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Research Article

A contribution to the mathematical modeling of immune-cancer competition

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Abstract

This paper deals with the modeling of interactions between the immune system and cancer cells, in the framework of the mathematical kinetic theory for active particles. The work deepens a previous paper of Belloquid et al. that assumes spatial homogeneity and discrete values of the activity of cancer and immune cells. A number of simulations are made with the aim to investigate how the state of the various cell populations evolves in time depending on the choice of the free parameters.

Keywords: Kinetic Theory,active particles,evolution.
AMS subject classification: 92D15, 34C60, 37N25

1. Introduction

Cancer is a large class of very different diseases, all of which grow uncontrollably and have the ability to spread, or metastasize, throughout the body. A solid basis for tumor and cancer researches was provided by the seminal article published by Hanahan and Weinberg [1], [2]. These authors argued that the complexity of cancer can be reduced to a small number of underlying principles.

Normal cells grow and divide, but its growth is kept under control by growth-inhibitors or signals. These inhibitors act on the cell cycle clock, by interrupting cell division. If normal cells are damaged, they interrupt its cycle of life, until the damage is repaired. If they can't be repaired, they commit cell suicide (apoptosis).

Cancer cells generally have severe chromosomal abnormalities, which worsen as the disease progresses. They have defects in the control mechanisms that govern how often they divide, and are able to stimulate their own growth, due to the dominant character of oncogenes. Embryonic stem cells have an innate programme for self-replication that does not require extrinsic instruction. In a similar way, tumor cells do not need stimulation from external signals (in the form of growth factors) to multiply. They are characteristically able to overcome apoptosis to progress. This lead to an uncontrolled cell proliferation, such as cancer.

Normal cells are part of a tissue structure, and remain where they belong. Cancer cells have the ability to stimulate the growth of blood vessels to supply nutrients to tumors. They can move away from their site of origin to invade adjacent tissue or spread to distant sites. Local chronic inflammation have an important role in inducing many types of cancer.

Recent medical and biological studies give evidence that immune system can recognize and eliminate malignant tumors. In fact, the immune system plays an important role in these dynamics. The term immune system identifies a variety of different cells and molecules which provide a strong and effective defense against pathogenic agents. As a matter of fact, immune cells have a strategy to learn the presence of carriers of a pathology and attempt to deplete them. It is a complex process where immune cells, starting from the innate immunity, improve their action by learning the so-called acquired immunity and identifies the hallmarks of cancer to escape the immune defence.

Mathematical models may be useful for a better understanding of the mechanisms that governs the interaction between immune system and cancer cells. In [3] an important first study was made to put the ideas of Hanahan and Weinberg in a general mathematical framework. The approach used is based on the *Kinetic Theory of Active Particles* [4], [5], [6], [7], [8], [9], that has been specifically developed to model complex systems [10], [11]. Mostly, this approach was initiated by the pioneer paper [12]. According to KTAP, the overall system is divided into different populations (functional subsystems) each of them consisting of entities called *active particles* which collectively express the same function called *activity*. The evolution of each functional subsystem is described by a distribution function and the time evolution of the subsystem is governed by interactions [13].

The model proposed in [3] to describe the competition between cancer cells and immune system is characterized by 8 functional subsystems. The first four subsystems contain epithelial (subsystem 1) and cancer cells (subsystems 2,3,4), the other functional subsystems contain cells of the immune system. Normal epithelial cells can generate daughter cells with the first hallmark of cancer. These newborn cells can generate, despite the contrast of the immune system, daughter cells with the subsequent hallmarks. The dynamics of the competition may end up either with the suppression of cancer cells or with their indefinite growth, with aggregation into tumor structures, characterizing the passage from the microscopic to the macroscopic scale.

In this paper, a detailed analysis of the model proposed in [3] is made, and a number of simulations is presented, aiming at investigating how the state of the various functional subsystems evolve in time, depending on the choice of the free parameters. In several cases the learning action of the immune system is sufficient to contrast this process. However, for some values of the free parameters present in the model, tumor cells may continue to grow. The goal of this analysis is to determine the critical values of the free parameters that characterize the transition to a malignant tumor (black swan).

This paper will be divided into four sections which follow this introduction. Specifically: Section 2, briefly outlines the paper of Bellouquid, De Angelis and Knopof [3], which is the starting point of this paper. Section 3 presents a variety of simulations to investigate how the different parameters influence the dynamical behavior of the system. In Section 4, the results of the previous section will be discussed.

2. Modeling immune-cancer competition

This section provides a concise description of the model proposed by Bellouquid et al. [3]. As it is known, the cancer is a kind of cellular disorder which allows certain cellular populations to manifest deviant characteristics. When abnormal 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. To put in a mathematical framework this process, Bellouquid et al. [3] make use of the KTAP, identifying the following eight different cell populations (functional subsystems).

- $i = 1$ *Normal epithelial cells.* It is supposed that the organism is a source of epithelial cells, so their quantity can be regarded as constant in time;
- $i = 2$ *Cancer cells of the first hallmark* that have the ability to thrive in a chronically inflamed micro-environment;
- $i = 3$ *Cancer cells of the second hallmark*, that have the ability to evade the immune recognition;
- $i = 4$ *Cancer cells of the third hallmark* that have acquired the ability of suppressing the immune reaction;
- $i = 5$ *Cells of the innate immune system* which have the ability to acquire, by a learning process, the capacity of contrasting the development of cancer cells of the first hallmark (labeled by $i = 2$);
- $i = 6$ *Cells of the adaptive immune system* which have the ability of contrasting the development of cancer cells labeled by $i = 2$;
- $i = 7$ *Cells of the adaptive immune system* which have the ability of contrasting the development of cancer cells labeled by $i = 2$ and $i = 3$;
- $i = 8$ *Cells of the adaptive immune system* which have the ability of contrasting the development

of cancer cells labeled by $i = 2$, $i = 3$ and $i = 4$.

In this model the activity variable attains values in a discrete set as follows:

$$u \in I_u = \{0 = u_1, \cdots, u_j, \cdots, u_m = 1\} \qquad \text{with } u_j < u_{j+1}$$

The overall state of the system is described by the discrete generalized distribution functions $f_{ij} = f_i(u_j, t) = f_{ij}(t)$, $i = 1, \cdots, 8$,$j = 1, \cdots, m$. The index i labels each subsystem, j labels the activity variable, and $f_{ij}(t)$ represents the number of active particles of the functional subsystem i which have the state u_j at time t. The number density of the i-th population is given by:

$$n_i[\mathbf{f}](t) = \sum_{j=1}^{m} f_{ij}(t), \qquad i = 1, \cdots, 8 \tag{1}$$

2.1. *Dynamics of Cellular Interactions*

In the KTAP, the interactions involve three types of particles: test, field and candidate. The interaction rule is as follows: candidate particles can acquire, in probability, the state of the test particles, after an interaction with field particles, while test particles lose their state after interactions. The time evolution of the distribution functions f_{ij} can be described with the following system of balance equations:

$$\frac{df_{ij}(t)}{dt} = C_{ij}[\mathbf{f}](t) + M_{ij}[\mathbf{f}](t) + P_{ij}[\mathbf{f}](t) - D_{ij}[\mathbf{f}](t) - L_{ij}[\mathbf{f}](t) \tag{2}$$

with C_{ij}, M_{ij}, P_{ij}, D_{ij} and L_{ij} suitable operators acting over the whole set of distribution functions and $\mathbf{f} = (f_{ij})$. Specifically,

- $C_{ij}[\mathbf{f}](t)$ is the net flux, at time $t \in [0, T]$, into the state u_j of the functional subsystem i, due to conservative interactions that only modify the micro-state;
- $P_{ij}[\mathbf{f}](t)$ is the gain, at time $t \in [0, T]$, into the state u_j of the functional subsystem i, due to proliferative events that occur within the same functional subsystem;
- $M_{ij}[\mathbf{f}](t)$ is the gain, at time $t \in [0, T]$, into the state u_j of the functional subsystem i, due to mutation events, where a daughter cell occurs in a subsystem different from that of the mother cell;
- $D_{ij}[\mathbf{f}](t)$ $(i = 2, 3, 4)$ is the loss, at time $t \in [0, T]$, in the state u_j of the functional subsystem i, due to destructive events;
- $L_{ij}[\mathbf{f}](t)$ $(i = 5, 6, 7, 8)$ model the natural relaxation (of the immune system) to a given healthy state.

