_{C_E} on the dormancy period and the recurrence of the disease. (b) Continuation of the non-dimensionalized solution for variable T with respect to k_{C_E}.

dormancy period, and the model suggests that elevated numbers of antigen presenting cells result in significantly delaying tumour recurrence. These results also suggest a potential role for antigen presenting cells as biological markers, indicating high-risk time periods for tumour recurrence.

Fig. 2(b) shows an interesting, counter-intuitive phenomenon. According to the model under investigation, elevated *initial* numbers of CTLs (as compared to the base value in Section 2.2) result in a reduced period of cancer dormancy and an early recurrence of the disease. Moreover, relatively reduced *initial* numbers of CTLs result in a prolonged dormancy period. This phenomenon should be attributed to the cytotoxicity of activated lymphocytes to each other (Fas/FasL interactions). Indeed, initial conditions that are characterized by elevated numbers of CTLs result not only to tumour cell killing, but also to CTL killing, enabling tumour cells to escape cancer dormancy on a faster time scale.

These results offer a possible explanation for a number of reported failures of CTL vaccine-based therapeutic approaches to certain carcinomas (see, for example, Zhang et al., 2007). The rationale of such approaches is based on the well-documented correlation between melanoma patient survival and tumour infiltrating lymphocyte (TIL) counts (Weinberg, 2007). However, TIL populations are highly heterogeneous, including among others CTLs (CD8 + cells), natural killer-like (NK-like) cells and/or lymphokine activated killer (LAK) cells, with different TIL subpopulationsshowing different degrees of sensitivity to Fas/FasL mediated apoptosis. Hence, the reported correlation between melanoma patient survival and TIL counts does not contradict the results in this section, since the latter are related to CTLs that are responsive to the Fas/FasL signalling pathway (see, however, the discussion of the results of Dudley et al. (2008) in Section 4). Moreover, the dynamics of the model under investigation are consistent with well-documented tumour recurrence phenomena, following the application of CTL-based vaccination protocols (Zhang et al., 2007).

In addition to observing the effect of different cell counts on the dormancy period, we also investigated how the latter is affected by the time scale on which lymphocytes detect and bind to tumour cells, as well as by the cytotoxicity of CTLs to each other. Fig. 3(a) shows the evolution in time of the tumour cell

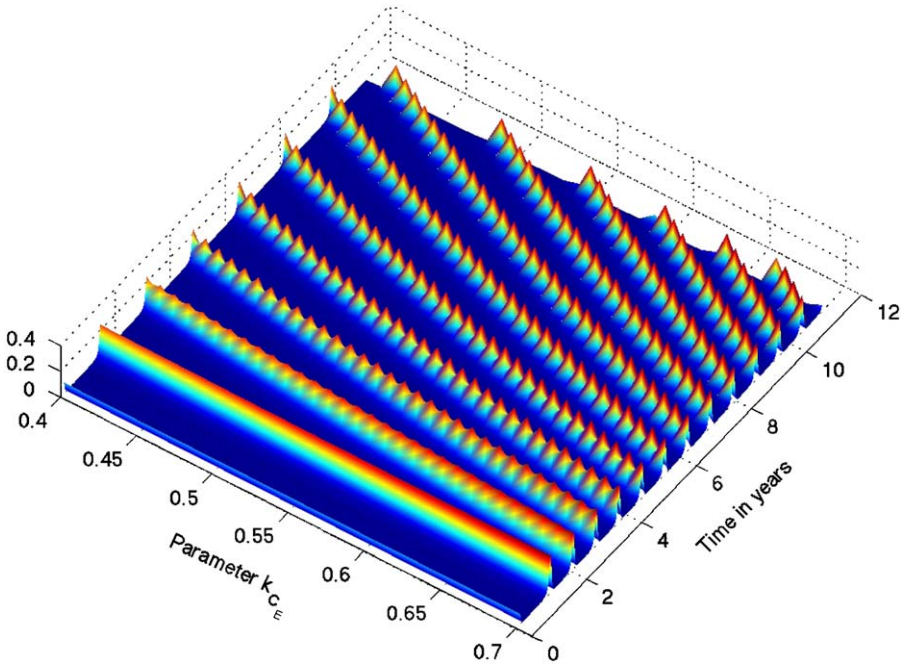

Fig. 4. Emergence of periodic recurrences for small values of parameter k_{C_E}.

