Int. J. Appl. Math. Comput. Sci., 2003, Vol. 13, No. 3, 289–296

MATHEMATICAL MODELING OF THE COMPETITION BETWEEN ACQUIRED IMMUNITY AND CANCER

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In this paper we propose and analyse a model of the competition between cancer and the acquired immune system. The model is a system of integro-differential bilinear equations. The role of the humoral response is analyzed. The simulations are related to the immunotherapy of tumors with antibodies.

Keywords: Leukemia, acquired immunity, immunotherapy, antibodies, integro-differential equations

1. Introduction

The present paper is devoted to the modeling of the acquired immune response to cancer. The model is a generalization of the recent models developed by Kolev *et al.* (2002), and Kolev (2002a), which describe the cellular immune response, as well as the model set forth by Kolev (2003), which is devoted to the description of humoral immunity.

In (Kolev *et al.*, 2002) the authors proposed and analyzed a model of the competition between single cell cancer and cell-mediated immunity. The model is a bilinear system of integro-differential equations. This model was modified and generalized in (Kolev, 2002a) in order to consider the role of Th cells and antigen-presenting cells (APCs) in cellular immunity. The simulations in (Kolev, 2002a) analyzed the vaccinations with antigen-loaded dendritic cells (DCs).

The model (1) which we propose here constitutes a generalization of the model proposed in (Kolev, 2002a). We describe in it both essential forms of acquired immunity: the cellular as well as humoral immunity.

The present model describes the interactions between a single cell system of a tumor and the acquired immune system. It refers to the so-called *free cell regime*, namely to physical situations in which all cells move freely and homogeneously in space, and cancer cells (CCs) are not yet condensed in a macroscopically observable quasi-spherical tumor (Bellomo *et al.*, 1996). The model describes early stages of solid tumors and all stages of leukemias.

The present model is formulated in terms of a system of Boltzmann-type integro-differential bilinear equations. The individuals (cells or molecules) of the interacting populations are characterized by a microscopic inner state variable $u \in [0,1]$ which is related to a specific biological function of each individual. The model describes the evolution of the number densities for each population. This research line was initiated in (Bellomo and Forni, 1994) and then developed by various authors through different papers; let us mention only the recent papers (Arlotti *et al.*, 2000; 2002; Bellomo and Preziosi, 2000; Lachowicz, 2000; 2002). We refer the reader to the review papers (Bellomo and De Angelis, 1998; De Angelis and Mesin, 2001) as well as to (Adam and Bellomo, 1997; Bellomo and Pulvirenti, 2000; Chaplain, 1999) for a general bibliography.

The present paper is structured as follows: This section deals with an introduction concerning the aims and the organization of the paper. In Section 2 a brief description of the main biological processes related to acquired immunity is presented. In Section 3 the description of the model is given. Interacting populations are introduced and significant interactions are described. The evolution model is presented. Section 4 is devoted to the numerical simulations of the model. Some of the results are related to possible immunotherapy with antibodies. The results are compared with those of the recent paper (Kolev, 2002a). The comparison shows the importance of humoral immunity as well as the complexity of the competition between a tumor and the immune system. In Section 5 some final conclusions are presented.

2. Acquired Immunity

The immune system is a remarkably adaptive defense system that has evolved in vertebrates to protect them from invading pathogenic microorganisms and cancer. Immunity has both nonspecific and specific components. Innate, or nonspecific, immunity refers to the basic resistance to a disease that an individual is born with. Acquired, or specific (adaptive), immunity requires an activity of a functional immune system, involving cells called lymphocytes and their products. Innate defense mechanisms provide the first line of host defense against invading pathogens until the acquired immune response develops. In general, most of the microorganisms encountered by a healthy individual are readily cleared within a few days by nonspecific defense mechanisms without enlisting a specific immune response (Kuby, 1997). Innate immunity responds rapidly to foreign antigens (Ags) but possesses no memory and has a low level of specificity (Lydyard *et al.*, 2000).