In general, a different modeling approach has to be considered for cells of the various different functional subsystems. Briefly, the addends in (2) are modeled as follows:

$$C_{ij}[\mathbf{f}] = \sum_{k=1}^{8} \sum_{p=1}^{m} \sum_{q=1}^{m} \eta_{ik}[\mathbf{f}]\, \mathcal{B}_{ik}^{pq}(j)[\mathbf{f}]\, f_{ip} f_{kq} - f_{ij} \sum_{k=1}^{8} \sum_{q=1}^{m} \eta_{ik} f_{kq}, \tag{3}$$

$$P_{ij}[\mathbf{f}] = \sum_{h=1}^{8} \sum_{k=1}^{8} \sum_{p=1}^{m} \sum_{q=1}^{m} \eta_{hk}[\mathbf{f}] \mathcal{P}_{hk}^{pq}(ij) f_{hp} f_{kq}, \tag{4}$$

$$M_{ij}[\mathbf{f}] = \sum_{h=1}^{8} \sum_{k=1}^{8} \sum_{p=1}^{m} \sum_{q=1}^{m} \eta_{hk}[\mathbf{f}] \mathcal{M}_{hk(h=i+1)}^{pq}(ij) f_{hp} f_{kq}, \tag{5}$$

$$D_{ij}[\mathbf{f}] = f_{ij} \sum_{k=1}^{8} \sum_{q=1}^{m} \eta_{ik}[\mathbf{f}] \mathcal{D}_{ik}^{jq} f_{kq}, \qquad (i = 2, 3, 4), \tag{6}$$

$$L_{ij}[\mathbf{f}] = \lambda_i (f_{ij} - f_{ij}^0), \qquad (i = 5, 6, 7, 8). \tag{7}$$

The quantities related to the interaction terms above are defined as follows:

- $\eta_{hk} = \eta_{hk}[\mathbf{f}](u_p, u^q)$ is the encounter rate between the hp candidate-cell, with state u_p, of the h-th subsystem and the kq field-cell, with state u^q, of the k-th subsystem;
- $\mathcal{B}_{ik}^{pq} = \mathcal{B}_{ik}^{pq}[\mathbf{f}](j)$ is the probability density that the ip candidate-cell, with state u_p, of the i-th subsystem ends up into the state j of the test-cell of the same subsystem after the interaction with the kq field-cell, with state u^q, of the k-th subsystem. $\mathcal{B}_{ik}^{pq}$ satisfies, for all $i, k \in \{1, 2, \ldots, 8\}$ and $j = 1, ..., m$, the following condition:

$$\sum_{i=1}^{8}\sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\mathcal{B}_{ik}^{pq}[\mathbf{f}](u_p \to u|u_p, u^q) = 1, \quad \forall\, u_p, u^q \in D_u. \tag{8}$$

- $\mathcal{P}_{hk}^{pq} = \mathcal{P}_{hk}^{pq}[\mathbf{f}](ij)$ models the proliferative events, where generation of a daughter cell occurs in the same subsystem of the mother cell.
- $\mathcal{M}_{hk}^{pq} = \mathcal{M}_{hk}^{pq}[\mathbf{f}](ij)$ models the mutations events, where generation of a daughter cell occurs in a subsystem different from that of the mother cell.
- $\mathcal{D}_{ik}^{pq} = \mathcal{D}_{ik}^{pq}[\mathbf{f}](ij)$ models the destruction events. Interactions can induce net destructive events in the sense that the immune system has the ability to kill a cancer cell.
- λ_i $(i = 5, 6, 7, 8)$ refer to the natural tendency of the (acquired) immune system to relax to a given (primitive) state.

2.2. *Encounter Rate*

An important concept, that is useful in the definition of the encounter rate, is the introduction of a *distance* d_{hk} between the cells of the h-th and the k-th functional subsystems. An hypothesis often used in the KTAP is that the encounter rate depends on the distance between the interacting particles: $\eta_{hk}[\mathbf{f}] = \eta_{hk}[\mathbf{f}](d_{hk})$. Different distances can be chosen depending on the system in consideration [10]. Bellouquid et al. [3] assumed that the distance d_{hk} is a functional of the distributions that characterize the two interacting populations, and defined the encounter rate $\eta_{hk}[\mathbf{f}]$ as follows:

$$\eta_{hk}[\mathbf{f}] = \eta_{hk}^{(0)}[\mathbf{f}]\, d_{hk}[\mathbf{f}], \tag{9}$$

where

$$d_{hk}[\mathbf{f}] = \begin{cases} \exp\left(-\tau \dfrac{\|f_h - f_k\|}{\|f_h\| + \|f_k\|}\right), & \|f_h\|, \|f_k\| \neq 0, \tau > 0, \\ 0, & \|f_h\| = \|f_k\| = 0, \end{cases} \tag{10}$$

and τ is a positive real constant. The function $\eta_{hk}^{(0)}$ is assumed proportional to h, for epithelial and cancer cells, ($\eta_{h1}[\mathbf{f}] = \eta_0 h\, d_{h1}[\mathbf{f}]$, for $h = 2, 3, 4$, and with $\eta_0 > 0$), while is assumed constant for the encounters between immune and cancer cells ($\eta_{hk}[\mathbf{f}] = \eta_0 \sigma\, d_{hk}[\mathbf{f}]$, with $\sigma > 0$). The dimensionless parameter η_0 corresponds to interaction between epithelial cells and cancer cells and can be included in the time scale. Thus one gets the following matrix expression for the encounter rate:

$$\eta_{hk} = \begin{pmatrix} d_{11} & 2d_{21} & 3d_{31} & 4d_{41} & 0 & 0 & 0 & 0 \\ 2d_{21} & 0 & 0 & 0 & \sigma d_{52} & \sigma d_{62} & \sigma d_{72} & \sigma d_{82} \\ 3d_{31} & 0 & 0 & 0 & 0 & \sigma d_{63} & \sigma d_{73} & \sigma d_{83} \\ 4d_{41} & 0 & 0 & 0 & 0 & 0 & \sigma d_{74} & \sigma d_{84} \\ 0 & \sigma d_{52} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma d_{62} & \sigma d_{63} & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma d_{72} & \sigma d_{73} & \sigma d_{74} & 0 & 0 & 0 & 0 \\ 0 & \sigma d_{82} & \sigma d_{83} & \sigma d_{84} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{11}$$

