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ASYMPTOTIC ANALYSIS OF AN INTEGRO-DIFFERENTIAL SYSTEM MODELING THE BLOW UP OF CANCER CELLS UNDER THE IMMUNE RESPONSE

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Abstract In this paper, we derive and analyze a phenomenological model at the cellular level of the immune response to cancer evolution based on the kinetic theory of active particles. The model consists of a system of nonlinear integro-differential equations describing the binary interactions between epithelial, tumor, naive immune cells, and activated immune cells. It also takes into account the phenotypic mutations in the epithelial and immune cells, which are known to result in the uncontrolled growth of tumor cells. We prove the well-posedness of the related Cauchy problem and the non-negativity of the solution. We give sufficient conditions for which the solution may exist globally in time. A detailed asymptotic analysis has been developed with the aim of predicting the effect of mutation events on the tumor-immune dynamics. The analysis shows that under some critical values of the model's parameters and initial conditions, we can specify some biological states of the blow up of tumor cells. Indeed, the analysis gives useful indications to be properly explored toward the design of therapeutical actions.

Keywords Mathematical modeling, cancer-immune competition, Kinetic theory of active particles, global existence, asymptotic analysis.

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1. Introduction

The significance of the immune system in tumor development, progression and destruction, as well as the complexity of the tumor-immune interactions have been extensively studied in recent decades (see reviews and references therein [17, 26, 31, 43, 45]). The evolution of tumor cells in a host is governed by more than just the activities of cancer cells alone. It is largely due to a plethora of inter- and intra-cellular interactions within the tumor microenvironment [43,44]. The immune cells play a key role in the tumor microenvironment, which contains heterogeneous cell populations such as cancer stem cells, stromal cells, fibroblasts, and epithelial cells [29].

The immune system is the organization of cells and molecules with specific role to protect organism against foreign pathogens and internal disorder [1]. Immune

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system needs to evolve and change in time, learning to identify new pathogen agent not previously encountered, as well as recognition of non-self-substances as non-offending entities (cellular feeding substance). Distinct populations of the immune system act to perform this task. The reaction of the immune cells against foreign pathogens is of two different kinds: innate response and adaptive response (acquired). The innate response is quickly activated every time the infectious agent is encountered, while the adaptive one is activated repeated exposures to this the infection. They collaborate together against infection, and the defense starts from the identification and recognition of the pathogen agent. On the other hand, tumor cells (e.g cells that are carrier of a particular pathology) may proliferate, rapidly increasing the number of individuals [1, 42]. From this point of view tumor cells may be regarded as an aggressive host, at least at an early stage of the competition. When tumor cells are recognized by immune cells, a competition starts and may end up, either with the control or depletion of tumor cells, or weakness of the immune ability to recognize foreign pathogens inducing an indefinite growth. The reader interested, from a biological standpoint, to the role of the immune system in detecting and depleting cancer cells is addressed to [18,19,21,30,37] and therein cited bibliography. Understanding such a complex and continuously changing network of multiple signals that control cancer-immune interactions calls for mathematical modeling in addition to experimental and clinical research of course. Several mathematical models of tumor-immune system interactions have been developed over the past decades. They have included a broad range of mathematical methods such as differential equations, spatial and non-spatial multiscale models, fractal-fractional models and agent based models to name just a few. These models have examined different characteristics of the cancer-immune complex interactions both in general and in other specific cases such as immune surveillance, suppression and escape, and during therapies (see among others, [2, 4, 8, 23–25, 34–36, 38–40]).

Various problems in the life sciences have been modeled using the general mathematical framework of the Kinetic theory of active particles (KTAP), as documented in the survey paper [8] and therein bibliography. Interactions, in this specific approach, are modeled by means of theoretical game theory tools see, among others, [3, 27]. Cells of the population are identified by their microscopic state, which includes a scalar variable, *the activity*, related to their functional behavior. The state of the overall system is then described by a set of distribution functions over the microscopic state of the interacting cells, and the evolution of the system is determined by the microscopic interactions, which are ruled by a somehow organized behavior or strategy. KTAP's methods have been applied since [9] to model cancer phenomena and cellular dynamics and the competition between tumor and immune cells as documented in [10] as well as in several papers, among others, [5, 7, 9, 11, 12, 14–16, 22].

In this paper, we build upon our previous model in [14] where we develop and present a detailed asymptotic analysis of a nonlinear integro-differential model of the tumor-immune competition mediated by the cytokines activity. The model describes the conservative interactions between the tumor and immune cells, that is, the competition where no cell proliferation/destruction occurred. The main result is that, under a suitable choice of initial cytokine level and parameters, the immune system acquired the ability to become more efficient in eliminating tumor cells. In [20], we extend the same model by introducing both the conservative and proliferative/destructive interactions of the tumor and immune cells. The numerical

study shows that, under a suitable choice of the model's key parameters and the cytokines initial activation levels, the activated immune system is able to achieve a total elimination of tumor cells. These two models, however, do not take into account the phenotypic mutations that occur at the level of epithelial and immune cells.

The focus of this study is improving our previous models by including the phenotype mutation events in the model and investigating their effects on the immune response against cancer evolution. To address the question of how phenotypic mutations, affect the immune response against cancer evolution, we present and analyze a phenomenological model of nonlinear integro-differential equation that includes phenotypic mutation events. The derivation is based on the description of the binary interactions between four interacting populations: epithelial, tumor, immune, and effector cells. We give sufficient conditions that guarantee the global existence of the solution as well as prove the finite time blow-up of the solution. A detailed asymptotic analysis is carried out based on some initial conditions and a suitable choice of the parameters. We establish the well-posedness of the related Cauchy problem and prove the non-negativity of the solution. We present a detailed asymptotic analysis with the aim to predict the impact of mutation events on the tumor-immune dynamics.

This paper is organized as follows. The formulation of the mathematical model is detailed in section 2. Section 3 summarizes analytical results about the well-posedness of the Cauchy Problem linked to the model and the asymptotic analysis of the solution. The proof of these analytical results is presented in 4. A numerical study is given in section 5. The conclusion and future perspectives are presented in section 6.

2. The mathematical model

2.1. Model description and assumptions

The biological system considered in this model consists of four interacting populations in the tumor microenvironment [10, 16]: epithelial cells, tumor cells, innate immune cells, and activated immune cells labeled by the indices 1, 2, 3 and 4 respectively. These populations are assumed to be structured by a real continuous variable ($u \in (0, \infty)$) which identifies the state of the cells and their biological meaning and varies from population to another. The following assumptions are made in setting up the model:

1. Epithelial cells are assumed to be constant considering that the apoptosis balances the mitosis number. In this case, u may represent the ability to exchange nutrient and protect to make their number constant.
2. Tumor cells generated from the first population of epithelial cells due to differentiation and mutation. In this case, the variable u stands for the capacity to suppress immune cells.
3. Innate immune cells have the ability to identify progressed tumors cells as well as to detect their presence. The variable u corresponds to the ability to identify progressing cells.

4. Activated immune cells generated from the population of immune cells and have acquired the ability to contrast progressed tumor cells. The variable u represents the capacity to contrast the developmental of tumor cells.