When an invading microorganism or tumor eludes nonspecific host defense mechanisms, a specific immune response is enlisted. The key cells in adaptive immunity are B lymphocytes (B cells) and T lymphocytes (T cells). Two major populations of T cells exist: T helper cells (Th) and cytotoxic T cells (CTLs). Both populations of T cells are involved in the first form of acquired immunity called cell-mediated (or cellular) immunity. CTLs are able to destroy altered self-cells, including virus-infected cells and CCs. Th cells secrete numerous cytokines which are required for the activation and proliferation of T cells, B cells and APCs. In the present paper we will consider separately the population of B cells and the population of other APCs (e.g. DCs, macrophages).

B cells give rise to the second form of acquired immunity called humoral immunity. On contact with Ag, B cells proliferate and differentiate. Some of them produce secreted antibodies (Abs) (immunoglobulins) which bind to and help eliminate the Ags or CCs.

Interactions between T and B cells as well as APCs, are critical to the development of specific immunity. In experimental and clinical observations tumor Ags have been shown to induce both humoral and cell-mediated immune responses. Thus acquired immunity plays the major role in the defense against cancer (Lydyard *et al.*, 2000).

3. Model Description

We consider the following nine interacting populations, each denoted by the corresponding subscript i (Tab. 1). The functional state of each individual of each population is given by a number $u \in [0,1]$. Let us denote by $f_i = f_i(t,u)$, $f_i : [0,\infty[\times[0,1] \to \mathbb{R}_+$ the distribution density of the i-th population with functional state $u \in [0,1]$ at time $t \geq 0$ and by $n_i(t) = \int_0^1 f_i(t,u)\,\mathrm{d}u$, $n_i : [0,\infty[\to \mathbb{R}_+$ the concentration of the i-th individuals at time $t \geq 0$, $i = 1,\ldots,9$.

Table 1. Nine interacting populations.

i	Population
1	CCs
2	Th cells
3	CTLs
4	B cells
5	APCs which are not B cells (e.g. DCs, macrophages)
6	antigen-loaded APCs ([Ag-APC])
7	secreted Abs
8	antigen-loaded B cells ([B-Ag])
9	cells of the host environment (HE), mainly endothelial cells

We will assume the following meaning of the functional state for the populations of CCs, CTLs and Th cells, which was introduced in (Kolev, 2002a): For a given CC the inner state denotes the probability that this CC is recognized by APCs. For example, if the functional state of a CC is small ($u \approx 0$), this CC is "invisible" for the immune system and therefore it is very dangerous.

For a given CTL the functional state (activity) is supposed to be the probability for a recognized CC to be killed after its interaction with the given CTL. For a given Th cell the functional state (activity) is supposed to be the normalized quantity of the cytokines produced by the Th cell after its interaction with an antigen-loaded APC, whose cytokines induce the generation of new T cells, B cells and APCs. The value $u = 1$ corresponds to the maximal possible production of cytokines, while the value $u = 0$ corresponds to the absence of produced cytokines (Kolev, 2002a).

In addition, in the present paper we define the functional state (activity) of a given B cell to be the normalized quantity (concentration) of secreted Abs, produced by the B cell for unit time.

Using the above definitions of the functional states, it is easy to organize experiments suitable for measuring the inner state of a given cell. For the populations denoted by $i = 5,\ldots,9$ we neglect the presence of internal degrees of freedom and assume that the distribution functions $f_5,\ldots,f_9$ are independent of their functional states.

To simplify the biological reality it is reasonable to assume that the number of environmental cells is constant in time. Therefore we have performed a natural normalization of f_i, $i = 1,\ldots,8$, similarly to (Arlotti *et al.*, 2002; Bellomo and De Angelis, 1998).

To simplify the reality we will take into account only binary interactions between individuals. We assume that the interactions are homogeneous in space and instantaneous (without time delays). They may change the functional states of CCs, T cells and B cells, as well as the size of each population by destroying or creating individuals or by antigen-loading of APCs or B cells.

The rate of interactions between the individuals of the j-th and the k-th population is given by the function $a_{jk}(u,v)$, and possible transition into the i-th population with state u is described by the function $A_{jk}^{(i)}(v,w;u)$ (Arlotti *et al.*, 2002; Bellomo and Forni, 1994).