2.3. *Transition Probability Density*

Conservative interactions refer to progression phenomena that lead to an increasing activity within the same subsystem. Thus, they do not modify the size of the populations. The terms $\mathcal{B}_{ik}^{pq}(j)$ represent the probability density that a candidate-cell with state u_p, of the i-th subsystem ends up into the state u_j of the test-cell of the same subsystem after the interaction with the field-cell, with state u^q, of the k-th subsystem. The function $\mathcal{B}_{ik}^{pq}(j)$ has different expressions for the subsystems $i = 1, 2, 3, 4$ corresponding to epithelial and cancer cells and the subsystems $k = 5, 6, 7, 8$ corresponding to immune system cells. Following Bellouquid et al. [3], we assume the following matrix expression for the transition probability density:

$$\mathcal{B}_{ik}^{pq} = \begin{pmatrix} \mathcal{B}_{11}^{pq} & 1 & 1 & 1 & 0\,0\,0\,0 \\ \mathcal{B}_{21}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ \mathcal{B}_{31}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ \mathcal{B}_{41}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ 0 & \mathcal{B}_{52}^{pq} & 0 & 0 & 0\,0\,0\,0 \\ 0 & \mathcal{B}_{62}^{pq} & 0 & 0 & 0\,0\,0\,0 \\ 0 & 0 & \mathcal{B}_{73}^{pq} & 0 & 0\,0\,0\,0 \\ 0 & 0 & 0 & \mathcal{B}_{84}^{pq} & 0\,0\,0\,0 \end{pmatrix} \tag{12}$$

In particular we have:

- *Interactions of subsystem $h = 1$ with subsystems $k = 2, 3, 4$.* In this case, epithelial cells are assumed to feed progression of cancer cells without changing their own state:

$$\mathcal{B}_{1k}^{pq}(p) = 1. \tag{13}$$

- *Interactions of subsystems $h = 1, 2, 3, 4$ with subsystem $k = 1$.* We will assume that the probability of transition depends on the interacting populations and decrease with the activity state of the candidate-cell. So we assume the following:

$$\mathcal{B}_{h1}^{pq}(j) = \begin{cases} \alpha\,(1 - u_p)\,, & j = p + 1,\ \alpha \in (0, 1], \\ 1 - \alpha\,(1 - u_p)\,, & j = p, \\ 0 & \text{otherwise.} \end{cases} \tag{14}$$

- *Interactions of subsystems $h = 5, 6, 7, 8$ with subsystems $k = 2, 3, 4$.* Immune cells acquire progressively the ability to identify functional subsystems of cancer cells. Thus, we assume:

$$\mathcal{B}_{52}^{pq}(j) = \mathcal{B}_{62}^{pq}(j) = \mathcal{B}_{73}^{pq}(j) = \mathcal{B}_{84}^{pq}(j) = \begin{cases} \alpha\,(1 - u_p)\,, & j = p + 1, \\ 1 - \alpha\,(1 - u_p)\,, & j = p, \\ 0, & \text{otherwise.} \end{cases}$$

and $\alpha \in (0, 1]$.

2.4. *Modeling Proliferative Events*

The proliferative events dynamics is modeled as follows: A candidate-cell (mother cell) of subsystem h with state p, by interacting with a field-cell from subsystem k, with state q, proliferate a daughter cell of the same subsystem, and with the same activity. Following Bellouquid et al. [3], these events are

modeled by the following matrix expression:

$$\mathcal{P}_{hk} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0\,0\,0\,0 \\ \mathcal{P}_{21}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ \mathcal{P}_{31}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ \mathcal{P}_{41}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ 0 & 0 & 0 & 0 & 0\,0\,0\,0 \\ 0 & \mathcal{P}_{62}^{pq} & 0 & 0 & 0\,0\,0\,0 \\ 0 & \mathcal{P}_{72}^{pq} & \mathcal{P}_{73}^{pq} & 0 & 0\,0\,0\,0 \\ 0 & \mathcal{P}_{82}^{pq} & \mathcal{P}_{83}^{pq} & \mathcal{P}_{84}^{pq} & 0\,0\,0\,0 \end{pmatrix} \tag{16}$$

In particular we assume the following:

- *Proliferation in Cancer Subsystems* is related with the encounters with cells of the subsystem $k = 1$. In this case, the proliferation increases with the hallmarks of cancer cells. So, we assume:

$$\mathcal{P}_{h1}^{pq}(hj) = \begin{cases} \beta_1 h u_p, & \text{with } j = p,\ \beta_1 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{17}$$

- *Proliferation in immune cells subsystems* $h = 6, 7, 8$. Immune cells proliferate due to the interactions with the cancer cells $k = 2, 3, 4$, with the following rule:

$$\mathcal{P}_{hk}^{pq}(hj) = \begin{cases} \beta_2, & \text{with } j = p,\ \beta_2 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{18}$$

2.5. *Modeling Mutation Events*

Mutation events refer to changing in the genes where a daughter cell occurs in a subsystem different from that of the mother cell. This event is modeled by the term $\mathcal{M}_{hk}^{pq}(ij)$, where $i = h + 1$ with output into the state $j = 1$. We will choose for the rate $\mathcal{M}_{hk}^{pq}(ij)$ the following matrix expression:

$$\mathcal{M}_{hk}^{pq} = \begin{pmatrix} \mathcal{M}_{11}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ \mathcal{M}_{21}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ \mathcal{M}_{31}^{pq} & 0 & 0 & 0 & 0\,0\,0\,0 \\ 0 & 0 & 0 & 0 & 0\,0\,0\,0 \\ 0 & \mathcal{M}_{52}^{pq} & 0 & 0 & 0\,0\,0\,0 \\ 0 & 0 & \mathcal{M}_{63}^{pq} & 0 & 0\,0\,0\,0 \\ 0 & 0 & 0 & \mathcal{M}_{74}^{pq} & 0\,0\,0\,0 \\ 0 & 0 & 0 & 0 & 0\,0\,0\,0 \end{pmatrix} \tag{19}$$

with the following assumptions [3]:

- *Mutations in the cancer subsystems* $h = 1, 2, 3$. These events are related to encounters with cells of subsystem $k = 1$. The rate $\mathcal{M}_{h1}^{pq}(ij)$ is defined as follows:

$$\mathcal{M}_{h1}^{pq}(ij) = \begin{cases} \varepsilon_1 u_p, & \text{with } i = h + 1, j = 1, \varepsilon_1 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{20}$$

- *Mutations in immune subsystems* $h = 5, 6, 7$. These are related to an increasing capability of the immune cells to recognize a specific cancer hallmark $k = 2, 3, 4$. As in [3], we assume:

$$\mathcal{M}_{52}^{pq}(6j) = \begin{cases} \varepsilon_{26} u_p, & \text{with } j = 1, \varepsilon_{26} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{21}$$

$$\mathcal{M}_{63}^{pq}(7j) = \begin{cases} \varepsilon_{27} u_p & \text{with } j = 1, \varepsilon_{27} > 0 \\ 0 & \text{otherwise.} \end{cases} \tag{22}$$

$$\mathcal{M}_{74}^{pq}(8j) = \begin{cases} \varepsilon_{28} u_p & \text{with } j = 1, \varepsilon_{28} > 0 \\ 0 & \text{otherwise.} \end{cases} \tag{23}$$

2.6. *Modeling Destructive Events*

The dynamics of the destructive interactions follows the subsequent rules. Only cancer cells can be destructed because immune cells have the ability to suppress them after they are identified. It is assumed that this ability increases with increasing activity of immune cells. For the rate $\mathcal{D}_{hk}^{pq}$, we assume the following matrix:

$$\mathcal{D}_{hk}^{pq} = \begin{pmatrix} 0\,0\,0\,0\,0 & 0 & 0 & 0 \\ 0\,0\,0\,0\,0 & \mathcal{D}_{26}^{pq} & \mathcal{D}_{27}^{pq} & \mathcal{D}_{28}^{pq} \\ 0\,0\,0\,0\,0 & 0 & \mathcal{D}_{37}^{pq} & \mathcal{D}_{38}^{pq} \\ 0\,0\,0\,0\,0 & 0 & 0 & \mathcal{D}_{48}^{pq} \\ 0\,0\,0\,0\,0 & 0 & 0 & 0 \\ 0\,0\,0\,0\,0 & 0 & 0 & 0 \\ 0\,0\,0\,0\,0 & 0 & 0 & 0 \\ 0\,0\,0\,0\,0 & 0 & 0 & 0 \end{pmatrix} \tag{24}$$

where $\mathcal{D}_{26}^{pq} = \mathcal{D}_{27}^{pq} = \mathcal{D}_{28}^{pq} = \mathcal{D}_{37}^{pq} = \mathcal{D}_{38}^{pq} = \mathcal{D}_{48}^{pq} = \gamma u_q$ and $\gamma > 0$.

