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On the discrete kinetic theory for active particles. Modelling the immune competition†

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This paper deals with the application of the mathematical kinetic theory for active particles, with discrete activity states, to the modelling of the immune competition between immune and cancer cells. The first part of the paper deals with the assessment of the mathematical framework suitable for the derivation of the models. Two specific models are derived in the second part, while some simulations visualize the applicability of the model to the description of biological events characterizing the immune competition. A final critical outlines some research perspectives.

Keywords: Kinetic theory; Active particles; Discrete microscopic variable; Immune competition

1. Introduction

A mathematical framework to model large systems of active particles with discrete activities was proposed in a recent paper [1], which develops the approach by Bertotti and Delitala [2] to discretize equations of the generalized mathematical kinetic theory [3]. The mathematical structures developed in Ref. [1] have been proposed in view of modelling large systems of interacting entities, called active particles, such that their microscopic state is characterized not only by mechanical variables, but also by an additional variable called activity, suitable to describe specific functions of the particles. The modelling dealt with in Refs. [1, 2] considers the activity as a discrete variable.

This paper deals with a specific application, with reference to the immune competition between tumor and immune cells. The application of methods of the mathematical kinetic theory to the above competition was initiated in Ref. [4] and developed by various authors as documented in the review papers [5, 6], as well as in various recent applications [7–11]. Additional contributions from the view point of biological sciences are offered in Refs. [12–15].

The contents of the paper are developed through four more sections, which follow the above introduction. In details:

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- Section 2 deals with a phenomenological description of the system analyzed in this paper, and defines the mathematical structure, referring from Ref. [1], which will be used for the modelling.
- Section 3 deals with the derivation of the mathematical model describing the immune competition process involving cells which are carrier of a pathological state and contrasted by immune cells activated by cytokine signals.
- Section 4 develops a qualitative and computational analysis of the models proposed in section 3 with the aim of visualizing the predictive ability of the model with special attention to the asymptotic behavior of the solution.
- Section 5 deals with a critical analysis on the contents of this paper, also focused on the problem of parameters identification and suggests some experiments to achieve the above objective.

2. Phenomenological description and mathematical framework

We refer to biological systems involving the competition of cells carrier of pathology and immune cells activated by cytokine signals, with some reasoning specifically related to the case of tumor modelling.

The immune system, in a multicellular organism, is the organization of cells and molecules with specific roles to defend organism against foreign pathogens (viruses, bacteria, parasites) as well as against internal cellular disorder. Its defensive action is evident through the recognition of non-self substances, revealing particular molecular patterns, the antigens, which are linked to the foreign pathogen agents. The process is complicated: the immune system needs to evolve and change in time, recognizing some non-self substances as non-offending elements (cellular feeding substances, growing embryos in the mother) and learning to identify new pathogen agents not previously encountered. The task is performed by distinct populations of specialized substances (proteins, enzymes, etc.).

The reaction of the immune system to pathogen agents is of two different kinds: innate response and acquired response. The innate response is quickly activated every time the infectious agent is encountered, while the acquired one is activated after repeated exposures to a given infection. They work together against the infection, but in both cases the defense starts from the recognition of the pathogen agents. It is an intricate process in which several components of the immune system cooperate in order to reach the objective, from the detection of the infection to the proliferation of the leukocytes specialized against the pathology.

On the other hand, abnormal cells, *e.g.* cells that are carriers of a particular pathology, virally infected or neoplastic cells, may proliferate, rapidly increasing the number of infected individuals or inhibiting in some way the functionality of the immune system. From this point of view, tumor cells may be regarded as an aggressive host, at least at an early stage of the tumor.

We may generally define a tumor as a disease originating in some kind of cellular disorder, which allows certain cellular populations to manifest deviant characteristics. When tumor cells are recognized by immune cells, a competition starts and may end up either with the destruction of tumor cells, or with the inhibition and depression of the immune system. Indeed tumor cells, if not recognized and depleted, start to condense into a solid form: this is the passage from the microscopic (cellular) scale to the macroscopic scale. As a matter of fact the defense ability of the immune system and the progress ability of the tumor are common features of the competition.

In this sophisticated competition, cellular and subcellular phenomena play a relevant role in the evolution of the process. It may be described through the interactions of several cellular populations, related to immune system cells as well as to abnormal cells. In this paper the complexity of the system is reduced by identifying only three different cell populations: endothelial cells; immune cells whose many species are gathered; and specific proteins, called cytokines, which are a kind of messenger whose function consists in their ability to participate in the activation of the immune cells.

Endothelial cells are the thin cells, which are the line of the interior face of blood vessels and can be found in the circulating blood. They are characterized by a natural trend to modify their biological state from normal to progressing (abnormal) which is the initial stage of the clonal expansion: abnormal cells may lose their programmed death ability (apoptosis) to start progressing towards metastatic states. Therefore, the biological state of these cells can be defined as a normal or abnormal state.

Immune cells, if active, have the ability to contrast the presence of tumor cells (abnormal endothelial cells) by reducing their progression; if inhibited, they lose this ability. As already mentioned, active cytokines are a kind of messenger able to active immune inhibited cells, but may lose this ability after having interacted with the last ones.

The biological state of each element of these interacting populations (cells or cytokines) may thus be described by two discrete values denoted u^h, for $h = 1, 2$, of the activity variable, taken as a scalar variable in our model.