The state of populations are characterized by the functions at time t,

$$f_i(t,u):\ \mathbb{R}_+\times\mathbb{R}_+\ \to\mathbb{R}_+,\ i=1,\dots 4.$$

At any fixed time, the quantity $f_i(t,u)\,du$ stands for the number of cells in population, whose state belongs to the element volume du centered at u, normalized with respect to the total number of cells inside the cellular system at time $t=0$, and the number density of each populations is computed as follows:

$$n_i(t)=\int_{\mathbb{R}_+} f_i(t,u)\,du, \tag{2.1}$$

and the total size of the cellular system at time t results

$$n(t)=\sum_{i=1}^{4} n_i(t).$$

2.2. Model derivation

The evolution equations of f_i are based on the Boltzmann type equation as detailed in [6, 22].

$$\begin{aligned}
&\frac{\partial f_i}{\partial t}(t,u)=J_i[f](t,u)\\
&=\underbrace{\sum_{j=1}^{4}\left(\int_{\mathbb{R}^+}\int_{\mathbb{R}^+}\delta(u-m_{ij}(u_*,u^*)f_i(t,u_*)f_j(t,u^*)du_*du^*-f_i(t,u)\int_{\mathbb{R}^+}f_j(t,u^*)du^*\right)}_{\text{Inlet and outlet flux due to conservative interactions}}\\
&+\underbrace{f_i(t,u)\sum_{j=1}^{4}\int_{\mathbb{R}^+}\mu_{ij}(u,u^*)f_j(t,u^*)du^*}_{\text{Net flux due to proliferation/destruction in the same population}} \qquad (2.2)\\
&+\underbrace{\sum_{h=1}^{4}\sum_{k=1}^{4}\int_{\mathbb{R}^+\times\mathbb{R}^+}\mu_{hk}^{i\neq h}(u_*,u^*;u)f_h(t,u_*)f_k(t,u^*)du_*du^*}_{\text{Net flux due to Proliferation in new population}},
\end{aligned}$$

where

- $m_{ij}(u_*\to u,u^*)$ is the most probable output of the cellular interaction that describes the modification in the micro state as transition from u^* to u.
- $\mu_{ij}(u_*,u^*)$ is the number of cells produced per unit volume and unit time due to the encounters of cell pairs of the $(i,j)^{th}$ population with states u_* and u^* respectively.

- $\mu_{hk}^{i\neq h}(u_*, u^*; u)$ stands for the net proliferation of a cell of the *h-th* population with state u_*, with another cell of the *k-th* population with state u^*, into the *i-th* population due to the interaction.

The interaction between the tumor cells and the immune cells as well as the interaction within the tumor cell and immune cells are described as binary instantaneous interactions as follows.

$\mathcal{A}_1$- *Microscopic conservative interactions*
Here, we focus on the nonzero interactions between pairs of cells that only modify biological states.
• Interaction with epithelial cells $i = 1, 2$ with $j = 1$. We assume that only interaction with epithelial cells implies an increasing of the state both for cancer and epithelial cells:

$$m_{i1} = u_* + \alpha_i. \tag{2.3}$$

where α_1, corresponds to the capacity to differentiate for the epithelial cells, while α_2 stands for capacity to progress and increase the malignity for tumor cells.
• Interaction of the population $i = 1$ with $j = 2$. Epithelial cells are assumed to feed progression of cancer cell without changing their own state:

$$m_{12} = u_*. \tag{2.4}$$

• Interaction of tumor cells $i = 2$ - Immune cells $j = 3, 4$: It is assumed that this type of interactions does not induce modification of the sates for tumor cells.
• Interaction of Immune cells from $i = 3, 4$ - tumor cells $j = 2$. Immune cells have the ability to identify tumor cells, if they have acquired this specific ability. This mechanism occurs progressively. Therefore, the state of immune cells may increase.

$$m_{32} = u_* + \alpha_3, \tag{2.5}$$
$$m_{42} = u_* + \alpha_4, \tag{2.6}$$

where α_3 stands for the capacity to increase the identification of progressing cells and α_4 corresponds to the ability to recognize and attack cancer cells.

$\mathcal{A}_2$- *Proliferation and competition for resources for tumor cells*
The proliferation of tumor cells increases due to a deregulated proliferation [28] which induce a rapid growth of malignant tumor cells, assumed to occur at constant rate $\beta_2 \in \mathbb{R}^+$. However, proliferation for tumor cells is hampered by competition for resources. Therefore, we assume that a tumor cell in state u can die due to encounter with cell in any state u^* at constant rate $d_2 \in \mathbb{R}^+$.

$\mathcal{A}_3$- *Proliferation and activation of immune cells*
The cell activation implies a depletion of number of innate immune cells, so many regulatory mechanisms act in order to restore its number [33]. Thus, we assume that immune cells in population ($i = 3$) can proliferate at constant rate $\beta_3 \in \mathbb{R}^+$ and die due to their interaction with other cells in the same population at constant rate $d_3 \in \mathbb{R}^+$. The aim of destructive interactions innate immune cells in the model is to keep their number under control. activated immune cells may proliferate due to encounter with tumor cells and

thus we assume that immune cells can proliferate at a rate of $\beta_4 \in \mathbb{R}^+$ and also because of the limited availability of nutrients, immune cells cannot proliferate in an unbounded way [32]. Hence, we assume that cells can die at constant rate $d_4 \in \mathbb{R}^+$ due to the encounter with other cells in the same population. Activated immune cells are able to recognize and attack tumor cells. This phenomenon is described as a binary interaction between cancer cells in state u and activated immune cells in state u^*. These interactions cause the destruction of cancer cells at rate μ_2.

$\mathcal{A}_4$- *Mutation events.*
Interactions can generate new daughter cells in a population different from of the mother cells. In particular, we assume that epithelial cells can mutate and become cancerous. In turn, immune cells mutate and acquire the capability to identify and attack tumor cells. Moreover, the biological state of mutated cells do not change during the transition. These interactions occur at constant rate as follow:
• Mutation of epithelial cells ($h = 1$) into cancerous state in population of tumor cells ($i = 2$), due to encounter with epithelial cells ($k = 1$)

$$\mu^i_{hk}(u_*, u^*; u) = \begin{cases} \varepsilon_1 \delta(u - u_*) & h = 1,\ k = 1, i = h + 1, \\ 0 \quad \text{otherwise} \end{cases} \tag{2.7}$$

where ε_1 models the mutation rate for tumor cells.
• Mutation from innate immune population to an activated state related to the capability of immune cells to recognize tumor cells.

$$\mu^i_{hk}(u_*, u^*; u) = \begin{cases} \varepsilon_2 \delta(u - u_*) & h = 3,\ k = 3, i = h + 1, \\ 0 \quad \text{otherwise.} \end{cases} \tag{2.8}$$

Based on the phenomenological assumptions ($\mathcal{A}_1$-$\mathcal{A}_4$) and using the mathematical framework given in (2.2), the corresponding evolution equations of the functions $(f_1, ..., f_4)$ read as follows:

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t,u) &= \Theta_1[f] \\ &= \underbrace{n_1(t)\left(f_1(t, u-\alpha_1)\chi_{(\alpha_1,+\infty)}(u) - f_1(t,u)\right)}_{\text{Differentiation and renewal of epithelial cells}}, \end{aligned} \tag{2.9}$$

$$\begin{aligned} \frac{\partial f_2}{\partial t}(t,u) =& \Theta_2[f] \\ =& \underbrace{n_1(t)\left(f_2(t, u-\alpha_2)\chi_{(\alpha_2,+\infty)}(u) - f_2(t,u)\right)}_{\text{Self progression toward advanced states of malignancy}} \\ &+ \underbrace{\beta_2 f_2(t,u) n_1(t)}_{\text{Proliferation of tumor cells}} + \underbrace{\varepsilon_1 f_1(t,u) n_1(t)}_{\text{Mutation in tumor cells}} \\ &\underbrace{-d_2\, f_2(t,u) n_2(t)}_{\text{Competition for resources}} - \underbrace{\mu_2 f_2(t,u) n_4(t)}_{\text{Destruction by actiated immune cells}}, \end{aligned} \tag{2.10}$$

$$\begin{aligned}\frac{\partial f_3}{\partial t}(t,u) =&\Theta_3[f]\\ =&\underbrace{n_2(t)\left(f_3(t,u-\alpha_3)\chi_{(\alpha_3,+\infty)}(u)-f_2(t,u)\right)}_{\text{Recognition of tumor cells}}\\ &+\underbrace{\beta_3 f_3(t,u)n_3(t)}_{\text{Proliferation}}-\underbrace{d_3\, f_3(t,u)n_3(t)}_{\text{Destruction}},\end{aligned} \tag{2.11}$$

and

$$\begin{aligned}\frac{\partial f_4}{\partial t}(t,u) =&\Theta_4[f]\\ =&\underbrace{n_2(t)\left(f_4(t,u-\alpha_4)\chi_{(\alpha_4,+\infty)}(u)-f_4(t,u)\right)}_{\text{Identification and Activation}}\\ &+\underbrace{\beta_4 f_4(t,u)n_2(t)}_{\text{Proliferation du to encounter with tumor cells}}\\ &-\underbrace{d_4 f_4(t,u)n_4(t)}_{\text{Homeostatic regulation}}+\underbrace{\varepsilon_2 f_3(t,u)n_3(t)}_{\text{Mutation term}},\end{aligned} \tag{2.12}$$

where

$$f=(f_1,f_2,f_3,f_4).$$

The system (2.9)-(2.12) characterizes a nonlinear integro-differential model with a quadratic type nonlinearity. All the biological parameters involved in the model take nonnegative values. Practical value of these parameters are small with respect to unity. The model parameters and their meaning are summarized in Table 1.

Integrating (2.9)-(2.12) with respect to u in $\mathbb{R}^+$ and using (2.1) yields the following equations for the densities $n_i,\ i=1,..,4$:

$$\frac{\partial n_1(t)}{\partial t}=0, \tag{2.13}$$

$$\frac{\partial n_2(t)}{\partial t}=\beta_2 n_1 n_2-d_2 n_2^2-\mu_2 n_2 n_4+\varepsilon_1 n_1^2, \tag{2.14}$$

$$\frac{\partial n_3(t)}{\partial t}=(\beta_3-d_3)n_3^2, \tag{2.15}$$

$$\frac{\partial n_4(t)}{\partial t}=\beta_4 n_4 n_2-d_4 n_4^2+\varepsilon_2 n_3^2. \tag{2.16}$$

This system is in a closed form.

3. Analytical results

This section is meant to provide some qualitative proprieties of the Cauchy Problem derived by endowing Eqs. (2.9)-(2.12) with suitable initial conditions. In more details:

In subsection (3.1) the well posedness of the initial value problem under consideration is analyzed.

Table 1. The model parameters and their description

Parameters	Meaning
α_1	The inner tendency of epithelial cells to degenerate and progress towards a pathological state
α_2	The ability of the progressing cells to increase their of progression
α_3	The inner tendency of naive immune cells to degenerate toward an activated state
α_4	The ability of activated immune cells to increase their malignancy
β_2	The proliferation rate of tumor cells
β_3	The proliferation rate immune cells
β_4	The proliferation rate of activated immune cells
d_2, d_2, d_3	destruction rate for tumor cells, immune cells, and activated immune cells respectively
μ_2	The immune destruction of tumor cells
ε_1	mutation rate for tumor cells
ε_2	mutation rate for activated immune cells.

3.1. A well-posedness result

The expression of functions f_i are delivered by the solution of the following Cauchy Problem, derived by endowing Eqs. (2.9)-(2.12) with suitable initial conditions:

$$\begin{cases} \dfrac{\partial f}{\partial t}(t,u) = \Theta[f](t,u), \quad (t,u) \in (0,\infty)\times(0,\infty), \\ f(0,u) = f_0(u) \in \mathcal{X}_+. \end{cases} \tag{3.1}$$

In the above expression, $\mathcal{X}_+$ is the positive cone of the Banach space

$$\mathcal{X} := \{f = (f_1, f_2, f_3, f_4) : \ f_1, f_2, f_3, f_4 \in L^1_u(0,\infty)\},$$

endowed with the norm

$$\| f \| = \sum_{i=0}^{4} \| f_i \|_1,$$

while $\Theta[f]$ is the componentwise defined by Eqs. (2.9)-(2.12).

Let $\mathcal{Y}$ be the Banach space $\mathcal{C}([0,T],\mathcal{X}_+)$ endowed with the norm.

Let $\mathcal{Y} = \mathcal{C}([0,T],\mathcal{X}_+)$ the space of the functions continuous on [0, T] with values in a Banach space $\mathcal{X}_+$, endowed with the uniform norm

$$\| f \|_{\mathcal{Y}} = \sup_{t\in[0,T]} \| f(t) \| .$$

Making use of standard fixed point arguments, it can be shown that our Cauchy Problem (3.1) is well-posed in the sense of Hadamard (i.e. the solution exists, it is unique and depends continuously on the initial condition), as stated by the following theorems:

Theorem 3.1 (Well-posedness of the problem and non-negativity of the solution)**.** *For any initial data $f_0 \in \mathcal{X}_+$, there exist two positive constants T and a_0 such that Problem (3.1) has a unique local temporal solution $f \in \mathcal{Y}$ which satisfies the following estimate:*

$$\| f(t) \| \leq a_0 \| f_0 \|, \quad \forall t \in [0, T], \tag{3.2}$$

and

$$f \in \mathcal{X}_+ \quad \forall t \in [0, T], \tag{3.3}$$

where both a_0 and T depend on the initial data as well as on the model parameters.

The solutions of Eq. (3.1) may not exist globally in time due to possibility of uncontrolled growth. We can show the blow up of solutions for (3.1) under the following assumptions (3.4) where solutions cease to exist globally in time because of infinite evolution of the cancer cells:

$$\beta_3 - d_3 > 0, \tag{3.4}$$

where β_3 and d_3 are the proliferation rate and the destruction rate of naive immune cells respectively.