2.7. *Modeling the Relaxation Terms*

The immune cells in the absence of tumor cells tend to return to their initial state. We will assume in Equation (7) $\lambda_i = 0$ for $i = 2, 3, 4$, and $\lambda_i = \lambda = constant$ for $i = 6, 7, 8$. Thus we have:

$$L_{ij}[\mathbf{f}] = \lambda(f_{ij} - f_{ij}^0) \tag{25}$$

where f_{ij}^0 refers to the initial value of the distribution f_{ij}.

3. Simulations and emerging behaviors

The dynamical equations can be obtained substituting the previous assumptions in the right-hand side of system (2). They are characterized by $8 \times m$ ordinary differential equations in the unknown distribution functions $f_{ij} : \mathbb{R}^+ \to \mathbb{R}^+$, where $i = 1, \cdots 8$, $j = 1, \cdots m$. The model is characterized by 11 parameters: $\alpha, \sigma, \tau, \beta_1, \beta_2, \gamma, \lambda, \varepsilon_1, \varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28}$; each one refers to a specific event, in order to clarify the phenomenon under consideration. In this section, we will make use of simulations for visualize the behavior of the models, with a detailed quantitative analysis of the role of parameters and of the initial conditions. Firstly, we will look at the initial value problem related to Equation (2) which can be written as follows:

$$\begin{cases} \dfrac{df_{ij}(t)}{dt} = J_{ij}[\mathbf{f}], \\ \\ f_{ij}(0) = f_{ij}^0, \end{cases} \tag{26}$$

where f_{ij}^0 are the $8 \times m$ initial conditions, and

$$J_{ij}[\mathbf{f}](t) = C_{ij}[\mathbf{f}](t) + M_{ij}[\mathbf{f}](t) + P_{ij}[\mathbf{f}](t) - D_{ij}[\mathbf{f}](t) - L_{ij}[\mathbf{f}](t).$$

We will make the following assumptions:

- The discrete microscopic state u_j is defined in the interval $[0,1]$. We select $m = 3$, then $u = 0$ corresponds to the lowest level of activity, while the greatest level corresponds to $u = 1$, and as the midpoint we have chosen $u = 0.5$.
- The dimensionless parameter τ is assumed to be constant and equal to unity for all interacting pairs.
- In this analysis, we will choose null initial condition except for $f_1^0 = (f_{1j}^0) = (1,0,0)$ and $f_5^0 = (f_{5j}^0) = (0.2,0,0)$, which refers to absence of cancer cells.
- In the figures, n(4) shows evolution of the number density of cancer cells of the last hallmark $n_4 = n_{41} + n_{42} + n_{43}$ and n(8) shows evolution of the number density of immune cells $n_8 = n_{81} + n_{82} + n_{83}$.

3.1. *Numerical analysis*

In our analysis, we apply computational methods to obtain simulations through MATLAB program.

- The simulations are developed, starting from the following values of parameters: $\sigma = 0.5$, $\tau = 1$, $\alpha = 10^{-2}$, $\lambda = 0.02$, $\beta_1 = 10^{-3}$, $\beta_2 = 10^{-1}$, $\varepsilon_1 = 10^{-3}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$, and different values of $\varepsilon_{28} = 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}$, that are those which had considered in paper [3]. The results are shown in the Figure 1. As one sees in the Figure 1, the plots show aperiodic oscillations with

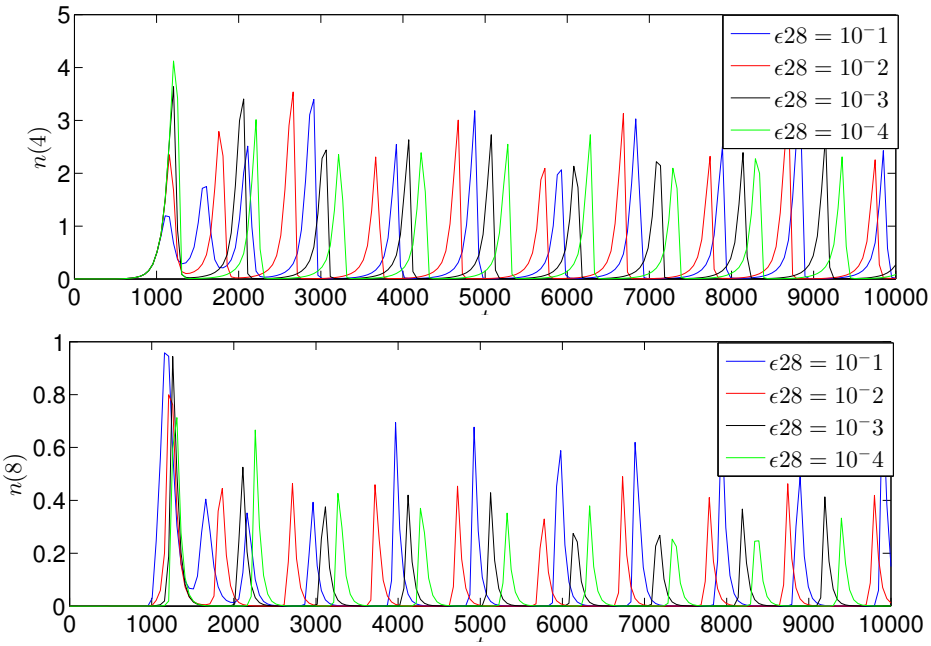

Figure 1. *Plot n(4) and n(8). The two figures are obtained with different values of parameter ε_{28} and with initial conditions $f_1^0 = (1,0,0)$, $f_5^0 = (0.2,0,0)$, at the time $t = 10000$.*

breadth for $n(4)$ in the range $[0,5]$ and $n(8)$ in the range $[0,1]$, i.e the number density of cancer cells of the last hallmark have a definitely oscillating behavior, as the immune cell is not able to deplete them.

- We first modify the parameters β_1 and β_2 that characterize the proliferation rate of cancer and immune system cells of the last hallmark. The best result is shown in Figure 2, it corresponds to $\varepsilon_1 = 10^{-3}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$, $\varepsilon_{28} = 10^{-2}$, $\alpha = 10^{-2}$, $\beta_1 = 10^{-4}$, $\beta_2 = 10^{-1}$ and $\lambda = 0.02$. Compared with n(4) and n(8) in Figure 1, the plot in Figure 2 shows almost periodic oscillations with n_4 in the range $[0, 0.8]$ and n_8 in the range $[0, 0.1]$, with a contraction in the number of oscillations.
- Now, we continue the analysis by making some changes in the parameter $\alpha = 10^{-2}$, that characterizes the transition probability density in cancer and immune system cells. The best result is