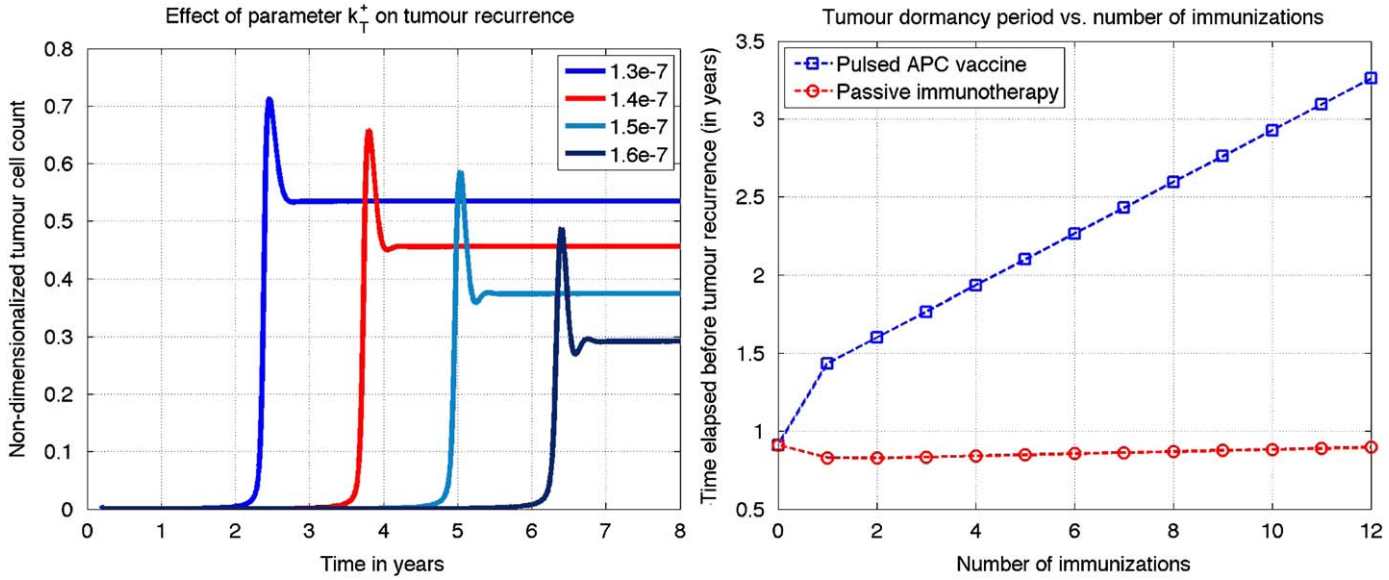

Fig. 5. (a) Effect of parameter k_T^+ on the dormancy period and the recurrence of the disease. (b) Plot of the tumour dormancy time period versus the number of immunizations for two different cancer vaccination protocols.

population for three different values of the kinetic parameter k_{C_E} that measures the rate by which CTLs inactivate/kill each other through Fas/FasL interactions. Interestingly enough, reducing the parameter k_{C_E} leads to early tumour recurrence associated with a reduced tumour bulk. In contrast, increasing k_{C_E} results in prolonging the dormancy period and delaying the recurrence of the disease. However, the model predicts that increasing k_{C_E} also results in an enlarged tumour bulk after recurrence. Fig. 3(b) shows a continuation of the (non-dimensionalized) solution for variable T with respect to parameter k_{C_E}.

Interestingly enough, reducing parameter k_{C_E} below the value of 1 day^{-1} does not result in complete eradication of the tumour mass, as one would expect by extrapolation of the data in Fig. 3(b). Instead, in this parameter regime, the evolution of the disease is characterized by periodic recurrences—a phenomenon that frequently appears in the context of general immune–pathogen interactions (Wodarz, 2007) and has also been documented in the specific case of tumour–immune interactions (Kirschner and Panetta, 1998; Kuznetsov et al., 1994; Matzavinos and Chaplain, 2004). Fig. 4 shows the dependence of the emerging oscillatory solutions on parameter k_{C_E}. The model predicts that, although the first recurrence of the disease is independent of the value of k_{C_E}, subsequent recurrences will strongly depend on the sensitivity of the effector cells to Fas/FasL mediated apoptosis. Numerical continuation of the system with the XPP implementation of the AUTO continuation software (Ermentrout, 2002) confirmed that these oscillatory dynamics emerge through a Hopf bifurcation with respect to parameter k_{C_E}.

Fig. 5(a) shows the evolution in time of the tumour cell population for four different values of the kinetic parameter k_T^+, which determines the time scale of CTL-binding to tumour cells. As can be seen, elevated values for k_T^+ result in *both* a prolonged dormancy period and a reduced tumour bulk after recurrence of the disease. This result indicates the importance of identifying immuno-dominant tumour peptides in the development of cancer vaccines (Raitakari et al., 2003) and suggests a cellular process, the facilitation of which would enhance the effectiveness of the vaccine.