We now proceed to the specification of the interaction structure characterizing our model. First, we take into account the interactions which are described in (Kolev, 2002a). They are related to the cell-mediated part of acquired immunity. The main populations participating in cell-mediated immunity are the populations denoted by $i = 1, 2, 3, 5, 6$ and 9. Following the model in (Kolev, 2002a), we consider the following processes:

- destruction of CCs by CTLs and macrophages, activated by Th cells; these processes are described respectively by the loss terms, cf. Eqn. (1a):

$$d_{1i} f_1(t,u) \int_0^1 v f_i(t,v)\,\mathrm{d}v, \quad i = 3, 2;$$

- destruction of Th cells, CTLs and [Ag-APC] by CCs, described respectively by the loss terms $d_{i1} f_i(t,u) \int_0^1 f_1(t,v)\,\mathrm{d}v$ for $i = 2, 3$, and $d_{61} n_6(t) \int_0^1 f_1(t,v)\,\mathrm{d}v$, see Eqns. (1b), (1c) and (1f);

- loading of APCs with tumor Ags, described by the term $b_{15}^{(6)} n_5(t) \int_0^1 v f_1(t,v)\,\mathrm{d}v$, which is a loss term for the population $i = 5$ and a gain term for the population $i = 6$, see Eqns. (1e) and (1f);

- production of new CCs, Th cells, CTLs and APCs by the HE, described respectively by the gain terms $p_{19}^{(1)} \int_0^1 f_1(t,v)\,\mathrm{d}v$, $p_{19}^{(h)}(1-u), h = 2, 3$, and $p_{19}^{(5)}$, see Eqns. (1a), (1b), (1c) and (1e);

- production of new Th cells, CTLs and APCs as a result of interactions between Th cells and antigen-loaded APCs, which imply the production of numerous cytokines by the Th cells; the rates of the proliferation of Th cells, CTLs and APCs are assumed to be proportional to the functional state of the Th cells; the respective production is described by the following gain terms, cf. Eqns. (1b), (1c) and (1e):

$$p_{26}^{(h)}(1-u) n_6(t) \int_0^1 v f_2(v)\,\mathrm{d}v, \quad h = 2, 3,$$

$$p_{26}^{(5)} n_6(t) \int_0^1 v f_2(v)\,\mathrm{d}v;$$

- reduction of the functional state of CCs by HE (CCs become less "visible"); this process is described by the conservative term, cf. Eqn. (1a):

$$c_{19}^{(1)} \Big[2u \int_u^1 f_1(t,v)\,\mathrm{d}v - u^2 f_1(t,u) \Big];$$

- raising the functional state of CTLs by Th cells, described by the conservative term, cf. Eqn. (1c):

$$c_{23}^{(3)} \int_0^1 f_2(t,v)\,\mathrm{d}v \Big[2 \int_0^u (u-v) f_3(t,v)\,\mathrm{d}v - (1-u)^2 f_3(t,u) \Big];$$

- raising the activation state of Th cells by antigen-loaded APCs described by the conservative term, cf. Eqn. (1b):

$$c_{26}^{(2)} n_6(t) \Big[2 \int_0^u (u-v) f_2(t,v)\,\mathrm{d}v - (1-u)^2 f_2(t,u) \Big];$$

- the natural death of Th cells, CTLs, APCs and [Ag-APC] described respectively by the loss terms $d_{i9} f_i(t,u), i = 2, 3$, and $d_{i9} n_i(t), i = 5, 6$, cf. Eqns. (1b), (1c), (1e) and (1f);

- possible influx of Th cells, CTLs and [Ag-APC] through medical therapy described respectively by the non-negative functions $S_i(t,u)$, $i = 2, 3$, and $S_6(t)$, see Eqns. (1b), (1c) and (1f);

- raising the functional state of CCs through suitable immunotherapy, leading to a better recognition of CCs by APCs; this process is described by the conservative term (see Eqn. (1a)):

$$c_{19} \Big[2(1-u) \int_0^u f_1(t,v)\,\mathrm{d}v - (1-u)^2 f_1(t,u) \Big].$$

In the present paper we generalize the model of (Kolev, 2002a) describing in addition the humoral part of acquired immunity. In humoral immunity the populations denoted by $i = 4, 7$ and 8 are involved. We assume that

the following interactions are significant for the description of humoral immunity:

(1–4) Interactions between Populations 1 and 4:

(a) Loading of B cells with tumor antigens. We assume that the interactions between CCs and B cells lead to the loading of a part of B cells with tumor Ags. Thus a concentration of new antigen-loaded B cells appears which is supposed to be proportional to the functional state of CCs. The respective gain term for the population $i = 8$ is

$$\int_0^1 \int_0^1 A_{14}^{(8)}(v, w; u) a_{14}(v, w) f_1(v) f_4(w)\, \mathrm{d}v\, \mathrm{d}w = b_{14}^{(8)} \int_0^1 f_4(w)\, \mathrm{d}w \int_0^1 v f_1(v)\, \mathrm{d}v, \quad \forall u, w \in [0, 1].$$

(b) B cells destructive interactions. Sometimes CCs express Fas ligand (FasL). When FasL on the CC interacts with Fas on B cells or on [B-Ag], the destruction of B cells or of [B-Ag] may occur (Lydyard *et al.*, 2000). We assume that the respective loss term for the population $i = 4$ is

$$L_4(t, u) = d_{41} f_4(t, u) \int_0^1 f_1(t, v)\, \mathrm{d}v.$$

(1–7) Interactions between Populations 1 and 7. We assume the following interactions between CCs and Abs:

(a) CCs destructive interactions. Some Abs can activate, on binding to Ag, the classical pathway of complement leading to the lysis of the CC on which the Ag is located, and/or to the attraction of effector cells (e.g. CTLs, macrophages) leading to the destruction of the CC by phagocytosis or ADCC (antibody-dependent cell-mediated cytotoxicity, see e.g. (Kolev, 2003) for details). In our model we assume that the number of the destroyed CCs is proportional to the activation states of CCs and the respective loss term is

$$d_{17} u n_7(t) f_1(t, u), \quad \forall u \in [0, 1].$$

(b) The above-mentioned attraction of CTLs leads to the raising of their activation state, which we model by

$$A_{73}^{(3)}(v, w; u) = \begin{cases} \dfrac{2(u - v)}{(1 - v)^2} & \text{if} \quad u \geq v, \\ 0 & \text{if} \quad u < v, \end{cases}$$

and $a_{73}(v, w) = c_{73}^{(3)}(1 - v)^2,\ \forall v, w \in [0, 1]$.

(1–8) Interactions between Populations 1 and 8. As was mentioned above, CCs are able to destroy a part of [B-Ag]. We assume that the respective loss term for Population 8 is

$$L_8(t) = d_{81} n_8(t) \int_0^1 f_1(t, v)\, \mathrm{d}v.$$

(1–9) Interactions between Populations 1 and 9. There exists evidence that the HE surveys constantly for neoplastic antigens associated with a newly developing tumor and destroys the cells bearing them. The B cell development within the thymus is independent of foreign Ags (Lydyard *et al.*, 2000). Thus we assume a constant production of B cells and Abs, taking into account the fact that the probability of producing new B cells with a small functional state is greater than that with a high activation state (Kuby, 1997). The respective gain terms are supposed to be

$$G_4(t, u) = p_{19}^{(4)}(1 - u), \quad G_7(t) = p_{19}^{(7)}.$$

(2–4) Interactions between Populations 2 and 4. We assume the following interactions between Th and B cells:

(a) B cells conservative interactions. The interactions between Th and B cells lead to the progress of B cells towards increasing their activation states through cytokines produced by Th cells. We model this process through

$$A_{24}^{(4)}(v, w; u) = \begin{cases} \dfrac{2(u - v)}{(1 - v)^2} & \text{if} \quad u \geq v, \\ 0 & \text{if} \quad u < v, \end{cases}$$

and $a_{24}(v, w) = c_{24}^{(4)}(1 - v)^2,\ \forall v, w \in [0, 1]$.