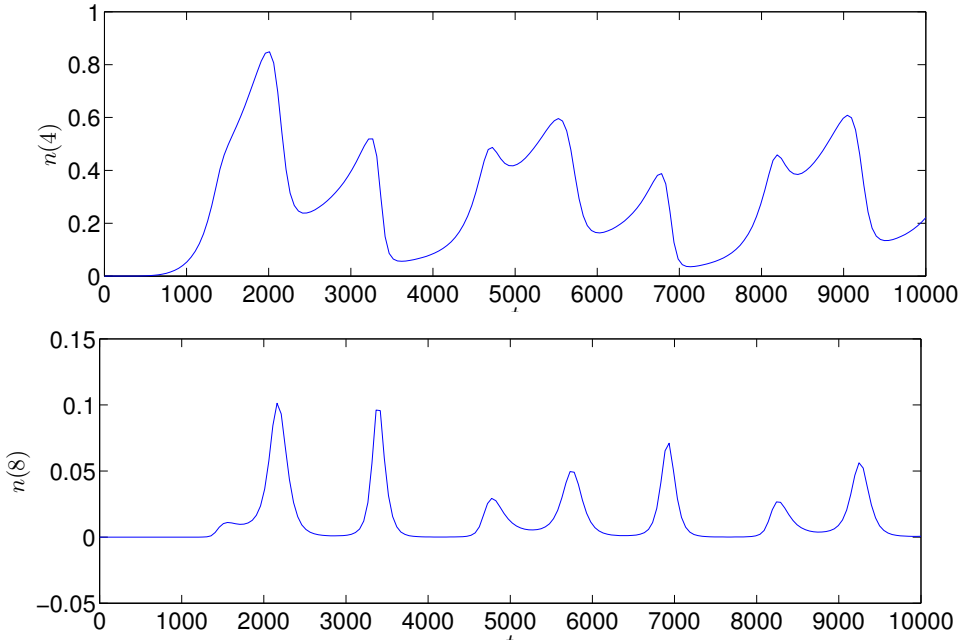

Figure 2. *Modify β_1 and β_2. Plot n(4) and n(8), obtained with $\beta_1 = 10^{-4}$ and $\beta_2 = 10^{-1}$, with initial conditions $f_1^0 = (1,0,0)$, $f_5^0 = (0.2,0,0)$, at the time $t = 10000$*

obtained with $\alpha = 10^{-3}$ (and again $\varepsilon_1 = 10^{-3}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$, $\varepsilon_{28} = 10^{-2}$, $\lambda = 0.02$, $\sigma = 0.5$, $\beta_1 = 10^{-4}$ and $\beta_2 = 10^{-1}$). The obtained plots are shown in Figure 3. One sees beginning diminishing oscillations of n_4 and n_8.

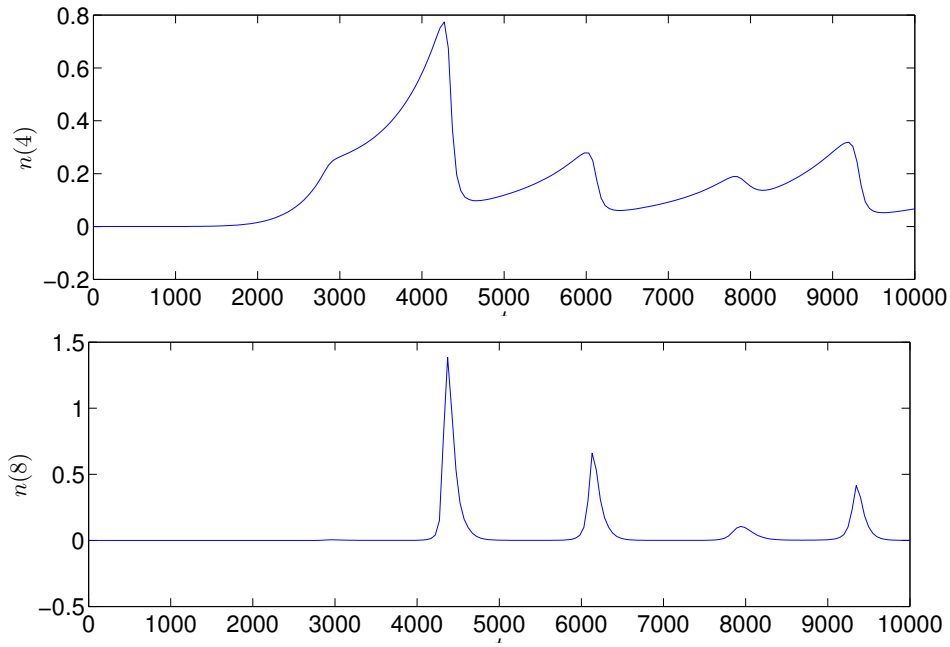

Figure 3. *Modify α. Plot n(4) and n(8), obtained with $\alpha = 10^{-3}$, with initial conditions $f_1^0 = (1,0,0)$, $f_5^0 = (0.2,0,0)$, at the time $t = 10000$.*

- Then we modify the parameter σ characterizing the encounter rate between immune and cancer cells. We found that the best values of σ are in the interval $[0.5, 1]$ where there are no much differences among themselves.
  In Figure 4, we show the plots obtained when $\sigma = 0.9$, $\alpha = 10^{-3}$, $\varepsilon_1 = 10^{-3}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-2}$,

$\varepsilon_{28} = 10^{-2}$, $\lambda = 0.02$, $\beta_1 = 10^{-4}$ and $\beta_2 = 10^{-1}$.

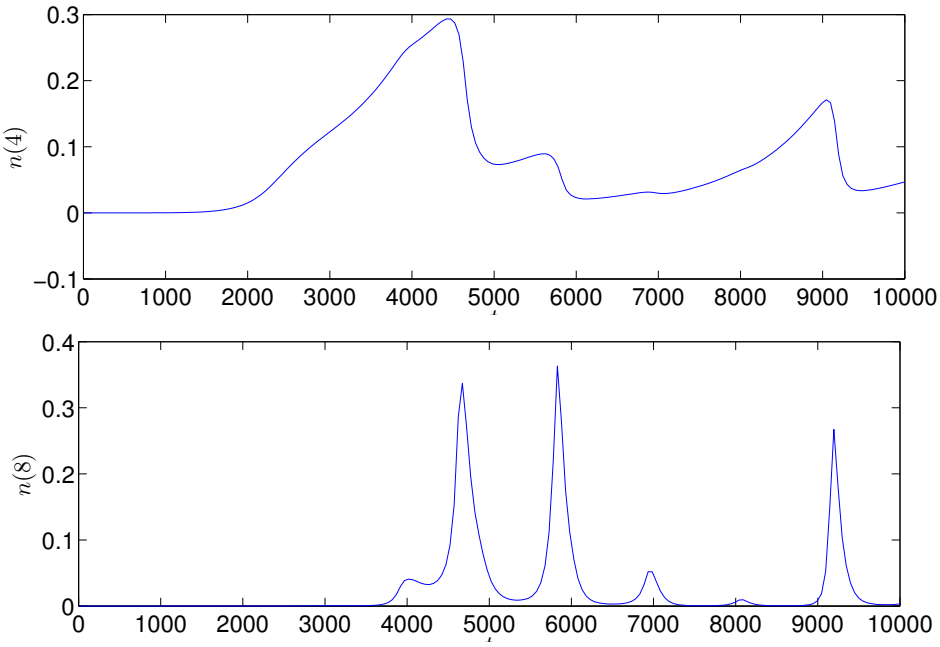

Figure 4. *Modify σ. Plot n(4) and n(8), obtained with $\sigma = 0.9$, and with initial conditions $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, at the time $t = 10000$.*

- Finally, we modify the parameter λ, characterizing the relaxation terms in the immune system cells. The best value for the parameter λ is obtained when $\lambda = 0.01$ and again $\alpha = 10^{-3}$, $\beta_1 = 10^{-4}$, $\beta_2 = 10^{-1}$, $\sigma = 0.9$, $\varepsilon_1 = 10^{-3}$ $\varepsilon_{28} = 10^{-2}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$.
  The plot of n_4 and n_8 are shown in Figure 5. One sees that, immune system cells are always present, that are able to kill cancer cells. Thus, they suppress them as soon as they appear.