Condition (3.4) describes the case where the proliferation rate of naive immune cells is considerable compared to their destruction rate due to the interaction with others naive immune cells.

Theorem 3.2 (blow-up of solutions)**.** *If assumption (3.4) holds, then the unique nonnegative solution of (3.1) blows up in finite time, that is, there exists a blow up time, T_* such that*

$$\lim_{t \to T_*} \| f(t, .) \| = \infty.$$

Whereas, under the condition

$$\beta_3 - d_3 \leq 0, \tag{3.5}$$

where the destruction rate of naive immune cells is higher that their proliferation rate, due to interaction with other cells in the same population. Destructive interactions are introduced in the model to keep the proliferation of naive immune cells under control. The existence of solution f of Problem (3.1) can be extended over the whole real positive axis $\mathbb{R}+$, by the following theorem 3.3:

Theorem 3.3 (global existence of solutions)**.** *Given the assumption (3.5), then for any $T > 0$, there exists a unique time global solution $f(t) \in C([0, T], X_+)$ of (3.1) with initial data $f_0 \in \mathcal{X}_+$. Moreover, the solution f satisfies*

$$\sup_{t \in [0,T]} \| f(t) \| \leq C_T, \tag{3.6}$$

where C_T is a constant that depends on T and on the initial data.

3.2. Asymptotic analysis

In this subsection, we investigate the asymptotic behavior of the solution $f(t)$ of (3.1). Specifically, we are interested in the evolution of the number densities of tumor cells, n_2 and of the active immune cells, n_4. Throughout the remainder of this paper, n_{10}, n_{20}, n_{30}, and n_{40} denote the initial number densities

$n_1(0)$, $n_2(0)$, $n_3(0)$, $n_4(0)$ for epithelial cells, tumor cells, naive immune cells and active immune cells respectively.

The asymptotic behavior in time of the system (3.1) is developed in Theorems (3.4) and (3.5), whose proof relies on Lemmas (4.1) and (4.2). The action of proliferation of activated immune cells is virtually turned off, that is $\beta_4 = 0$, in order to prevent a controlled number of activated immune cells and to predict the effect of mutation events both for cancer cells (ε_1) and for active immune cells (ε_2). Referring to Eqs. (2.9)-(2.12), and to simplify notation, we introduce the following quantities:

$$K := \beta_2 n_{10} - \mu_2 n_{40} - \frac{\varepsilon_2 n_{30}}{\beta_3 - d_3}. \tag{3.7}$$

The first main result is developed in theorem (3.4). We neglect the effect of mutation in cancer progression ($\varepsilon_1 = 0$).

Theorem 3.4. *Let f be the unique solutions of Eqs.* (3.1). *If $\varepsilon_1 = 0$ then the following results ensue:*

$$\lim_{t\to+\infty} n_1(t) = n_{10}, \quad \lim_{t\to+\infty} n_3(t) = 0, \tag{3.8}$$

$$\lim_{t\to+\infty} n_2(t) \leq \frac{\beta_2 n_{10}}{d_2},\ \beta_2 \neq 0, \tag{3.9}$$

$$\lim_{t\to+\infty} n_2(t) = 0, \quad \beta_2 = 0, \tag{3.10}$$

$$\lim_{t\to+\infty} n_4(t) \leq n_{40} + \frac{\varepsilon_2 n_{30}}{d_3 - \beta_3}. \tag{3.11}$$

Theorem 3.4 reproduces the case of the immune tumor interaction. Thus under the absence of mutation event in tumor cells, the immune response could achieve, or at least control the progression of the tumor cells. The proliferation rate of the tumor cells plays a relevant role in this competition.

The second main result is presented in theorem (3.5). We give some scenarios when tumor cells escape the immune recognition and blow up, that is when $n_2(t)$ goes to infinity. The analysis takes into account the effect of mutation events on cancer. The incorporation of mutation ($\varepsilon_1 \neq 0$) on activated immune cells play a relevant role in the competition. We assume that the proliferation rate of activated cells is almost zero. In other words, we virtually turn off their value, that is $\beta_4 = 0$, in order to show how mutation events can change the progression of cancer cells.

Theorem 3.5. *Let f be the unique solutions of Eqs.* (3.1). *If $\varepsilon_1 \geq 0$ then the following results hold for the density n_2:*

• *If $\mu_2 \neq 0$, then $\exists\, n_{40}^*$, ε_2^* such that if $n_{40} < n_{40}^*$ and $\varepsilon_2 < \varepsilon_2^*$, $\exists K > 0$ such that:*

$$\lim_{t\to+\infty} n_2(t) = +\infty \quad if\ d_2 = 0, \tag{3.12}$$

$$\lim_{t\to+\infty} n_2(t) \geq \frac{K}{d_2} \qquad if d_2 \neq 0, \tag{3.13}$$

and for $d_2 = 0$, $n_{40} < n_{40}^*$ and $\varepsilon_2 > \varepsilon_2^*$ or, only if $d_2 = 0$, and $n_{40} > n_{40}^*$, $\exists\, K_1 > 0$ such that:

$$\lim_{t\to+\infty} n_2(t) \geq \frac{\varepsilon_1 n_{10}^2}{K_1}. \tag{3.14}$$

• *If $\mu_2 = 0$ then*

$$\lim_{t\to+\infty} n_2(t) = +\infty, \quad d_2 = 0, \tag{3.15}$$

$$\lim_{t\to+\infty} n_2(t) \geq \frac{\beta_2 n_{10}}{d_2}, \quad d_2 \neq 0, \tag{3.16}$$

where $K_1 = -K$ *and* K *is given by (3.7).*

Where d_2 is the destruction rate of tumor cells, and μ_2 is the immune destruction of tumor cells.

It is worth noting that the assumptions introduced here are consistent from a biological perspective. If immune response starts at $t > 0$, it seem natural to consider the effect of proliferation of tumor cells in connection with mutation effects. Finally, we point out that the above theorems apply to those cases where the focus is on the interplay between mutation and initial number of tumor and immune cells. Therefore the proliferation of activated immune cells is virtually turned off ($\beta_4 = 0$) [19, 41] in order to give critical value of ε_2 and n_{40} that separate a blow-up situation from a controlled one (see remark bellow (3.17)). Finally, we point out that theorem 3.5 reproduces some relevant cases where tumor cells escape the immune surveillance.

Remark 3.1. Using the above theorems, one can easily prove the following assertions:
1. Let $\varepsilon_1 = 0, \beta_4 = 0$, and $\mu_2, d_2 \neq 0$, which means that in the absence of the mutation events in tumor cells, and the proliferation events are almost zero, the destruction rate of tumor cells and the immune destruction of tumor cells play relevant role in the outcome of the immune-tumor competition such that then by using (3.9), and (3.13), $\exists\ n_{40}^*$, ε_2^* such that if $n_{40} < n_{40}^*$ and $\varepsilon_2 < \varepsilon_2^*$, $\exists K > 0$ such that:

$$\frac{K}{d_2} \leq \lim_{t\to+\infty} n_2(t) \leq \frac{\beta_2 n_{10}}{d_2}. \tag{3.17}$$

2. Let $\varepsilon_1 = 0$ and $\mu_2 = 0$, and $d_2 \neq 0$, which means that the immune destruction of tumor cells is also absent then, from (3.9), and (3.16), yields

$$\lim_{t\to+\infty} n_2(t) = \frac{\beta_2 n_{10}}{d_2}. \tag{3.18}$$

4. Proof of Theorems

4.1. Proof of Theorems 3.1, 3.2, and 3.3

Proof of theorem 3.1.