(b) Production of Abs by B cells. Some B cells (plasma cells) produce and secrete large amounts of Abs. We suppose that the interactions induce the production of Abs with a rate proportional to the activation states of B cells and the respective gain term to be

$$\int_0^1 \int_0^1 A_{24}^{(7)}(v, w; u) a_{24}(v, w) f_2(v) f_4(w)\, \mathrm{d}v\, \mathrm{d}w = p_{24}^{(7)} \int_0^1 f_2(v)\, \mathrm{d}v \int_0^1 w f_4(w)\, \mathrm{d}w.$$

(2–8) Interactions between Populations 2 and 8. We assume that the interactions between Th cells and antigen-loaded B cells are characterized by the following effects:

(a) T and B cells proliferative interactions. The interactions between Th cells and antigen-loaded B cells trigger the secretion of numerous cytokines by Th cells, which induce the proliferation of Th cells, CTLs and B cells. We suppose that the rate of the production of new cells is proportional to the functional states of the Th cells and the respective gain terms are

$$p_{28}^{(h)}(1 - u) n_8(t) \int_0^1 v f_2(v)\, \mathrm{d}v, \quad h = 2, 3, 4.$$

We have taken into account the observations that the probability of producing new T and B cells with small activation states is greater than that with high activation states (Kuby, 1997).

(b) Th conservative interactions. They lead to the progress of Th cells towards increasing their activation states. We model this process through

$$A_{28}^{(2)}(v,w;u)=\begin{cases}\dfrac{2(u-v)}{(1-v)^2} & \text{if} \quad u\geq v,\\ 0 & \text{if} \quad u<v,\end{cases}$$

and $a_{28}(v,w)=c_{28}^{(2)}(1-v)^2,\ \forall v,w\in[0,1]$.

(4–7) Interactions between Populations 4 and 7. Finally, we take into account the possible inhibition of the humoral response by Abs in some cases when the Abs deliver negative signals to B cells (Lydyard *et al.*, 2000). We model lowering the activation states of the B cells through

$$A_{47}^{(4)}(v,w;u)=\begin{cases}\dfrac{2u}{v^2} & \text{if} \quad u\leq v,\\ 0 & \text{if} \quad u>v,\end{cases}$$

and $a_{47}(v,w)=c_{47}^{(4)}v^2,\ \forall v,w\in[0,1]$.

(i–9) Interactions between Populations 9 and i, $i=4,7,8$. We consider the natural death processes of B cells, Abs and [B-Ag] and assume them to be linear with coefficients $d_{i9},\ i=4,7,8$.

We assume that an inlet of B cells, [B-Ag] and Abs is possible (e.g. through medical therapy) and model this by the respective source terms $S_4(t,u),\ S_7(t)$ and $S_8(t)$.

Using balance arguments similar to those of kinetic theory, we obtain the following evolution model for the interacting populations:

$$\begin{aligned}\partial_t f_1 &= p_{19}^{(1)}\int_0^1 f_1(v)\,\mathrm{d}v\\ &\quad + c_{19}^{(1)}\Big(2u\int_u^1 f_1(v)\,\mathrm{d}v-u^2f_1(t,u)\Big)\\ &\quad - d_{12}f_1(t,u)\int_0^1 vf_2(v)\,\mathrm{d}v\\ &\quad - d_{13}f_1(t,u)\int_0^1 vf_3(v)\,\mathrm{d}v\\ &\quad + c_{19}\Big(2(1-u)\int_0^u f_1(v)\,\mathrm{d}v-(1-u)^2f_1(t,u)\Big)\\ &\quad - d_{17}un_7(t)f_1(t,u),\end{aligned}\tag{1a}$$

$$\begin{aligned}\partial_t f_2 &= p_{19}^{(2)}(1-u)\\ &\quad + \Big(p_{26}^{(2)}n_6(t)+p_{28}^{(2)}n_8(t)\Big)(1-u)\int_0^1 vf_2(v)\,\mathrm{d}v\\ &\quad - d_{21}f_2(t,u)\int_0^1 f_1(v)\,\mathrm{d}v-d_{29}f_2(t,u)\\ &\quad + \Big(c_{26}^{(2)}n_6(t)+c_{28}^{(2)}n_8(t)\Big)\Big(2\int_0^u (u-v)f_2(v)\,\mathrm{d}v\\ &\quad - (1-u)^2f_2(t,u)\Big)+S_2(t,u),\end{aligned}\tag{1b}$$