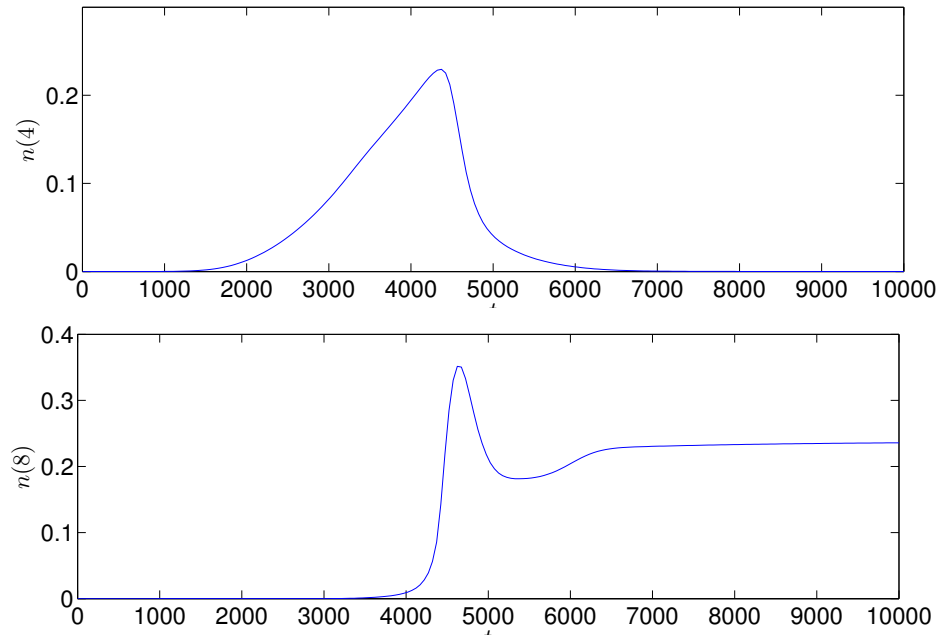

Figure 5. *Modify λ. Plot n(4) and n(8), obtained with $\lambda = 0.01$, and with initial conditions $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, at the time $t = 10000$.*

After the satisfactory results that are shown in Figure 5, we have compared them with the result

obtained by choosing different initial conditions. We have compared the previous results (initial conditions $f_1^0 = (f_{1j}^0) = (1,0,0)$ and $f_5^0 = (f_{5j}^0) = (0.2,0,0)$) with the conditions $f_1^0 = (f_{1j}^0) = (1,0,0)$ and $f_5^0 = (f_{5j}^0) = (0.1,0.05,0.05)$, and with the initial conditions $f_1^0 = (f_{1j}^0) = (0.4,0.3,0.3)$ and $f_5^0 = (f_{5j}^0) = (0.4,0.3,0.3)$. The plots are shown in Figure 6. As one sees the values of the parameters we have found lead to a complete suppression of the cancer cells, also when the initial conditions are modified.

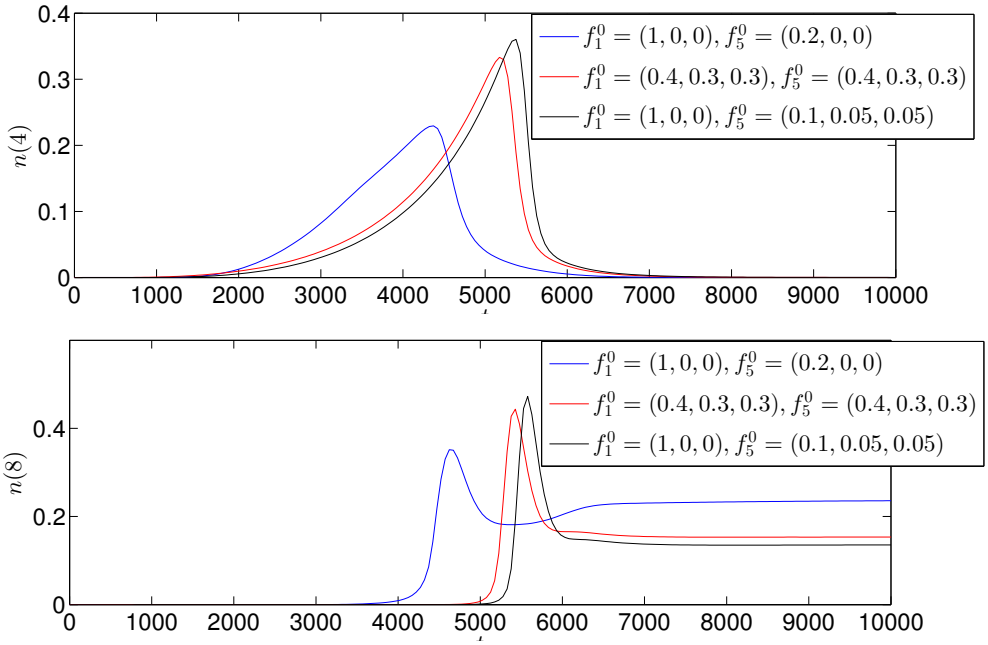

Figure 6. *Modify the initial conditions. Plot n(4) and n(8) obtained varying the initial conditions.*

On the other hand, it is encouraging to see the competition between the evolution of n_2 and n_3 with the development in n_6 and n_7, which will be shown in Figures 7 and 8.

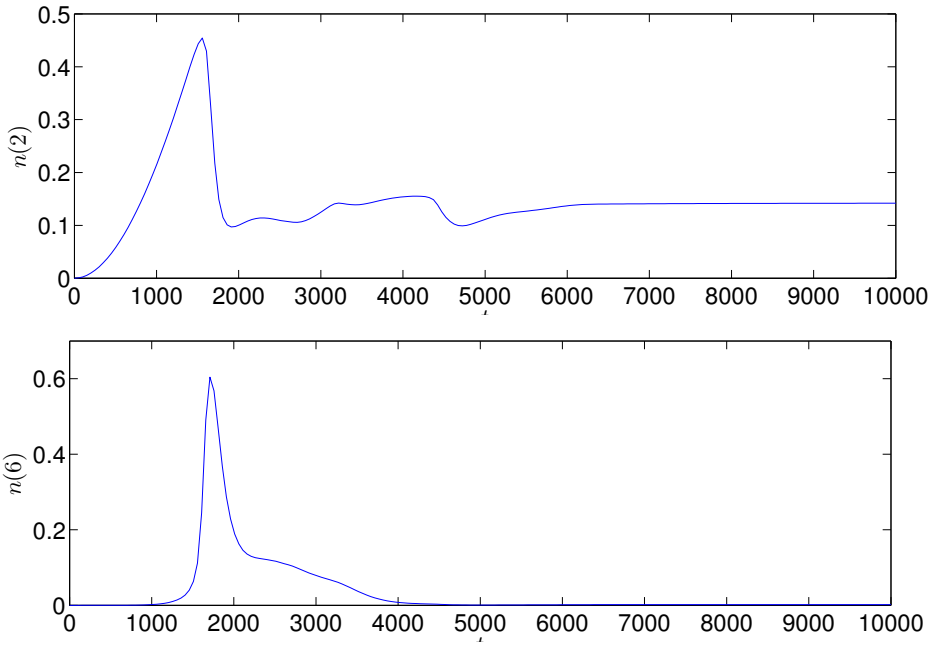

Figure 7. *Plot of n(2) and n(6), with initial conditions* $f_1^0 = (1,0,0)$, $f_5^0 = (0.2,0,0)$, *at the time* $t = 10000$.