Problem (3.1) can be reduced to an integral equation $\Lambda[f] := f$, where Λ is a map defined by:

$$\Lambda[f] := f_0(u) + \int_0^t \Theta[f](s)ds. \tag{4.1}$$

To establish the local existence and uniqueness of solutions, we show that the map Λ is a contraction in a ball of $\mathcal{Y}$. This requires uniform estimates of Θ. Technical calculations from (2.9)-(2.12) give that $\Theta[f] \in \mathcal{X}$ for all $f,\ g\ \in \mathcal{X}$, and the following estimates hold true:

$$\| \Theta[f] \| \leq C \| f \|^2, \tag{4.2}$$
$$\| \Theta[f] - \Theta[g] \| \leq C(\| f \| + \| g \|) \| f - g \|, \tag{4.3}$$

for some constant $C > 0$ depending on the parameters and initial conditions. Therefore, for all $f,\ g\ \in \mathcal{Y}$, the following estimations hold for Λ:

$$\| \Lambda[f] \|_{\mathcal{Y}} \leq \| f_0 \| + CT \| f \|_{\mathcal{Y}}^2, \tag{4.4}$$

and

$$\| \Lambda[f] - \Lambda[g] \|_{\mathcal{Y}} \leq CT(\| f \|_{\mathcal{Y}} + \| g \|_{\mathcal{Y}}) \| f - g \|_{\mathcal{Y}} . \tag{4.5}$$

This implies there exist two constants a_0 and T, determined only by C and $\| f_0 \|$ such that Λ maps the ball in $\mathcal{Y}$ of radius a_0 into itself; on that ball Λ is Lipschitz continuous with Lipschitz constant less than 1. Thus, there exists a unique local solution $f(t)$ of (3.1) on $[0, T]$.

Next we check the nonnegativity of solution. We first re-write problem (3.1) in the following equivalent form:

$$\begin{cases} \dfrac{\partial f_i}{\partial t}(t,u) + f_i(t,u)\Psi_i[f](t,u) = \Phi_i[f](t,u), \quad (t,u) \in (0,\infty) \times (0,\infty), \\ f_{i0} = f_i(t=0,u) \in \mathcal{X}_+, \quad i = 1,..,4, \end{cases}$$

where the operators $\Psi_i[f]$ and $\Phi_i[f]$ are given by:

$$\begin{aligned}
&\Psi_1[f](t,u) = n_1(t), \\
&\Psi_2[f](t,u) = n_2(t) - \beta_2 n_1(t) + d_2 n_2(t) + \mu_2 n_4(t), \\
&\Psi_3[f](t,u) = n_3(t) - \beta_3 n_3(t) - d_3 n_3(t), \\
&\Psi_4[f](t,u) = n_4(t) - \beta_4 n_2(t) + d_4 n_4(t), \\
&\Phi_1[f](t,u) = f_1(t, u-\alpha_1)\chi_{[\alpha_1,+\infty)}(u)\, n_1(t), \\
&\Phi_2[f](t,u) = f_2(t, u-\alpha_2)\chi_{[\alpha_2,+\infty)}(u)\, n_1(t) + \varepsilon_1 f_1(t,u) n_1(t), \\
&\Phi_3[f](t,u) = f_3(t, u-\alpha_3)\chi_{[\alpha_3,+\infty)}(u)\, n_2(t),
\end{aligned}$$

and

$$\Phi_4[f](t,u) = f_4(t, u-\alpha_4)\chi_{[\alpha_4,+\infty)}(u)\, n_2(t) + \varepsilon_2 f_3(t,u) n_3(t).$$

One can check that the map Λ satisfy the following integral relation:

$$\Lambda[f] = exp\left(-\int_0^t \Psi(f)(s)ds\right) f_0(u) + \int_0^t exp\left(\int_t^\tau \Psi(f)(s)ds\right) \Phi(f)(\tau)d\tau, \tag{4.6}$$

where

$$\Psi = (\Psi_1, \Psi_2, \Psi_3, \Psi_4), \qquad \Phi = (\Phi_1, \Phi_2, \Phi_3, \Phi_4).$$

□

Proof of theorem 3.2.

Let f the non-negative maximal solution of (3.1). Integrating the third equation of (3.1) over t in $\mathbb{R}^+$, we get for all t, with $0 < t < T_{max}$:

$$\frac{\partial n_3(t)}{\partial t} = (\beta_3 - d_3) n_3^2.$$

Hence, n_3 is given by, $n_3(t) = \dfrac{1}{\frac{1}{n_{30}} - (\beta_3 - d_3)t}$, which blows up in finite time if $\beta_3 - d_3 > 0$. This completes the proof of Theorem (3.2). □

Proof of theorem 3.3.

Bearing in mind the result of Theorem (3.1), it remains to find a *priori* estimates for the solution. Integrating Eq. (2.9) with respect to u in $\mathbb{R}^+$ yields $n_1(t) = n_{10}$, then after integrating Eq. (2.10), one check that

$$\frac{\partial n_2(t)}{\partial t} \leq \beta_2 n_{10} n_2 + \varepsilon_1 n_{10}^2,$$

which gives by Gronwall's Lemma the following:

$$n_2(t) \leq (n_{20} + \frac{\varepsilon_1 n_{10}}{\beta_2}) \exp(\beta_2 n_{10} t). \tag{4.7}$$

Hence the total number of cancer cells is bounded in each finite interval $[0\ T]$.

Integrating Eq. (2.11) with respect to u, it follows under condition (3.5) that n_3 is bounded $n_3(t) \leq n_{30}$. Now, integrating (2.12) with respect to u in $\mathbb{R}^+$, yields

$$\frac{\partial n_4}{\partial t} \leq F(t) n_4 + \varepsilon_2 n_{30}^2,$$

where

$$F(t) = \beta_4 (n_{20} + \frac{\varepsilon_1 n_{10}}{\beta_2}) \exp(\beta_2 n_{10} t),$$

therefore, using Gronwall's Lemma yields

$$n_4(t) \leq n_{40} \exp(\mathcal{N}(t)) + \varepsilon_2 n_{30}^2 \exp(\mathcal{N}(t)) \int_0^t \exp(-\mathcal{N}(s)) ds := \mathcal{G}(t), \tag{4.8}$$

where $\mathcal{N}(t) = \displaystyle\int_0^t F(s) ds$.