In addition to vaccine effectiveness, we investigated computationally the effectiveness of different vaccine administration protocols. Fig. 5(b) shows how the time period elapsed before recurrence of the disease depends on the number of monthly immunizations under two different vaccination strategies. As can be seen active vaccination with tumour-antigen pulsed APCs is associated with a positive correlation between the number of immunizations and the tumour dormancy period, and it is generally more effective than adoptive immunotherapy protocols. In contrast, the adoptive (passive) immunotherapy protocol simulated (based on CTL vaccines) fails to mount an effective immune response even in the case of a significant number of repeated immunizations. We note however, that current protocols of adoptive immunotherapy combine the administration of autologous tumour-infiltrating lymphocytes with chemotherapy and/or total-body irradiation (Dudley et al., 2008), the effects of which are not investigated here.

4. Discussion

In this paper we have developed a mathematical model to describe the growth dynamics of an immunogenic tumour in the presence of an active immune response. In particular, we focused attention upon the interaction of tumour cells with $CD8^+$ cytotoxic T-lymphocytes and professional antigen presenting cells in a relatively small, multicellular tumour, without central necrosis and at some stage prior to tumour-induced angiogenesis (Weinberg, 2007). Following the approach of Matzavinos et al. (2004) and Matzavinos and Chaplain (2004), the cytotoxic T-lymphocytes were assumed to interact with the tumour cells in such a way that lymphocyte–tumour cell complexes were formed. These complexes resulted in either the death of the tumour cells (the normal situation) or the inactivation (sometimes even the death) of the lymphocytes.

The model developed in this paper extends the work of Chaplain and Matzavinos (2006) by investigating the role of antigen presentation and costimulatory signaling pathways on the well-documented phenomena of cancer dormancy and recurrence. In particular, in the formulation of the model we considered a generic type of professional antigen presenting cell that was assumed to internalize tumour cells through either phagocytosis or endocytosis and display selected tumour antigenic peptides to the effector cells, i.e., the cytotoxic T-lymphocytes (Abbas et al., 2007).

The dynamics of the model were investigated by means of numerical simulations, and a number of interesting, counter-intuitive phenomena were discovered. It was demonstrated that, under the assumptions of the model, adoptive immunotherapy protocols have the potential to promote tumour growth instead of inhibiting it. These results are consistent with well-documented tumour recurrence phenomena following the application of CTL-based vaccination protocols (Zhang et al., 2007). In contrast, active vaccination with tumour-antigen pulsed APCs (Banchereau and Palucka, 2005) was shown to be generally more effective than adoptive immunotherapy protocols in inhibiting tumour growth and recurrence in the model under investigation. We note however, that current protocols of adoptive immunotherapy combine the administration of autologous tumour-infiltrating lymphocytes with chemotherapy and/or total-body irradiation (Dudley et al., 2008), the effects of which were not investigated in this paper. In a paper in preparation, we extend the model developed here to analyse the effects of host lymphodepletion (as a result of total-body irradiation) to the dynamics of adoptive immunotherapy protocols. Future work will also investigate how regulatory $CD25^+CD4^+$ T cells affect the dynamics reported in this paper (Mihalyo et al., 2007; Leon et al., 2007).

The predictions of our model offer a possible explanation for the uncontrolled behaviour of a number of lymphocyte vaccine-based therapeutic approaches to certain carcinomas, and our modelling and analysis offers the potential for quantitative analysis of mechanisms of tumour-cell–host-cell interactions and for the optimization of immunotherapy and genetically engineered anti-tumour vaccines.

Acknowledgements

The authors would like to thank Avner Friedman for advice and encouragement. This material is based upon work supported by the National Science Foundation under agreement no. 0635561. M.A.J.C. was supported by a Leverhulme Trust Personal Research Fellowship. Part of this work has appeared in the Mathematical Biosciences Institute Technical Report Series (Report No. 75).