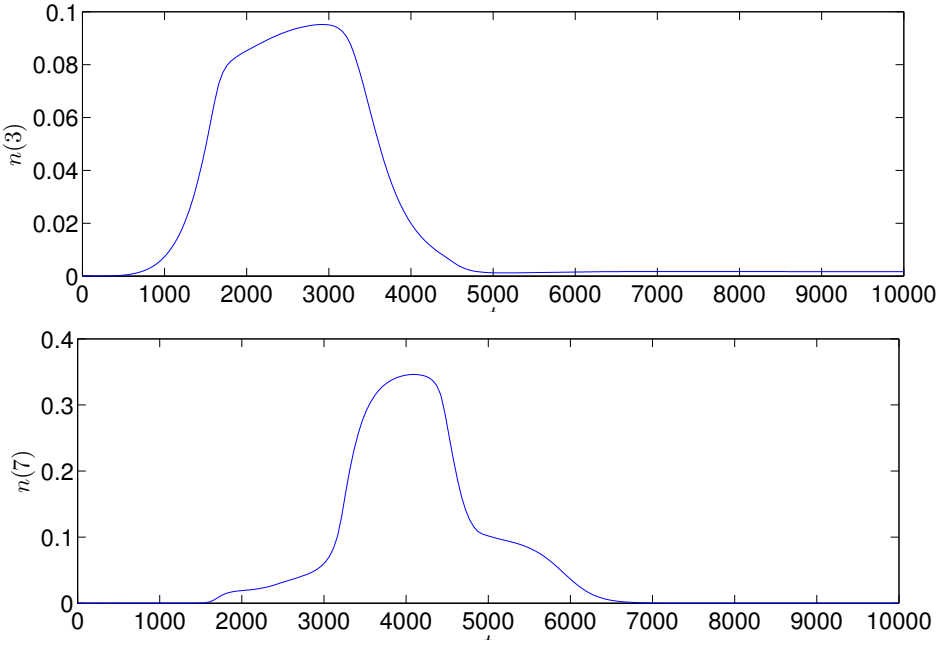

Figure 8. *Plot n(3) and n(7), with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

3.2. *Some more simulations*

The results we have obtained showed that the immune system is able to suppress cancer cells by selecting the parameters $\alpha = 10^{-3}$, $\beta_1 = 10^{-4}$, $\beta_2 = 10^{-1}$, $\sigma = 0.9$, $\lambda = 0.01$, $\varepsilon_1 = 10^{-3}$, $\varepsilon_{28} = 10^{-2}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$. We complete our analysis going back to make some changes on these final values for some of the free parameters with the aim to observe the effect of these changes on the behavior of the system.

$\lambda = 10^{-2}$ is the last parameter we have modified and played an active role in stability of the behavior of the system as shown in Figure 5. We will see the effects of selecting larger and smaller values than 10^{-2} on the behavior of the system. The results obtained are illustrated in Figure 9. One observes that the behavior of the system began to change for $\lambda = 0.016$. More precisely, for values of $\lambda \leq 0.016$ the immune cell population remains in its active state unlike cancer cells that tend to decay to 0, instead $\lambda \geq 0.016$ leads to growing of the number of cancer cells which starts to oscillate dramatically.

Consider now the parameter σ. In the previous section, we have selected $\sigma = 0.9$. Now we shall see the effect of smaller values on the system behavior, choosing $\sigma = 0.2$ and $\sigma = 0.3$, and comparing this with $\sigma = 0.5$ and $\sigma = 0.9$. The results are in Fig. 10. One sees persistent oscillations of tumor and immune cells when $\sigma = 0.3$ and $\sigma = 0.2$ (values less than 0.5). We deduce that, the critical value of σ is 0.5.

Consider now the parameters that are responsible of the mutations both in the immune system and in cancer cells, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$ and $\varepsilon_{28} = 10^{-2}$ are the selected values for the parameters that characterize the rate of mutations in the immune system. We made some changes in these parameters to determine the effect of the change on the behavior of the system, see Fig. 11.

One observes that immune system is able to suppress completely the cancer cells in all cases considered. This means that the rate of mutation in the immune system is not very significant in the suppression of cancer cells. This is an unexpected result.

$\varepsilon_1 = 10^{-3}$: Now we test the effect of change in ε_1 (that characterizes the rate of mutation in the cancer cell population) on the behavior of the system by selecting values smaller and greater than 10^{-3}. The results are illustrated in Fig. 12.

One notes that the immune system is not able to suppress cancer cells for $\varepsilon_1 = 10^{-4}$ and $\varepsilon_1 = 10^{-5}$, i.e. when the rate of mutations in the cancer cells is very small. This result deserves some considerations. Why immune system is incapable to suppress definitely the cancer cells when they have a very little rate

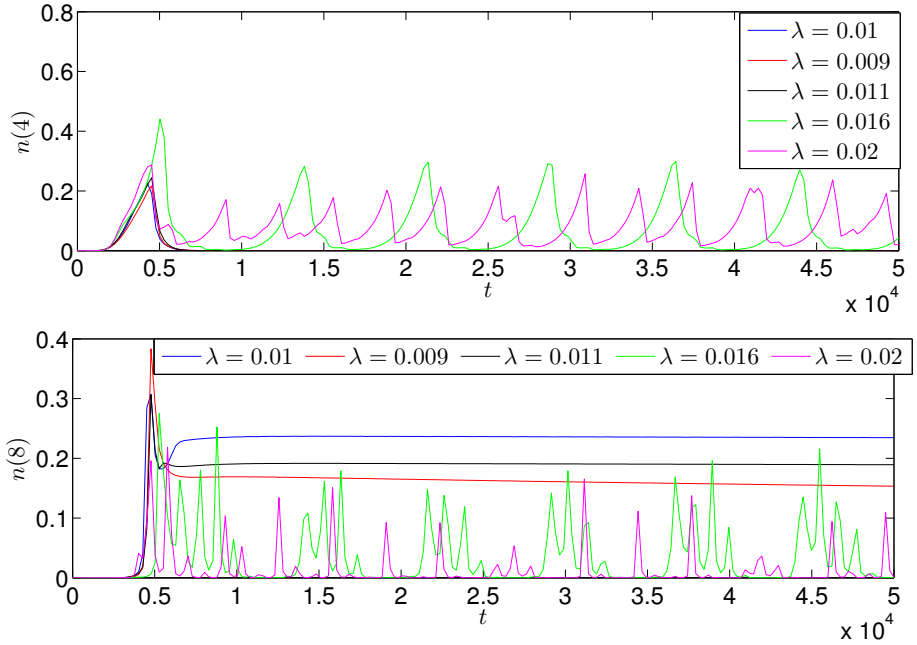

Figure 9. *Modify* $\lambda = 10^{-2}$. *Plot n(4) and n(8), obtained with different values of* λ, *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 50000$.