From (4.8) one check that, n_4 is bounded on each finite time interval $[0\ T]$, and C_T in (3.6) is given by

$$C_T = n_{10} + (n_{20} + \frac{\varepsilon_1 n_{10}}{\beta_2}) \exp(\beta_2 n_{10} T) + n_{30} + \mathcal{G}(T).$$

This completes the proof of Theorem 3.3. □

4.2. Proof of Theorems 3.4 and 3.5

The proof of Theorems 3.4 and 3.5 relies on the following Lemmas:

Lemma 4.1. *Assume that $\varepsilon_1 = 0$ and $d_2 \neq 0$, then the number density of cancer cell n_2 satisfy*

1. *If $\beta_2 \neq 0$, one has the following estimate:*

$$n_2(t) \leq \frac{1}{(\frac{1}{n_{20}} - \frac{d_2}{\beta_2 n_{10}})\, e^{-\beta_2 n_{10} t} + \frac{d_2}{\beta_2 n_{10}}}, \quad \lim_{t \to +\infty} n_2(t) \leq \frac{\beta_2 n_{10}}{d_2}. \tag{4.9}$$

2. *If $\beta_2 = 0$ then,*

$$n_2(t) \leq \frac{1}{\dfrac{1}{n_{20}} + d_2 t}, \quad \lim_{t \to +\infty} n_2(t) = 0. \tag{4.10}$$

Proof. From Eq. (2.14), one has

$$\frac{\partial n_2(t)}{\partial t} \leq \beta_2 n_{10} n_2 - d_2 n_2^2, \tag{4.11}$$

then using $z = \frac{1}{n_2}$, (4.11) is reduced to the following form:

$$-\frac{\partial_t z}{z^2} \leq \frac{\beta_2 n_{10}}{z} - \frac{d_2}{z^2},$$

and hence,

$$\partial_t z \geq -\beta_2 n_{10} z + d_2.$$

Let now $\beta_2 \neq 0$, then using Gronwall's Lemma yields the following estimate:

$$z(t) \geq z_0 e^{-\beta_2 n_{10} t} + \frac{d_2}{\beta_2 n_{10}}[1 - e^{-\beta_2 n_{10} t}].$$

This completes the proof of (4.9). The proof of (4.10) can be easily derived from (2.14). This completes the proof of 4.1. □

To prove theorem 3.5, one need the following lemma 4.2:

Lemma 4.2. *Assume that $\varepsilon_1 \neq 0$ and $\beta_4 = 0$, then the number density of activated cells satisfy*

$$n_4(t) \leq n_{40} + \frac{\varepsilon_2}{\beta_3 - d_3}\left(\frac{n_{30}}{1 - n_{30}\,(\beta_3 - d_3)\,t} - n_{30}\right), \quad \forall t \geq 0. \tag{4.12}$$

Moreover the number density of cancer cell n_2 verify

- *If $d_2 = 0$, then there exists $K \in \mathbb{R}^*$ such that*

$$n_2(t) \geq n_{20} e^{Kt} + \frac{\varepsilon_1 n_{10}^2}{K}\left(e^{Kt} - 1\right), \quad \forall t \geq 0. \tag{4.13}$$

- *If $d_2 \geq 0$, then there exists $K \in \mathbb{R}^*$ such that*

$$n_2(t) \geq \frac{1}{\frac{1}{n_{20}}\exp(-Kt) + \frac{d_2}{K}(1 - \exp(-Kt))}, \quad \forall t \geq 0. \tag{4.14}$$

Proof. First, remark that from (2.15), one has $n_3(t) = \dfrac{1}{\frac{1}{n_{30}} - \alpha t}$, then by integrating (2.16) over $(0, t)$ yields (4.12). Let K given by (3.7), then, from (2.14), and (4.12), yields the following estimate:

$$\partial_t n_2 \geq K n_2 + \varepsilon_1 n_{10}^2,$$

and then Gronwall's Lemma gives (4.13). Let now $d_2 \geq 0$, then from (36.b), one has:

$$\partial_t n_2 \geq K n_2 - d_2 n_2^2$$

which can be written by using $z = \frac{1}{n_2}$ in the following form:

$$\partial_t z(t) \leq -K z + d_2,$$

therefore

$$z \leq z_0 exp(-Kt) + \frac{d_2}{K}(1 - exp(-Kt)),$$

This completes the proof of Lemma (4.2) □

Proof of Theorems 3.4 and 3.5. The proof of Theorem 3.4 comes directly from Lemma 4.1. The proof of Theorem 3.5 comes from Lemma 4.2. Indeed, the result in (3.11) comes from (4.12). To prove the results in (3.12)-(3.14), we assume that $\mu_2 \neq 0$, that is, the immune destruction rate of tumor cells take nonzero value , then if $d_2 = 0$, that is the destruction rate of tumor cells equals to zero, one has (4.13). Let n_{40}, ε_2 are such that

$$n_{40} < \frac{\beta_2 n_{10}}{\mu_2} := n_{40}^*, \quad \varepsilon_2 < \frac{\beta_3 - d_3}{\mu_2 n_{30}}\Big(\mu_2 n_{40} - \beta_2 n_{10}\Big) := \varepsilon_2^*,$$

then K given by (3.7) is strictly positive, and (3.12), (3.13) come respectively from (4.13), and (4.14).

Now let $d_2 = 0$, then if $n_{40} < n_{40}^*$, and $\varepsilon_2 > \varepsilon_2^*$, or if only $n_{40} > n_{40}^*$, one has $K < 0$. Let $K_1 = -K > 0$, and then (3.14) comes from (4.13).

Let $\mu_2 = 0$, then if $d_2 = 0$, one has from (2.14):

$$\partial_t n_2 \geq \beta_2 n_{10} n_2 + \varepsilon_1 n_{10}^2,$$

and Gronwall's Lemma gives (3.15).

Now let $d_2 \neq 0$, then again using (2.14), yields

$$\partial_t n_2 \geq \beta_2 n_{10} n_2 - d_2 n_2^2,$$

and hence

$$n_2(t) \geq \frac{1}{\frac{1}{n_{20}} exp(-\beta_2 n_{10} t) + \frac{d_2}{\beta_2 n_{10}}(1 - exp(-\beta_2 n_{10} t))}, \quad \forall t \geq 0, \tag{4.15}$$

and then (3.16) comes from (4.15). This completes the proof of Theorems 3.4 and 3.5. □

5. Numerical study

The system (2.9)-(2.10) is first solved numerically by discretizing the equations with respect to the variable u [13] and then using a quadrature rule to approximate integral terms.

5.1. The approximation methods

Here, we consider a partition of the set $[a, b]$ of the variable u with N collocation points

$$h = \frac{b-a}{N-1}, \; u_j = \frac{j-1}{h}, \; j = 1, ..., N.$$

The distribution functions are interpolated as follows:

$$f_i^N(t, u) = \sum_{j=1}^{j=N} \mathcal{S}_j(u, h) f_{ij}(t), \quad \forall i \in 1, .., 4,$$

where

$$\mathcal{S}_j(u,h) = \frac{h}{\pi\,(u-(j-1)h)}\sin(\frac{\pi}{h}(u-(j-1)h)),$$

$S_j(u_k,h) = \delta_{jk}$, where δ_{jk} is the Kronecker delta.