References

Abbas, A., Lichtman, A., Pillai, S., 2007. Cellular and Molecular Immunology, sixth ed. Saunders, Elsevier, New York, Amsterdam.
Ambrosi, D., Bellomo, N., Preziosi, L., 2002. Modelling tumor progression, heterogeneity, and immune competition. J. Theor. Med. 4, 51–65.
Arciero, J., Jackson, T., Kirschner, D., 2004. A mathematical model of tumor-immune evasion and siRNA treatment. Discrete Continuous Dynamical Syst. Ser. B 4, 39–58.
Arlotti, L., Gamba, A., Lachowicz, M., 2002. A kinetic model of tumor/immune system cellular interactions. J. Theor. Med. 4, 39–50.
Banchereau, J., Palucka, A., 2005. Dendritic cells as therapeutic vaccines against cancer. Nat. Rev. Immunol. 5, 296–306.
Bellomo, N., Bellouquid, A., De Angelis, E., 2003. The modelling of the immune competition by generalized kinetic (Boltzmann) models: review and research perspectives. Math. Comput. Modelling 37, 65–86.
Bellomo, N., Bellouquid, A., Delitala, M., 2004. Mathematical topics on the modelling complex multicellular systems and tumor immune cells competition. Math. Models Methods Appl. Sci. 14, 1683–1733.
Bellomo, N., Delitala, M., 2008. From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells. Phys. Life Rev. 5, 183–206.
Bellomo, N., Firmani, B., Guerri, L., 1999. Bifurcation analysis for a nonlinear system of integro-differential equations modelling tumor-immune cells competition. Appl. Math. Lett. 12, 39–44.
Bellomo, N., Preziosi, L., 2000. Modelling and mathematical problems related to tumor evolution and its interaction with the immune system. Math. Comput. Modelling 32, 413–452.
Bodnar, M., Foryś, U., 2007. Three types of simple DDEs describing tumor growth. J. Biol. Syst. 15, 453–471.
Chaplain, M., Kuznetsov, V., James, Z., Stepanova, L., 1998. Spatio-temporal dynamics of the immune system response to cancer. In: Horn, M.A., Simonett, G., Webb, G. (Eds.), Mathematical Models in Medical and Health Sciences. Vanderbilt University Press, pp. 1–20.
Chaplain, M., Matzavinos, A., 2006. Mathematical modelling of spatio-temporal phenomena in tumour immunology. In: Friedman, A. (Ed.), Tutorials in Mathematical Biosciences III: Cell Cycle, Proliferation, and Cancer. Lecture Notes in Mathematics, vol. 1872. Springer, Berlin, pp. 131–183.
De Angelis, E., Delitala, M., Marasco, A., Romano, A., 2003. Bifurcation analysis for a mean field modelling of tumor and immune system competition. Math. Comput. Modelling 37, 1131–1142.
de Pillis, L., Gu, W., Radunskaya, A., 2006. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. J. Theor. Biol. 238, 841–862.
Delitala, M., 2002. Critical analysis and perspectives on kinetic (cellular) theory of immune competition. Math. Comput. Modelling 35, 63–75.

Dudley, M., Yang, J., Sherry, R., Hughes, M., Royal, R., Kammula, U., Robbins, P., Huang, J., Citrin, D., Leitman, S., Wunderlich, J., Restifo, N., Thomasian, A., Downey, S., Smith, F., Klapper, J., Morton, K., Laurencot, C., White, D., Rosenberg, S., 2008. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. J. Clin. Oncol. 26, 5233–5239.

Durand, R., Sutherland, R., 1984. Growth and cellular characteristics of multicell spheroids. Recent Results Cancer Res. 95, 24–49.

Ermentrout, G., 2002. Simulating, analyzing, and animating dynamical systems: a guide to XPPAUT for researchers and students. In: Software Environ. Tools, vol. 14. SIAM.

Foryś, U., 2002. Marchuk's model of immune system dynamics with application to tumour growth. J. Theor. Med. 4, 85–93.

Gatenby, R., 1995. Models of tumor–host interaction as competing populations: implications for tumor biology and treatment. J. Theor. Biol. 176, 447–455.

Gatenby, R., 1996. Application of competition theory to tumour growth: implications for tumour biology and treatment. Eur. J. Cancer 32A, 722–726.

Gattinoni, L., Powell Jr., D., Rosenberg, S., Restifo, N., 2006. Adoptive immunotherapy for cancer: building on success. Nat. Rev. Immunol. 6, 383–393.

Gilboa, E., 2004. The promise of cancer vaccines. Nat. Rev. Immunol. 4, 401–411.

Kelly, C., Leek, R., Byrne, H., Cox, S., Harris, A., Lewis, C., 2002. Modelling macrophage infiltration into avascular tumours. J. Theor. Med. 4, 21–38.

Kirschner, D., Panetta, J., 1998. Modeling immunotherapy of the tumor immune interaction. J. Math. Biol. 37, 235–252.

Kronik, N., Kogan, Y., Vainstein, V., Agur, Z., 2008. Improving alloreactive CTL immunotherapy for malignant gliomas using a simulation model of their interactive dynamics. Cancer Immunol. Immunother. 57, 425–439.