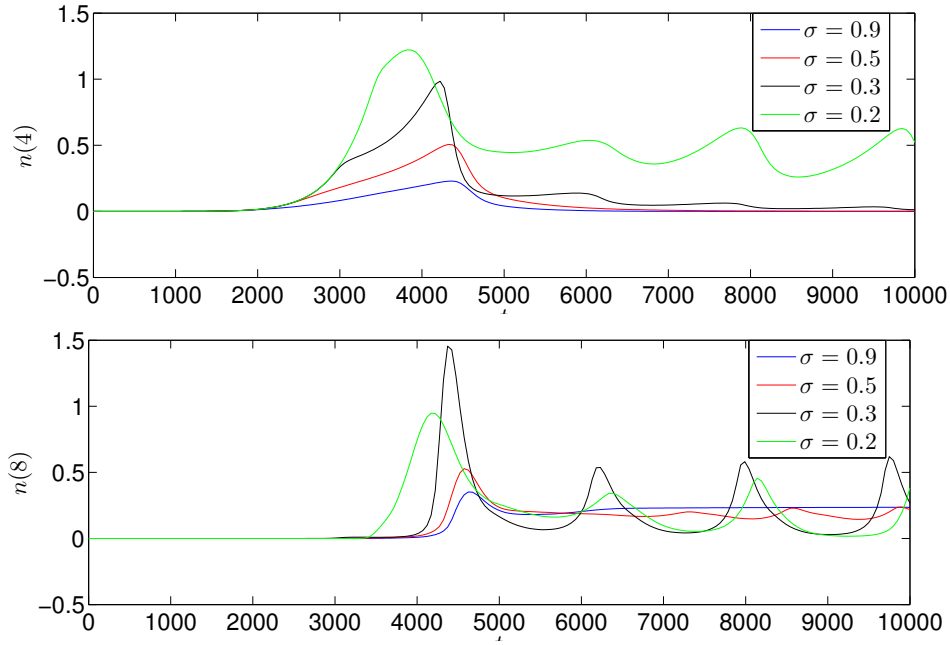

Figure 10. *Modify* $\sigma = 0.9$. *Plot n(4) and n(8), obtained with* $\sigma = 0.2, 0.3, 0.5, 0.9$, *and with an initial condition* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

of mutation? A possible explanation is the following: The immune system is not sufficiently activated to recognize the cancer cells. So, they have time to re-grow as shown in the plots in figure 12. This could be due to the fact that in this situation the immune system relaxes too quickly to recognize malignant cancer cells.

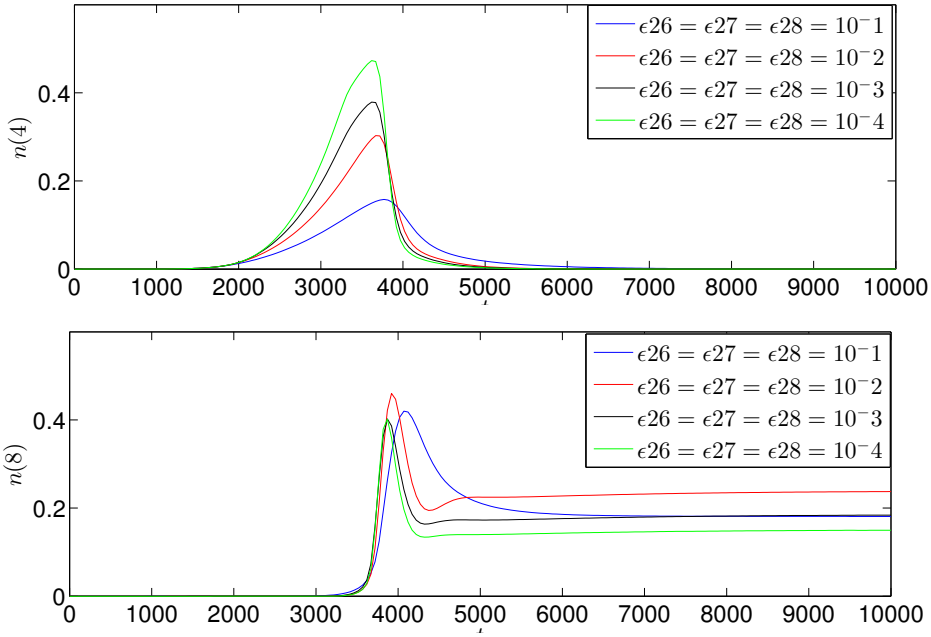

Figure 11. *Modify $\varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28}$. Plot n(4) of n(4) and n(8), obtained with $\varepsilon_{26} = \varepsilon_{27} = \varepsilon_{28} = 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}$, and with initial conditions $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, at the time $t = 10000$.*

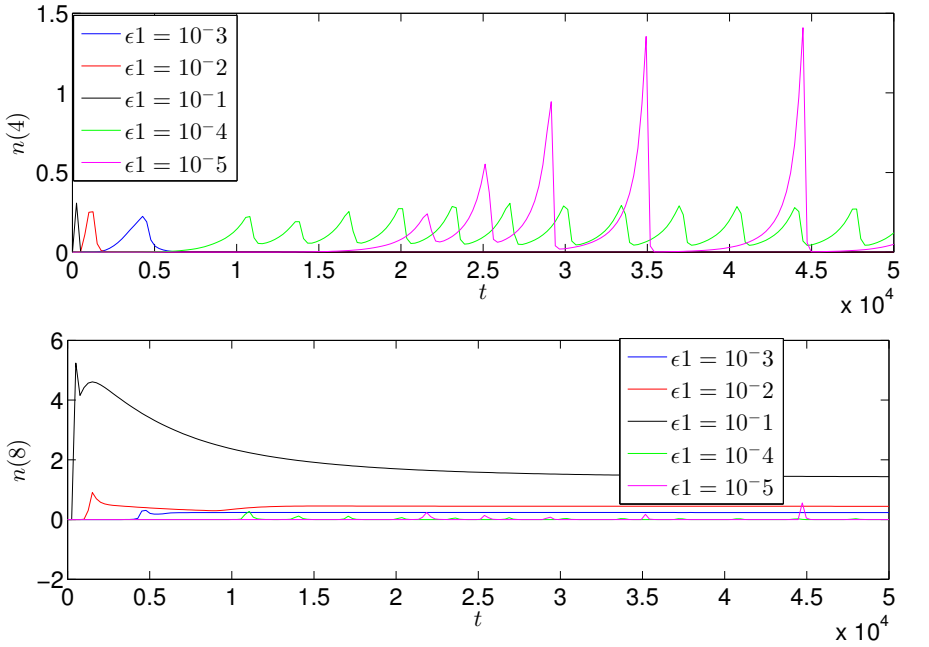

Figure 12. *Modify ε_1. Plot n(4) and n(8), obtained with different values of ε_1, and with an initial condition $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, at the time $t = 50000$.*

4. Discussion of the results and concluding remarks

In this work, we have followed the paper of Bellouquid, De Angelis and Knopoff [3], where a model describing immune-cancer competition was proposed.

A variety of calculations and simulations have been made to put in evidence how the state of the functional subsystems develops in the time, thus, determining critical values of the free parameters that allow the suppression of cancer cells. The model is characterized by 11 parameters, and we have seen that each one of them plays a role in the modeling process, and have a significant effect on the behavior

of the system.

Some results deserve more attention. First, the parameters ε_{26}, ε_{27} and ε_{28}, that characterize the rate of production of mutated cells in the immune system do not have a significant meaning in the depletion of cancer cells. Indeed, simulations made with four different orders of magnitude of these parameters (from 10^{-1} to 10^{-4}) do not produce significant modifications of the behaviour of the system and furnish equivalent results. Second, the parameter ε_1, that characterizes the rate of mutation in the cancer cell population, contrary to what we expected, presents a critical lower bound at $\varepsilon_1^c = 10^{-3}$.

Instead, our simulations show that in the competition between cancer and immune system other parameters played an important role, as coefficients β_1 and β_2, that characterize the rate of production of cells in the same population. One of the most important parameters seems to be λ, that is the parameter that characterizes the relaxation time of the immune system. We have found as the upper limit for it $\lambda_c = 0.016$.

Naturally, the model studied in this paper does not describe phenomena as the angiogenesis, the tissue invasion and metastasis. However, the results of our simulation show that the importance of the immune system in the competition with cancer cells cannot be underestimated. This result is in agreement with recent medical researches that show the importance of the immune system in the therapy of malignant tumor [14].

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