The number density is approximated by the following quadrature rule:

$$\int_0^b f_i(t,u)du \simeq \sum_{j=1}^{M} f_{ij}(t), \tag{5.1}$$

Accordingly, we obtain a system of ordinary differential equations which define the evolution of the distribution functions f_j in the node u_j, where

$$f_{ij}(t) = f_i(t,u_j).$$

5.2. Simulation results

Numerical simulations are addressed to show the onset of tumor cells and activated immune cells. In particular, as objectives of simulations, we focus on the following two aspects among conceivable ones:

The aim of the numerical study is to show some dynamics of the tumor-immune cell competition in the presence of the mutation events. We are also interested in determining the conditions under which the activated immune system can win the competition by achieving a total regression of the tumor activity. Herein, we address the following two main aspects of the tumor-immune dynamics: (1) the sensitivity of the proliferation rate (β_2) of tumor cells and phenotypic mutation of activated immune cells (ε_2), and (2) the sensitivity of phenotypic mutations of tumor cells (ε_1) and activated immune cells (ε_2). In view of this, we assume that nine of the twelve parameters are fixed. While the others span from zero to higher values; for the first objective, we vary β_2 and ε_2, and for the second objective, we vary ε_1 and ε_2.

Simulations are performed by assuming small amount of epithelial, tumor and immune cells. That is, we take $f_i(0)$, $i = 1,2,3,4$ to be of the order 10^{-2} cells.

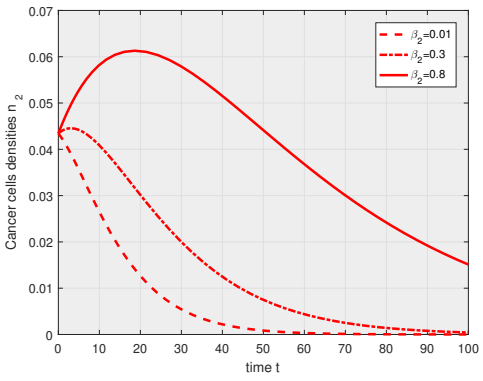


Figure 1. Numerical simulation of the model showing the evolution of the number density of cancer cells versus time for different value of their proliferation rate. The mutation events are absent, that is, $\varepsilon_1 = 0$ and $\varepsilon_2 = 0$

The parameters values used in this simulation are: $\alpha_1 = 0.2$, $\alpha_2 = 0.3$, $\alpha_3 = 0.3$, $\alpha_4 = 0.3$, $\mu_2 = 0.5$, $\beta_4 = 0$, $d_4 = 0.05$, $\beta_3 = 0.2$, $d_3 = 0.5$ corresponding to a non-negligible effect to the progression (α_1 and α_2), a low ability to degenerate (α_3), low ability to increase the malignancy (α_4), low proliferation rate of naive immune cells (β_3), absence of proliferation events (β_4), an low destruction of immune cells (d_3 and d_4), and not to aggressive immune response of the activated immune cells (μ_2).

(i) *Effect of the proliferation rate β_2 and the immune mutation rate ε_2.*

As a first step of simulations and in consistency with Theorem 3.4, we consider the onset of tumor cells and their competition with activated immune cells for different value of the proliferation rate β_2. Specifically, fixing the parameters of the model as indicated above. We set $\varepsilon_1 = 0$ which corresponds to the absence of mutation effect in tumor progression and let β_2 vary. It is expected that increasing values of β_2 generate increasing manifestation of cancer cells progression.

For low *proliferation rate* ($\beta_2 = 0.01$), see Fig. 1, the number density of tumor cells decreases until a total depletion. This trend toward zero becomes low with the increase of β_2 to an intermediate value. However, higher value of $\beta_2 = 0.8$ tumor cells express a tendency to progress. Indeed, the role of conservative interactions that shift population of tumor cells toward increasing value of malignancy is evident (by parameter α_2 in Eq. 2.10).

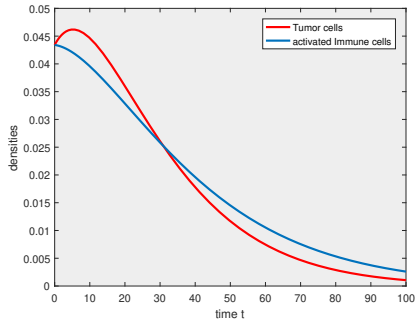
Now, as second step, we chose an intermediate value of $\beta_2 = 0.5$ and vary the mutation rate of activated immune cells ε_2 from lower value $\varepsilon_2 = 0$ to higher one $\varepsilon_2 = 0.7$. Fig. 2 illustrates the impact of small mutation in activated immune cells on the immune competition. Comparing panels of Fig. 2, it is clear that increasing ε_2 the activated immune cells are able to contrast and achieve the regression of tumor cells. Increasing ε_2, simulations show an initial growth of activated immune cells up to a maximum value, corresponding to an initial phase characterized by a strong ability to destroy cancer cells. In the meantime, activated immune system start to decrease down to an asymptotic value, where the number of tumor cells are kept under control. Fig. 3 highlights how increasing ε_2 from 0 to 0.6 affect the behavior of the distribution functions of activated immune cells.

(ii) *Effect of the phenotypic mutation rates of the tumor and immune cells ε_1 and ε_2 respectively.*

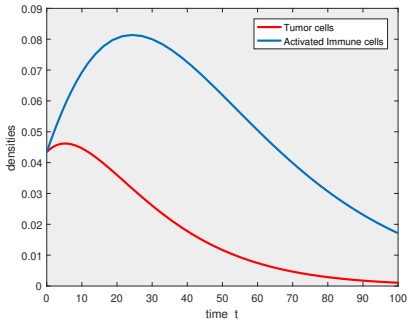
In this second part of simulation, we analyze the sensitivity of the model with respect to the parameters ε_1 and ε_2 To do so, we perform another simulation by changing the values of mutation rates of tumor cells ε_1 accordingly. Fixing the parameters of the model as indicated above and in consistency with theorem (3.5) we set

$$n_{40}^* = 0.1, \quad \varepsilon_2^* = 0.03, \quad d_2 = 0.1.$$

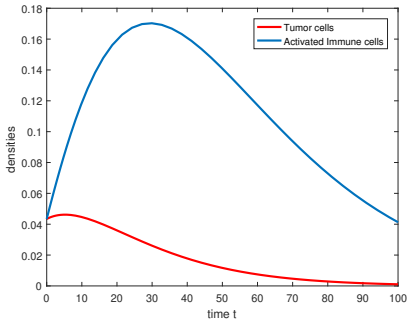
The results are shown in Fig. 4 where the number density of tumor cells n_2 versus time for fixed $\varepsilon_2 = 0$. Increasing the mutation rate of tumor cells ε_1 from $\varepsilon_1 = 0.01$ on, simulations show an initial growth of tumor cells up to a maximum value, corresponding to an initial phase characterized by a rapid clonal expansion, able to suppress the immune reaction. In the main time, mutated tumor cells start



(a) $\varepsilon_1 = 0$ $\beta_2 = 0.6$ and $\varepsilon_2 = 0$

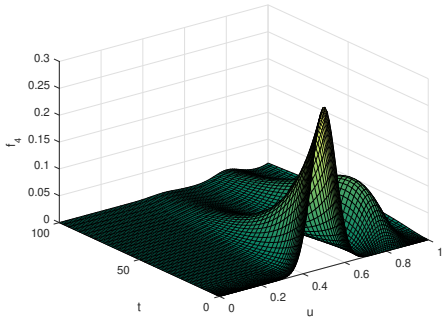


(b) $\varepsilon_1 = 0$ $\beta_2 = 0.6$ and $\varepsilon_2 = 0.3$



(c) $\varepsilon_1 = 0$ $\beta_2 = 0.6$ and $\varepsilon_2 = 0.7$

Figure 2. Numerical simulation of the model (2.9)-(2.10) showing the evolution the evolution of tumor cells (n_2) and activated immune cells (n_4) versus time t.