In the very early stage of the immune competition, proliferating and destructive phenomena may not play a relevant role. Therefore, at this stage, the mathematical modelling of the immune competition between tumor and immune cells, considering the action of cytokines, simply deals with the variation, due to interactions, of the biological state of each cell's population. Taking into account only conservative encounters, the aim of this particular model is the ability to describe the onset of progressing cells as a transition from the normal state of endothelial cells. At a later stage, encounters generating proliferation or destruction processes occur. This perturbation of the cellular dynamics presented above is then modelled by non-conservative encounters able to describe this new phenomenology.

We provide the mathematical structure, which will be used in the modelling of the complex immune competition detailed above. Consider the general case of proliferating–destructive interactions, which generate death or birth of the various cells playing the game. Then we assume that the three populations are homogeneously distributed in space, so that the distribution function corresponding to the i-th population depends on time and discrete activity only, and we note

$$f_i^h(t) = f_i(t, u^h), \tag{1}$$

for $i = 1, 2, 3$ and $h = 1, 2$.

The subscript $i = 1$ corresponds to endothelial cells whose biological state may shift from normal (u^1) to abnormal (u^2). The subscript $i = 2$ corresponds to immune cells whose biological state may shift from inhibited (u^2) to active (u^1). Finally the immune-activating cells (cytokines), whose state also may shift from active (u^1) to inhibited (u^2), are labelled with the subscript $i = 3$. Using the mathematical structure developed in Ref. [1] to model the

evolution of the system leads to the following system of ordinary differential equations:

$$\frac{\mathrm{d}f_i^h}{\mathrm{d}t} = \sum_{j=1}^{3}\sum_{p,q=1}^{2} \eta_{ij}\mathcal{B}_{ij}^{pq}(h) f_i^p f_j^q - f_i^h \sum_{j=1}^{3}\sum_{q=1}^{2} \eta_{ij}(1-\mu_{ij}^{hq}) f_j^q, \tag{2}$$

in which the coefficients are:

- the encounter rate η_{ij}, which gives the number of encounters per unit of time between two interacting cells of respective populations i and j.
- the discrete transition density $\mathcal{B}_{ij}^{pq}(h)$, which is the probability that a cell of the i-th population with biological state u^p, falls into the state u^h, after an interaction with a cell of the j-th population with state u^q. This term has the structure of a probability density with respect to the outgoing variable. This leads to the following property:

$$\forall i,j, \quad \forall p,q: \quad \mathcal{B}_{ij}^{pq}(1) + \mathcal{B}_{ij}^{pq}(2) = 1, \tag{3}$$

  which gives $\mathcal{B}_{ij}^{pq}(1)$ when $\mathcal{B}_{ij}^{pq}(2)$ is known, and vice versa.
- the source/sink rate μ_{ij}^{hq}, which is, for each encounter between a cell of the i-th population in the biological state u^h and a cell of the j-th population with biological state u^q, the number of cells generated (in the case of proliferating interactions) or destroyed (in the case of destructive ones) with state u^h in the same population. This term is negative in case of destructive interactions and positive for proliferating ones. Note that proliferation and/or destruction occur with the above defined encounter rate.

The knowledge of f_i^h leads to the computation of macroscopic quantities, as moments weighted by the above distribution function. Referring to the biological application we are dealing with, the interesting quantities for the understanding of the results are the number densities and the activations.

n_i^h is the number density of cells of the i-th population with activity u^h at time t. It provides information on the size of the i-th population and is defined by the zero-*th* order moment of the function f_i^h, which means simply in the homogeneous case

$$n_i^h(t) = f_i^h(t). \tag{4}$$

The sum over the activities gives the number density n_i corresponding to the i-th population:

$$n_i(t) = f_i^1(t) + f_i^2(t), \quad i = 1,\ldots,3, \tag{5}$$

while the total number density n is the sum of the number densities n_i. When proliferating–destructive events play a role, the density number n_i changes in time. On the contrary, in the conservative case, this number remains constant in time for each population that yields

$$f_i^1(t) + f_i^2(t) = n_{i0}, \tag{6}$$

for all time t, where n_{i0} is the cells number of the i-th population at time $t = 0$.

The h-th activation, denoted $\mathcal{A}_i^h$, provides information on the biological activity state of the i-th population at time t. It is defined by

$$\mathcal{A}_i^h(t) = u^h n_i^h(t), \tag{7}$$

as the first order moment of the activity u^h related to the i-th population, while the overall activation of the i-th population is thus given by

$$\mathcal{A}_i(t) = u^1 n_i^1(t) + u^2 n_i^2(t). \tag{8}$$

It has a specific and different meaning for each cell population. Indeed it denotes, respectively, the tendency of the endothelial cells to reach the pathologic state, the ability of immune cells to reduce the progression of the tumor cells and the capacity of cytokines to activate the immune system.

3. The mathematical model

This section deals with the derivation of a mathematical model of the immune competition between cancer and immune cells with the mediation of cytokines. The model refers to the mathematical structure reported in equation (2), while the derivation of specific models is developed by identification of the various terms η_{ij}, $\mathcal{B}_{ij}^{pq}(h)$, and μ_{ij}^{hq} which appear in this equation.

The analysis is developed through three sub-sections, which follow the above brief introduction. The first one deals with the modelling of conservative microscopic interactions, the second one develops the same analysis for proliferating–destructive encounters, while the mathematical model is derived in the last subsection.