$$\begin{aligned}\partial_t f_3 &= p_{19}^{(3)}(1-u)\\ &\quad + \Big(p_{26}^{(3)}n_6(t)+p_{28}^{(3)}n_8(t)\Big)(1-u)\int_0^1 vf_2(v)\,\mathrm{d}v\\ &\quad - d_{31}f_3(t,u)\int_0^1 f_1(v)\,\mathrm{d}v\\ &\quad + \Big(2\int_0^u (u-v)f_3(v)\,\mathrm{d}v-(1-u)^2f_3(t,u)\Big)\\ &\quad \times\Big(c_{23}^{(3)}\int_0^1 f_2(v)\,\mathrm{d}v+c_{73}^{(3)}n_7(t)\Big)\\ &\quad - d_{39}f_3(t,u)+S_3(t,u),\end{aligned}\tag{1c}$$

$$\begin{aligned}\partial_t f_4 &= p_{19}^{(4)}(1-u)\\ &\quad + p_{28}^{(4)}n_8(t)(1-u)\int_0^1 vf_2(v)\,\mathrm{d}v\\ &\quad - d_{41}f_4(t,u)\int_0^1 f_1(v)\,\mathrm{d}v\\ &\quad + c_{24}^{(4)}\int_0^1 f_2(v)\,\mathrm{d}v\Big(2\int_0^u (u-v)f_4(v)\,\mathrm{d}v\\ &\quad - (1-u)^2f_4(t,u)\Big)-d_{49}f_4(t,u)+S_4(t,u)\\ &\quad + c_{47}^{(4)}n_7(t)\Big(2u\int_u^1 f_4(v)\,\mathrm{d}v-u^2f_4(t,u)\Big)\\ &\quad - b_{14}^{(8)}f_4(t,u)\int_0^1 vf_1(v)\,\mathrm{d}v,\end{aligned}\tag{1d}$$

$$\partial_t n_5 = p_{19}^{(5)} + p_{26}^{(5)} n_6(t) \int_0^1 v f_2(v)\,\mathrm{d}v - b_{15}^{(6)} n_5(t) \int_0^1 v f_1(v)\,\mathrm{d}v - d_{59} n_5(t), \quad (1e)$$

$$\partial_t n_6 = b_{15}^{(6)} n_5(t) \int_0^1 v f_1(t,v)\,\mathrm{d}v - d_{61} n_6(t) \int_0^1 f_1(t,v)\,\mathrm{d}v - d_{69} n_6(t) + S_6(t), \quad (1f)$$

$$\partial_t n_7 = p_{19}^{(7)} + p_{24}^{(7)} \int_0^1 f_2(t,v)\,\mathrm{d}v \int_0^1 w f_4(t,w)\,\mathrm{d}w - d_{79} n_7(t) + S_7(t), \quad (1g)$$

$$\partial_t n_8 = b_{14}^{(8)} \int_0^1 f_4(w)\,\mathrm{d}w \int_0^1 v f_1(v)\,\mathrm{d}v - d_{81} n_8(t) \int_0^1 f_1(v)\,\mathrm{d}v - d_{89} n_8(t) + S_8(t). \quad (1h)$$

In this bilinear system of eight integro-differential equations for distribution densities $f_i,\ i = 1, \ldots, 4$ and concentrations $n_i,\ i = 5, \ldots, 8$, the coefficients are assumed to be non-negative constants, and n_9 is assumed to be constant in time.

Using standard arguments, it is not difficult to prove the existence and uniqueness of a non-negative solution to the system (1), similarly to the models in (Arlotti *et al.*, 2002; Kolev, 2002b; Kolev *et al.*, 2002).

4. Simulations

The numerical scheme used to solve the system (1) is similar to the one described in (Kolev, 2003; Kolev *et al.*, 2002). As the initial condition we assume the presence of a small amount of easy recognizable CCs (i.e. with high state values) and the absence of T cells, B cells and APCs. The biological problem of the technical evaluation of the parameters of (1) is not dealt with in the present paper.