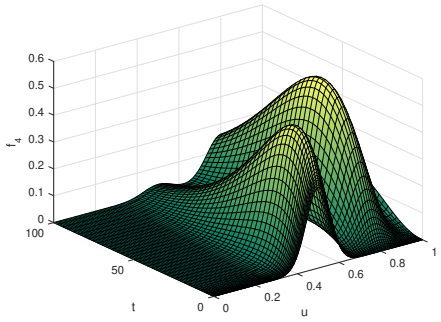


Figure 3. Numerical simulation of the model (2.9)-(2.10) showing the evolution of the distribution functions $f_2(t, u)$ for $\varepsilon_2 = 0$ (left panel) and $\varepsilon_2 = 0.6$ (right panel). These two figures are performed with an intermediate value of $\beta_2 = 0.2$ and $\varepsilon_1 = 0$

to decreases down to an asymptotic value. This behavior is consistent with results in remark (3.17) and (3.18).

Letting an intermediate mutation rate of tumor cells $\varepsilon_1 = 0.2$, we choose $n_{40} = 0.015$ and $\varepsilon_2 = 0.01$. The graphs in Fig. 5 illustrates the results established in

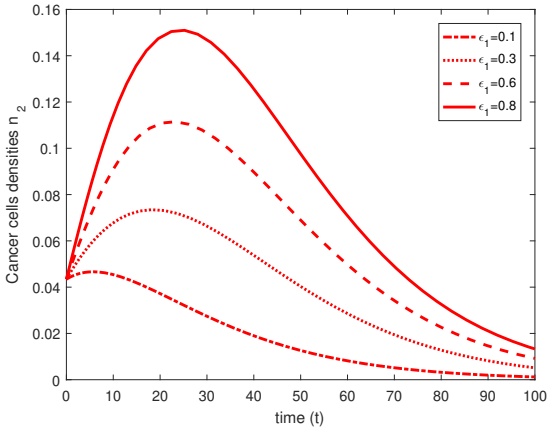


Figure 4. Numerical simulation of the model (2.9)-(2.10) showing the evolution of n_2 versus time, for different values of ε_1. The mutation events in activated immune cells are absents $\varepsilon_2 = 0$

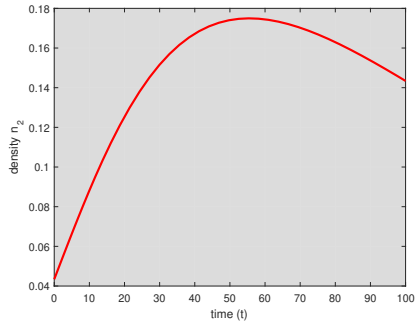
theorem (3.5) depending on the value of the destruction rate of tumor cells d_2. Indeed, activated immune cells acquire the ability to contrast and control a rapid progression of tumor cells.

6. Conclusion

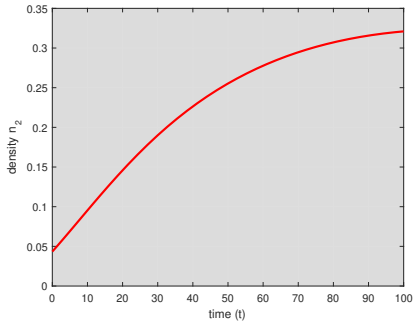
In this work, we have derived a phenomenological model base on the kinetic theory of active particles describing the tumor-immune interactions under some phenotypic mutations. In doing so, we considered four interacting cell populations, that are the main players in the immune competition process, which are, epithelial cells, tumor cells, naive, and activated immune cells. For all participating cells populations, we have defined an activity variable based on their biological functions. By describing the binary cell interactions, we were able to derive the kinetic equations, namely the evolution equations of the distribution functions related to each interacting population. We proved the well-posedness of the related Cauchy problem and the non-negativity of the solution. We gave sufficient condition for which the solution may not exist globally in time. In particular, we proved the blow up result for the initial value problem. A detailed asymptotic analysis is developed in Theorems 3.4 and 3.5, with the aim to predict the effect of mutation events both on tumor cells and activated immune cells. We showed that under some critical value of the mutation rate and initial number densities of activated immune cells, we can specify some biological states of the blow up of tumor cells. Indeed, the analysis gives useful indications to be properly explored toward the design of therapeutical actions.

Additionally, the numerical simulations show some cases where the tumors cell are completely eliminated. An initial time growth up to maximum value corresponding to a faster activation of activated immune cells is also noted. In the main time, the tumor is suppressed or controlled, and activated immune cells is still being activated. Identifying the phenomenological parameters of the model is a challenge due to the lack of the experimental data at the microscopic level.

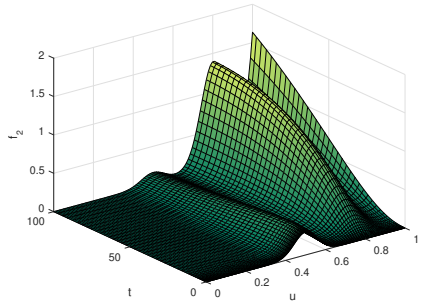
Nonetheless, developing such single-cell mathematical models of the tumor-immune competition may lead to the characterization of these parameters by the-



(a) $n_{40} = 0.015$ $\varepsilon_1 = 0.2$ $d_2 = 0.6$ and $\varepsilon_2 = 0.01$



(b) $n_{40} = 0.015$ $\varepsilon_1 = 0.2$ $d_2 = 0.0$ and $\varepsilon_2 = 0.01$



(c) $n_{40} = 0.015$ $\varepsilon_1 = 0.2$ $\beta_2 = 0.6$ and $\varepsilon_2 = 0.01$

Figure 5. Numerical simulation of the model (2.9)-(2.10) showing the evolution the evolution of tumor cells (n_2) versus time t in the case $\varepsilon_2 < \varepsilon_2^* = 0.03$ et $n_{40} < n_{40}^* = 0.1$

oretical approaches based on methods of immunology. In this paper, we modeled activated immune system as one whole population. Our model can be easily extended to include other subpopulations of the immune system with the aim of specializing the biological functions within each population. For example we can distinguish multiple stages of activation based on the idea of post-Darwinian evolution developed in [16, 22]. We plan to develop an asymptotic analysis with the challenge to include an artificial inlet which represents an external drug therapy.

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