3.1 Modelling microscopic conservative interactions

Consider interactions between pairs of cells of the three populations, which play the game, and focus our analysis to encounters, which modify only the biological state. Moreover, we assume that the encounter rate is constant for all encounters:

$$\eta_{ij} = \eta = 1, \quad \forall i,j = 1,2,3. \tag{9}$$

In order to build up the model, we have now to compute the transition coefficients $\mathcal{B}_{ij}^{pq}(h)$ according to the following phenomenology:

- Interactions between cells of the first population, both normal and progressing endothelial cells, present an inner tendency to degenerate and progress to the abnormal state u^2.
- Referring to interactions between cells of the first population with cells of the second population, we assume that the biological state of a non-progressing endothelial cell remains unchanged after interactions with immune cells, while cell progression can be reduced by the action of the active immune cells.
- Interactions between cells of the second population with cells of the first population present ability of tumor cells to inhibit immune cells.
- Interactions between cells of the second population do not involve cell modification.

- Referring to interactions with cells of the third population, the only non-trivial one is related to encounters with immune cells. Active cytokines may activate inhibited immune cells, but may lose this ability after an encounter with immune cells (either inhibited or not).

The above assumptions lead to the following expressions of the transition probability density terms:

- $\mathcal{B}_{11}^{11}(2) = \mathcal{B}_{11}^{12}(2) = \varepsilon_{11}$, where ε_{11} is the probability that endothelial normal cells become abnormal after having interacted with other endothelial cells (normal or abnormal);
- $\mathcal{B}_{12}^{22}(1) = \varepsilon_{12}$, where ε_{12} is the probability that endothelial abnormal cells become normal after having interacted with active immune cells;
- $\mathcal{B}_{21}^{22}(1) = \varepsilon_{21}$, where ε_{21} is the probability that active immune cells are inhibited after having interacted with abnormal cells;
- $\mathcal{B}_{23}^{12}(2) = \varepsilon_{23}$, where ε_{23} is the probability that inhibited immune cells are activated after having interacted with active cytokines;
- $\mathcal{B}_{32}^{21}(1) = \mathcal{B}_{32}^{22}(1) = \varepsilon_{32}$, where ε_{32} is the probability that cytokines are inhibited after having interacted with immune cells (active or not).

When one of the above transition term is known, for a fixed biological state, the one related to the complementary biological state is given by the relation (3). The other terms model trivial interactions that let unchanged the biological state of the cells involved in an encounter, and are given by:

$$\begin{cases} \mathcal{B}_{ij}^{pq}(h) = 1 & \text{if } p = h, \\ \mathcal{B}_{ij}^{pq}(h) = 0 & \text{if } p \neq h. \end{cases} \tag{10}$$

The phenomenological parameters ε_{ij} describe the probability that a cell may change its biological state during an encounter; thus they belong to the interval $[0, 1]$.

3.2 Modelling microscopic proliferating/destructive interactions

We develop in this section the modelling of proliferation/destruction processes, which appear at the later stage of the competition.

Microscopic proliferating/destructive interactions involving the three populations appear with a source/sink rate μ_{ij}^{hq} which depends on the microscopic state of the pair of the interacting cells. The modelling of these interactions describes the following phenomenology:

- Interactions between normal endothelial cells with cells of the first population, both normal and abnormal, do not lead to proliferation or destruction. On the other hand, abnormal cells undergo uncontrolled mitosis stimulated by encounters with non-progressing cells, which show a feeding ability. Encounters between tumor cells do not lead to any proliferation or destruction.
- Referring to interactions between cells of the first population with cells of the second population, the proliferating rate of non-progressing cells, due to encounters with immune cells, is equal to zero. On the other hand, tumor cells are partially destroyed during encounters with active immune cells.

- Interactions between inhibited immune cells of the second population with cells of the first population do not involve proliferation or destruction. On the other hand, active immune cells proliferate due to encounters with progressing cells, while showing a self-destruction to the sentinel level $f_{20}^1 = f_2^1(t=0)$ when interacting with normal endothelial cells.
- Interactions between cells of the second population and interactions involving cytokines always have a trivial output.

Bearing in mind the above phenomenological considerations, the proliferating/destructive phenomena are modelled by the following source/sink terms:

- $\mu_{11}^{21} = \beta_{11}$, where β_{11} is a parameter which characterizes the proliferating ability of tumor cells due to their encounters with normal endothelial cells;
- $\mu_{12}^{22} = -\beta_{12}$, where β_{12} is a parameter which characterizes the ability of active immune cells to destroy tumor cells;
- $\mu_{21}^{21} = -\beta_{21}^*$, where β_{21}^* is the parameter corresponding to the self-destruction of active immune cells due to their interaction with normal endothelial cells;
- $\mu_{21}^{22} = \beta_{21}$, where β_{21} is the parameter corresponding to the proliferation rate of active immune cells due to their interaction with progressing cells.

The parameters β_{ij} are positive constants, as underlined in the definition of the source/sink rate reported in the first section. The other values of the terms μ_{ij}^{hq} are equal to zero.

3.3 Derivation of the evolution equation

The evolution equation, e.g. the mathematical model, is obtained considering the elementary volume of the space of the microscopic state and equating, for each population, the variation rate of the cells in the volume to the net flux (inlet minus outlet) due to microscopic interactions. Technical calculations analogous to those developed in Ref. [2] lead to the following models.