In the first part of our simulations we analyze the role of the humoral response in acquired immunity. Let us note that the model of cellular immunity presented in (Kolev, 2002a) can be considered as a particular case of our model of acquired immunity if we set $d_{17} = p_{28}^{(2)} = c_{28}^{(2)} = p_{28}^{(3)} = c_{73}^{(3)} = 0$ (in this case there is no influence of B cells and Abs on CCs, T cells and APCs). Cellular immunity plays a very important role in the anticancer defense (see, e.g. (Kolev, 2002a; Kolev *et al.*, 2002)). We consider this particular case of cellular immunity and set the following values of the other parameters:

$$d_{13} = d_{21} = d_{61} = d_{41} = d_{81} = d_{79} = p_{19}^{(2)} = p_{19}^{(7)} = p_{19}^{(3)} = p_{19}^{(4)} = p_{19}^{(5)} = 1,$$

$$p_{26}^{(3)} = 0.5, \quad b_{14}^{(5)} = 7.7,$$

$$b_{14}^{(8)} = p_{19}^{(1)} = p_{26}^{(2)} = 5, \quad d_{31} = 0.1,$$

$$p_{26}^{(5)} = p_{28}^{(4)} = p_{24}^{(7)} = c_{24}^{(4)} = c_{26}^{(2)} = c_{23}^{(3)} = c_{19}^{(1)} = d_{12} = 10.$$

All the other parameters are set as zeros. We do not consider inlets of cells of the immune system, thus choosing $S_i(t,u) = 0,\ i = 2,3,4$ and $S_i(t) = 0,\ i = 6,7,8$. The result of the simulations for the temporal evolution of CCs is presented in Fig. 1 as a $3D$ plot of the tumor density f_1 against the functional state u and time t. The simulations show that in this first example the insufficient cell-mediated response of the immune system leads to an unlimited tumor growth.

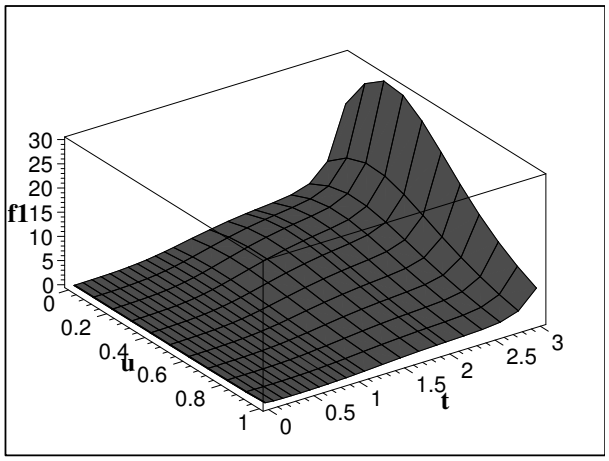

Fig. 1. Evolution of cancer cell densities in Case 1 (cellular immunity).

In our second example we add the influence of the humoral response changing only the value of the parameter d_{17}, describing the destruction of CCs as a result of the activity of Abs, setting $d_{17} = 0.0033$. The temporal evolution of the total number $n_1(t)$ of CCs in this second case is presented in Fig. 2. It is compared with the total number of CCs in Case 1, where $d_{17} = 0.0$. The simulations show that with the help of the humoral response the immune system is able to control the growth of CCs.

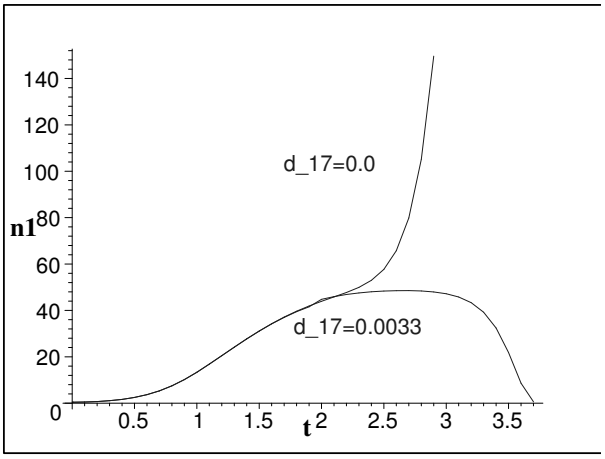

Fig. 2. Evolution of the number of cancer cells for Case 1 (cellular immunity, $d_{17} = 0$) and Case 2 (acquired immunity, $d_{17} = 0.0033$).