Kuznetsov, V., Makalkin, I., Taylor, M., Perelson, A., 1994. Nonlinear dynamics of immunogenic tumours: parameter estimation and global bifurcation analysis. Bull. Math. Biol. 56, 295–321.

Kyle, A., Chan, C., Minchinton, A., 1999. Characterization of three-dimensional tissue cultures using electrical impedance spectroscopy. Biophys. J. 76 (5), 2640–2648.

Leon, K., Garcia, K., Carneiro, J., Lage, A., 2007. How regulatory $CD25^{+}CD4^{+}$ T cells impinge on tumor immunobiology: the differential response of tumors to therapies. J. Immunol. 179, 5659–5668.

Marsden, V., Strasser, A., 2003. Control of apoptosis in the immune system: Bcl-2, BH3-only proteins and more. Annu. Rev. Immunol. 21, 71–105.

Matzavinos, A., Chaplain, M., 2004. Travelling-wave analysis of a model of the immune response to cancer. C.R. Biol. 327, 995–1008.

Matzavinos, A., Chaplain, M., Kuznetsov, V., 2004. Mathematical modelling of the spatio-temporal response of cytotoxic T-lymphocytes to a solid tumour. IMA J. Math. Med. Biol. 21, 1–34.

Mihalyo, M., Hagymasi, A., Slaiby, A., Nevius, E., Adler, A., 2007. Dendritic cells program non-immunogenic prostate-specific T cell responses beginning at early stages of prostate tumorigenesis. Prostate 67, 536–546.

O'Connell, J., Bennett, M., O'Sullivan, G., Collins, J., Shanahan, F., 1999. The Fas counterattack: cancer as a site of immune privilege. Immunol. Today 20 (1), 46–50.

Owen, M., Sherratt, J., 1997. Pattern formation and spatio-temporal irregularity in a model for macrophage–tumour interactions. J. Theor. Biol. 189, 63–80.

Owen, M., Sherratt, J., 1998. Modelling the macrophage invasion of tumours: effects on growth and composition. IMA J. Math. Appl. Med. Biol. 15, 165–185.

Owen, M., Sherratt, J., 1999. Mathematical modelling of macrophage dynamics in tumours. Math. Models Methods Appl. Sci. 9, 513–539.

Parmiani, G., Lotze, M., (Eds.), 2002. Tumor immunology: molecularly defined antigens and clinical applications. In: Tumor Immunology and Immunotherapy Series, vol. 1. Taylor & Francis, London.

Prigogine, I., Lefever, R., 1980. Stability problems in cancer growth and nucleation. Comput. Biochem. Physiol. 67, 389–393.

Raitakari, M., Brown, R., Gibson, J., Joshua, D., 2003. T cells in myeloma. Hematol. Oncol. 21 (1), 33–42.

Ries, L., Melbert, D., Krapcho, M., Mariotto, A., Miller, B., Feuer, E., Clegg, L., Horner, M., Howlader, N., Eisner, M., Reichman, M., Edwards, B. (Eds.), 2007. SEER Cancer Statistics Review, 1975–2004. National Cancer Institute, Bethesda, MD ⟨http://seer.cancer.gov/csr/1975_2004/⟩.

Sherratt, J., Perumpanani, A., Owen, M., 1999. Pattern formation in cancer. In: Chaplain, M., Singh, G., McLachlan, J. (Eds.), On Growth and Form: Spatio-temporal Pattern Formation in Biology. Wiley.

Siu, H., Vitetta, E., May, R., Uhr, J., 1986. Tumour dormancy. regression of BCL tumour and induction of a dormant tumour state in mice chimeric at the major histocompatibility complex. J. Immunol. 137, 1376–1382.

Szymańska, Z., 2003. Analysis of immunotherapy models in the context of cancer dynamics. Appl. Math. Comput. Sci. 13, 407–418.

Uhr, J., Marches, R., 2001. Dormancy in a model of murine B cell lymphoma. Semin. Cancer Biol. 11, 277–283.

Webb, S., Sherratt, J., Fish, R., 2002. Cells behaving badly: a theoretical model for the Fas/FasL system in tumour immunology. Math. Biosci. 179, 113–129.

Weinberg, R., 2007. The Biology of Cancer, Garland Science. Taylor & Francis, London.

Wodarz, D., 2007. Killer cell dynamics: mathematical and computational approaches to immunology. In: Interdisciplinary Applied Mathematics, vol. 32. Springer, Berlin.

Zhang, X., Moche, J., Farber, D., Strome, S., 2007. Vaccine-based approaches to squamous cell carcinoma of the head and neck. Oral Dis. 13, 17–22.