3.3.1 Model Ia – general case

$$\begin{cases} \dfrac{dg_1}{dt} = -\varepsilon_{11} g_1 (g_1 + g_2) + \varepsilon_{12} g_2 g_3, \\ \dfrac{dg_2}{dt} = \varepsilon_{11} g_1 (g_1 + g_2) - \varepsilon_{12} g_2 g_3 + \beta_{11} g_2 g_1 - \beta_{12} g_2 g_3, \\ \dfrac{dg_3}{dt} = \varepsilon_{23} g_4 g_5 - \varepsilon_{21} g_3 g_2 + \beta_{21} g_3 g_2 - \beta_{21}^* (g_3 - g_{30}) g_1, \\ \dfrac{dg_4}{dt} = -\varepsilon_{23} g_4 g_5 + \varepsilon_{21} g_3 g_2, \\ \dfrac{dg_5}{dt} = -\varepsilon_{32} g_5 (g_3 + g_4), \\ \dfrac{dg_6}{dt} = \varepsilon_{32} g_5 (g_3 + g_4), \end{cases} \tag{11}$$

where all above number densities are normalized with respect to the density $f_1^1(t=0) = n_{10}$ of the normal endothelial cells at $t = 0$. The normalization is applied using the following

notations:

$$\frac{f_1^1}{n_{10}} = g_1, \quad \frac{f_1^2}{n_{10}} = g_2, \quad \frac{f_2^1}{n_{10}} = g_3, \quad \frac{f_2^2}{n_{10}} = g_4, \quad \frac{f_3^1}{n_{10}} = g_5 \quad \text{and} \quad \frac{f_3^2}{n_{10}} = g_6. \tag{12}$$

The above model is characterized by five ε-type parameters corresponding to conservative encounters and four β-type parameters corresponding to proliferating/destructive encounters. It is worth characterizing, before developing simulations addressed to visualize the predictive ability of the model, some specific particularizations of the general model. Specifically consider, among various conceivable cases, the following particularizations:

3.3.2 Model Ib–absence of cytokine action. This model, which corresponds to absence of interaction between the immune system and the cytokine proteins, is obtained by putting $\varepsilon_{32} = \varepsilon_{23} = 0$. Then the model writes:

$$\begin{cases} \dfrac{\mathrm{d}g_1}{\mathrm{d}t} = -\varepsilon_{11} g_1 (g_1 + g_2) + \varepsilon_{12} g_2 g_3, \\ \dfrac{\mathrm{d}g_2}{\mathrm{d}t} = \varepsilon_{11} g_1 (g_1 + g_2) - \varepsilon_{12} g_2 g_3 + \beta_{11} g_2 g_1 - \beta_{12} g_2 g_3, \\ \dfrac{\mathrm{d}g_3}{\mathrm{d}t} = -\varepsilon_{21} g_3 g_2 + \beta_{21} g_3 g_2 - \beta_{21}^* (g_3 - g_{30}) g_1, \\ \dfrac{\mathrm{d}g_4}{\mathrm{d}t} = \varepsilon_{21} g_3 g_2. \end{cases} \tag{13}$$

3.3.3 Model II–constant number of normal cells. This particularization corresponds to a physical situation where the number of normal cells is kept constant by the outer environment, which replaces cells, which degenerate or are used towards the proliferation of degenerated cells. The model is obtained putting $g_1 = g_1(t = 0) = 1$. In this case the model writes:

$$\begin{cases} \dfrac{\mathrm{d}g_2}{\mathrm{d}t} = \varepsilon_{11} (1 + g_2) - \varepsilon_{12} g_2 g_3 + \beta_{11} g_2 - \beta_{12} g_2 g_3, \\ \dfrac{\mathrm{d}g_3}{\mathrm{d}t} = \varepsilon_{23} g_4 g_5 - \varepsilon_{21} g_3 g_2 + \beta_{21} g_3 g_2 - \beta_{21}^* (g_3 - g_{30}), \\ \dfrac{\mathrm{d}g_4}{\mathrm{d}t} = -\varepsilon_{23} g_4 g_5 + \varepsilon_{21} g_3 g_2, \\ \dfrac{\mathrm{d}g_5}{\mathrm{d}t} = -\varepsilon_{32} g_5 (g_3 + g_4), \\ \dfrac{\mathrm{d}g_6}{\mathrm{d}t} = \varepsilon_{32} g_5 (g_3 + g_4). \end{cases} \tag{14}$$

4. On the initial value problem

Two classes of models have been proposed in Section 3 corresponding, respectively, to biological *in vitro* and *in vivo* situations. Moreover, the first model has been particularized to the case of absence of cytokine signals, while the second one includes the above action and is derived assuming that the number of endothelial normal cells is kept constant by feeding from the outer environment. Therefore an additional difference between Models I and II corresponds to closed (*in vitro*) and open (*in vivo*) systems.