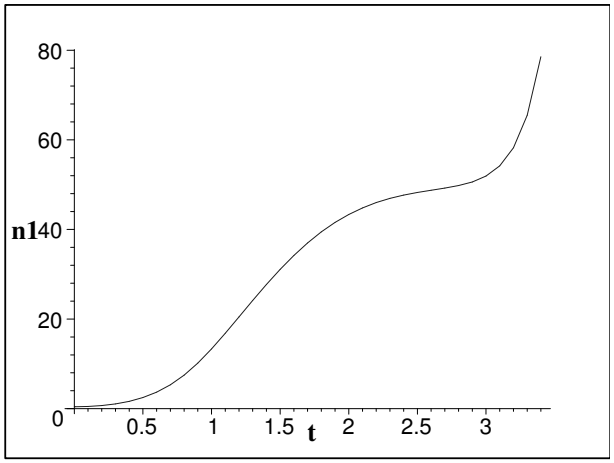

Fig. 3. Evolution of the number of cancer cells for Case 3 (negative feedback by Abs, $c_{47}^{(4)} = 10,\ d_{17} = 0.0033$).

However, in some cases the role of the Abs can be negative. One possible explanation for this is the potential modulation of the tumor Ag expression. The binding of Ab to Ags of the surface of tumor cells may result in a rapid internalization of the Ag and its loss from the cell surface, permitting the tumor cell to temporarily escape from further detection by Ab or APC and thus from effector cells (e.g. CTLs) (Kuby, 1997; Lydyard *et al.*, 2000).

Another possible negative feedback by some Abs can be the inhibition of the B cells response as a result of delivering negative signals to the B cells by Abs or Ab-Ag complexes. We model this process by the term lowering the activation states of the B cells. Changing the value of the parameter $c_{47}^{(4)}$ and setting $c_{47}^{(4)} = 10$ ($d_{17} = 0.0033$), we conclude from the simulations that in this case, called Case 3, the immune response is not sufficient to control the tumor growth. The results are shown in Fig. 3, where the total number $n_1(t)$ of CCs is presented.

In the second part of our simulations we analyze one popular method of immunotherapy. Recently, the clearer appreciation that developed of how to use monoclonal Abs more effectively in cancer therapy has resulted in a renaissance in antibody therapy (Chen and Wu, 1998; Moingeon, 2001). We model this approach by a constant influx of antibodies $S_7(t) = 1$ (Case 5). The numerical results of evolution in Case 4 (without influx) and therapy with antibodies (Case 5) are presented in Fig. 4 ($d_{17} = 0.0032,\ c_{47}^{(4)} = 0.$)

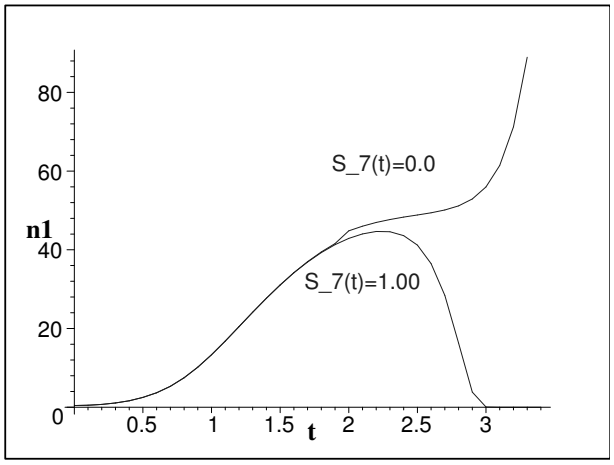

Fig. 4. Evolution of the number of cancer cells for Case 4 (no influx of Abs, $d_{17} = 0.0032, S_7(t) = 0$) and Case 5 (influx of Abs, $S_7(t) = 1$).

5. Conclusions

The results of the present paper demonstrate the complexity of the competition between the tumor and the immune system, whose very important part is acquired immunity. The simulations analyze some of the mechanisms which play a major role in the anticancer defense. This can improve our understanding of cancer and could help in a future search for a cure.

Acknowledgements

The present work was performed within the framework of the EC Programme *Improving the Human Research Potential and Socio-Economic Knowledge Base* — Research Training Network, Contract No. HPRN–CT–2000–00105, *Using Mathematical Modelling and Computer Simulation to Improve Cancer Therapy*.

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