The application of the above models to the analysis of phenomena of interest in biological sciences means solving the related initial value problem, which can be formally written as follows:

$$\begin{cases} \dfrac{\mathrm{d}\mathbf{g}}{\mathrm{d}t} = \mathbf{G}(\mathbf{g}; \varepsilon, \beta), \\ \mathbf{g}(t=0) = \mathbf{g}_0, \end{cases} \tag{15}$$

where $\mathbf{g}$ denotes the set $\{g_i\}$ of the normalized number densities, $\mathbf{G}$ is the set of the right hand side terms $\{G_i\}$, while ε and β denote the set of parameters $\{\varepsilon_i\}$ and $\{\beta_i\}$, respectively, and $\mathbf{g}_0$ is the set of initial conditions chosen with the assumption that they model a sane organism in which both immune cells and cytokines are all active.

4.1 Well-posedness of the model

The analysis developed, in what follows, is limited to the proof that problem (15) is well posed locally in time. Consider the Banach space of the functions continuous with respect to the time endowed with maximum modulus norm. The RHS in system (15) is defined for $\mathbf{g}$ belonging to the above space. Note that $\mathbf{g} \in \mathbb{R}^6$ and is on $\mathbb{R}^6$ of class $\mathcal{C}^1$ (actually, $\mathcal{C}^\infty$). Hence $\mathbf{g}$ is locally Lipschitz. This guarantees the local existence and the uniqueness of the Cauchy problem (15).

Remark. The occurrence of the global existence of a solution $\mathbf{g}$ would be violated only in the case $|\mathbf{g}| \to \infty$ as $t \to t^*$ for some $t^* < \infty$. However, for the solutions under consideration, this eventuality is ruled out by the following properties of the g_i:

(i)

$$g_i \geq 0 \quad \forall i = 1, \ldots, 6;$$

(ii)

$$\sum_{i=1}^{6} g_i(t) = \frac{[n_1(t) + n_2(t) + n_3(t)]}{n_{10}} \text{ is bounded.}$$

The proof of the property (i) is reported in what follows, while (ii) depends on the choice of the parameters. Let us consider the notation adopted in Section 2 for the number densities, before applying the normalization with respect to n_{10}. We want to prove that the solution $\mathbf{f}(t) = \{f_i^h(t)\}$ of the system (2) with non negative initial data $f_i^h(t=0) = f_{i0}^h$, satisfies the following condition:

$$\forall t \geq 0: \quad f_i^h(t) \geq 0, \tag{16}$$

for any $i = 1, 2, 3$ and $h = 1, 2$. To this aim, call for simplicity, for any $i = 1, 2, 3$ and $h = 1, 2$,

$$Q_i^h(\mathbf{f}, \mathbf{f})(t) = \sum_{j=1}^{3} \sum_{p,q=1}^{2} \eta_{ij} \mathcal{B}_{ij}^{pq}(h) f_i^p(t) f_j^q(t), \tag{17}$$

and

$$L_i^h(\mathbf{f})(t) = \sum_{j=1}^{3}\sum_{q=1}^{2} \eta_{ij}\left(1 - \mu_{ij}^{hq}\right) f_j^q(t). \tag{18}$$

We have assumed that η_{ij} is constant, while μ_{ij}^{hq} are quantities of a small order with respect to one. Equation (2) can be rewritten as

$$\frac{\mathrm{d}f_i^h}{\mathrm{d}t}(t) + f_i^h(t) L_i^h(\mathbf{f})(t) = Q_i^h(\mathbf{f},\mathbf{f})(t). \tag{19}$$

Put now

$$\lambda_i^h(t) = \int_0^t L_i^h(\mathbf{f})(s)\mathrm{d}(s).$$

If $f_i^h(t)$ is a solution of above equation, then

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\exp\left(\lambda_i^h(t)\right) f_i^h(t)\right) = \exp\left(\lambda_i^h(t)\right) Q_i^h(\mathbf{f},\mathbf{f})(t), \tag{20}$$

which in turn yields

$$f_i^h(t) = \exp\left(-\lambda_i^h(t)\right) f_{i0}^h + \int_0^t \left[\exp\left(\lambda_i^h(s) - \lambda_i^h(t)\right) Q_i^h(\mathbf{f},\mathbf{f})(s)\right]\mathrm{d}s. \tag{21}$$

From equation (21), the validity of the thesis (16) follows in view of the positivity of the exponential and of the fact that $f_{i0}^h \geq 0$ for any $i = 1, 2, 3$ and $h = 1, 2$.

4.2 Simulations of immune competition

In this subsection we show how the models derived in section 3 are able to describe some interesting phenomena of immune competition.

The above local and global existence theorems enable the application of standard integration techniques for systems of ordinary differential equations. In what follows in more detail, we present some simulations, which aim to focus on the following aspects:

- The model, under suitable selection of the parameters ε and β, is able to show, after an initial situation of growth, the progressive destruction of tumor cells, due to the action of active immune cells;
- The activation of immune cells may modify the output of the competition.

Consider Model Ib, which corresponds to an absence of an action of the immune activators. We can observe a situation where, in the initial stage of the competition, tumor cells increase (figure 1(a)). The development of the tumor is then limited by the immune response, this last one reaching a threshold value after a first decrease (figure 1(b)).

The introduction of the effect of cytokines (model Ia) modifies the outcome of the competition. Indeed the situation shown in figure 1(a),(b) is replaced by the one presented in figure 2(a),(b), where the parameters non-related to the cytokines are the same selected in

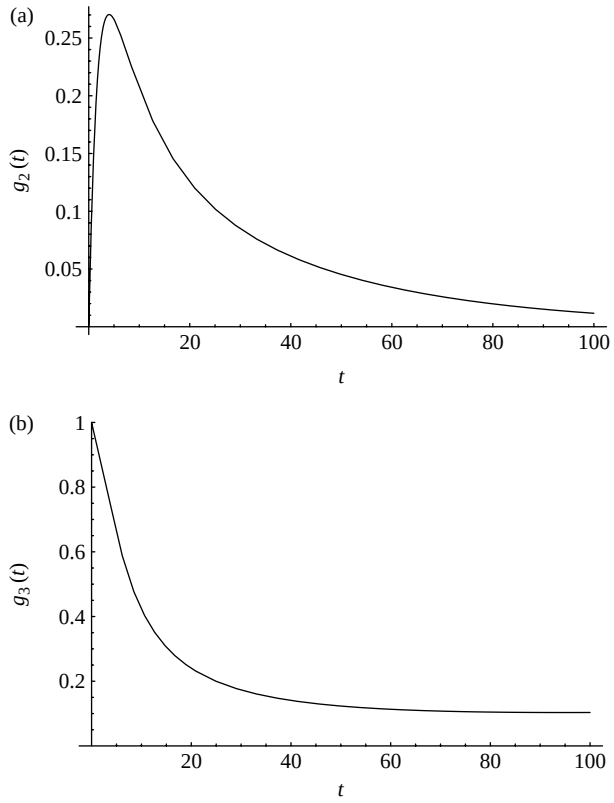
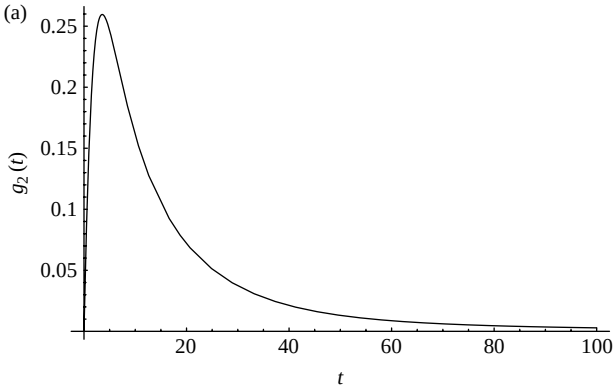


Figure 1. (a) Evolution in time of tumor cells for the Model Ib. (b) Evolution in time of active immune cells for the Model Ib.

figure 1(a),(b). Now the immune response allows the tumor cells to decrease more quickly, while the progressive inhibition of active immune cells towards the threshold value is slower.

Consider Model II in which we have assumed that the number of normal cells is kept constant by feeding from the outer environment. In this particular case, we can note a blow up



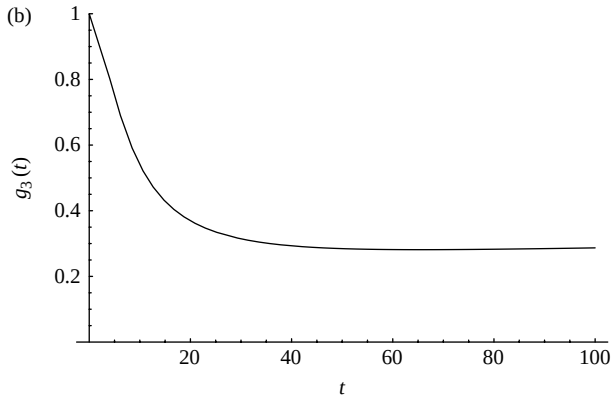


Figure 2. (a) Evolution in time of tumor cells for $\varepsilon_{23} = 0.7$ and $\varepsilon_{32} = 0.5$ in the Model Ia. (b) Evolution in time of active immune cells for $\varepsilon_{23} = 0.7$ and $\varepsilon_{32} = 0.5$ in the Model Ia.

of tumor (figure 3(a)) and a total inhibition of the immune defense (figure 3(b)). The parameters are those chosen in figure 2(a),(b).

In the two last figures we present some interesting phenomena resulting from the immune competition described by Model II for a particular selection of the parameters

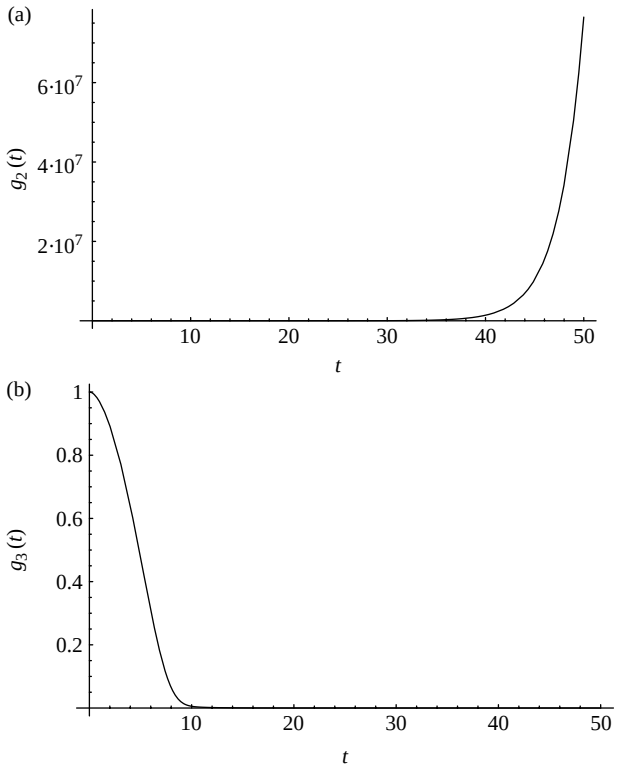


Figure 3. (a) Evolution in time of tumor cells for the Model II. (b) Evolution in time of active immune cells for the Model II.

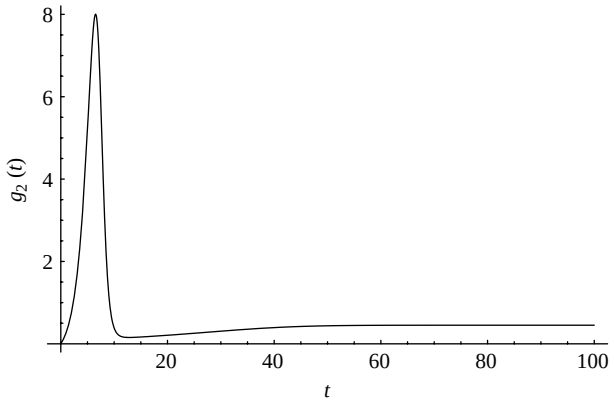


Figure 4. Evolution in time of tumor cells for $\varepsilon_{23} = 1$ and $\varepsilon_{32} = 0.7$ in the Model II.

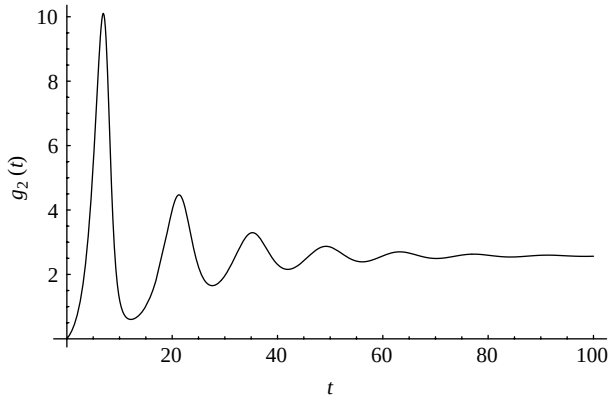


Figure 5. Evolution in time of tumor cells for $\varepsilon_{23} = 0.4$ and $\varepsilon_{32} = 0.3$ in the Model II.

ε and β. The figure 4 describes a competition in which tumor cells first present an increase. Then we cannot observe a complete depletion but they are controlled by a threshold level. Figure 5 shows how tumor cells are able to compete with immune active cells, before reaching this level.

5. Critical analysis

A mathematical model of the competition between tumor and cells of the immune system has been proposed in this paper with reference to the mathematical kinetic theory for active particles with discrete states developed in Ref. [1], starting from the approach proposed in Ref. [2].

The model attempts to reduce the overall complexity of the system considering that:

(i) it deals with a spatially homogeneous case;
(ii) only a small number of cell populations are involved in the game.

On the other hand, despite the above simplicity, it has shown to be able to describe various phenomena of interest in biological sciences. This encourages the development of additional analysis towards its application to a deeper understanding of biological phenomena.

The first step towards an effective application of the model is the identification of its parameters. It is not an easy task, considering the stochastic nature of the biological system we are dealing with, as documented in Ref. [16]. Some reasoning can be developed following Chapter 7 in Ref. [17], referring to Model II in absence of the immune activators.

In details, Model II in absence of cytokine action writes:

$$\begin{cases} \dfrac{\mathrm{d}g_2}{\mathrm{d}t} = \varepsilon_{11}(1+g_2) - \varepsilon_{12}g_2g_3 + \beta_{11}g_2 - \beta_{12}g_2g_3, \\ \dfrac{\mathrm{d}g_3}{\mathrm{d}t} = -\varepsilon_{21}g_3g_2 + \beta_{21}g_3g_2 - \beta^*_{21}(g_3 - g_{30}), \\ \dfrac{\mathrm{d}g_4}{\mathrm{d}t} = \varepsilon_{21}g_3g_2, \end{cases} \tag{22}$$

while the stage corresponding to the proliferation phase only writes:

$$\begin{cases} \dfrac{\mathrm{d}g_2}{\mathrm{d}t} = \beta_{11}g_2 - \beta_{12}g_2g_3, \\ \dfrac{\mathrm{d}g_3}{\mathrm{d}t} = -\beta_{21}g_3g_2 - \beta^*_{21}(g_3 - g_{30}). \end{cases} \tag{23}$$

An exponential growth is described by the model in the case of absence of contrast from the immune system. Comparisons with empirical data corresponding to the above different biological stages leads to the identification, in cascade, of the various parameters of the model. Nevertheless, the reasoning proposed in Ref. [16] points out that the identification of the parameters does not lead to a universal result as it may be related to the specific system under consideration, which is characterized by non negligible stochastic features.

Moreover, it is worth mentioning that although the computational experiments of section 4 have visualized some phenomena of interest in biological sciences, additional ones can be developed possibly linked to a qualitative analysis of the initial value problem as in Refs. [7] or [8]. The analysis should be related to specific aspects of the immune competition [18], while more generally the mathematical approach may refer to modelling population dynamics with internal structures [19–22].

Finally, it is worth remarking that cancer phenomena appear at three scales: the subcellular, cellular and macroscopic as described in Ref. [14]. This paper develops the modelling at the cellular scales by equations whose parameters should be delivered by an analysis at the subcellular scale [23, 24]. At present this challenging objective does not seem yet effectively available despite valuable contributions such as those reported in Ref. [23, 24]. On the other hand, macroscopic equations can be obtained by asymptotic analysis as documented in Ref. [25], where it is shown how the mathematical structure of macroscopic equations depends on the entity of the rates of variation of the three biological events dealt with in this paper: modification of the biological functions, and proliferating/destructive interactions.

References

[1] Chauviere, A. and Brazzoli, I., 2006, On the discrete kinetic theory for active particles. Mathematical tools, *Math. Comput. Modelling*, **43**, 933–944.

[2] Bertotti, L. and Delitala, M., 2004, From discrete kinetic theory and stochastic game theory to modelling complex systems in applied sciences, *Math. Models Methods Appl. Sci.*, **14**, 1061–1084.

[3] Arlotti, L., Bellomo, N. and De Angelis, E., 2002, Generalized kinetic (Boltzmann) models: mathematical structures and applications, *Math. Models Methods Appl. Sci.*, **12**, 579–604.

[4] Bellomo, N. and Forni, G., 1994, Dynamics of tumor interaction with the host immune system, *Math. Comput. Modelling*, **20**, 107–122.

[5] Bellomo, N., De Angelis, E. and Preziosi, L., 2003, Multiscale modelling and mathematical problems related to tumor evolution and medical therapy, *J. Theor. Med.*, **5**, 111–136.

[6] Bellomo, N., Bellouquid, A. and Delitala, M., 2004, Mathematical topics on the modelling of complex multicellular systems and tumor immune system competition, *Math. Models Methods Appl. Sci.*, **14**, 1683–1733.

[7] Bellouquid, A. and Delitala, M., 2004, Kinetic (cellular) models of cell progression and competition with the immune system, *Z. Angew. Math. Phys.*, **55**, 1–24.

[8] Derbel, L., 2004, Analysis of a new model for tumor-immune system competition including long time scale effects, *Math. Models Methods Appl. Sci.*, **14**, 1657–1682.

[9] Bellouquid, A. and Delitala, M., 2005, Mathematical methods and tools of kinetic theory towards modelling complex biological system, *Math. Models Methods Appl. Sci.*, **15**, 1639–1666.

[10] Kolev, M., Kozlowsko, E. and Lachowicz, M., 2005, Mathematical model of tumor invasion along linear or tubolar structures, *Math. Comput. Modelling*, **41**, 1083–1096.

[11] De Angelis, E. and Jabin, P.E., 2005, Mathematical models of therapeutical actions related to tumour and immune system competition, *Math. Methods Appl. Sci.*, **28**, 2061–2083.

[12] Greller, L., Tobin, F. and Poste, G., 1996, Tumor heterogeneity and progression: conceptual foundation for modelling, *Invas. Metast.*, **16**, 177–208.

[13] Reed, R., 2004, Why is mathematical biology so hard?, *Notices Am. Math. Soc.*, **51**, 338–342.

[14] Bellomo, N. and Maini, P., 2005, Preface, *Math. Models Methods Appl. Sci.*, **15**, iii–viii.

[15] Gatenby, R.A., Vincent, T.L. and Gillies, R.J., 2005, Evolutionary dynamics in carcinogenesis, *Math. Models Methods Appl. Sci.*, **15**, 1619–1638.

[16] Gillet, E., 2005, A chaque cancer son scénario alétoire, *La Recherche*, **390**, 73.

[17] Bellouquid, A. and Delitala, M., 2006, *Modelling Complex Biological Systems: A Kinetic Theory Approach* (Boston: Birkhäuser).

[18] Lollini, P.L., Cavallo, F., Nanni, P. and Forni, G., 2006, Vaccines for tumor prevention, *Nat. Rev.*, 204–216.

[19] Arlotti, L., Bellomo, N. and Latrach, K., 1999, From Jager and Segel model to kinetic population dynamics: nonlinear evolution problems and applications, *Math. Comput. Modelling*, **30**, 15–40.

[20] Delitala, M., 2004, Generalized kinetic theory approach to modelling spread and evolution of epidemics, *Math. Comput. Modelling*, **39**, 1–12.

[21] Michel, P., 2006, Existence of solutions to the cell division eigenproblem, *Math. Models Methods Appl. Sci.*, to appear **16**.

[22] Kheifetz, Y., Kogan, Y. and Agur, Z., 2006, Long-range predictability in models of cell populations subject to phase-specific drugs: growth rate approximation using properties of positive compact operators, *Math. Models Methods Appl. Sci.*, to appear **16**.

[23] Komarova, N.L. and Wodarz, D., 2004, The optimal rate of chromosome loss for the inactivation of tumor suppressor genes in cancer, *Proc. Math. Acad. Sci. USA*, **101**, 7017–7021.

[24] Komarova, N.L. and Cheng, P., 2006, Epithelial tissue architecture protects against cancer, *Math. Biosci.*, **200**, 90–117.

[25] Bellomo, N. and Bellouquid, A., 2006, On the set of non-linearity for diffusion models of binary mixtures of biological materials by asymptotic analysis, *Int. J. Nonlinear Mech.*, **41**, 281–293.