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On Modeling the Immune Competition with Darwinian Dynamics

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On Modeling the Immune Competition with Darwinian Dynamics

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DEDICATION

To my parents, in gratitude and love

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Introduction

Mathematical and computational models are increasingly used in this century to help modeling of living systems. Mathematical modeling presents many methods for studying and analyzing the behavior of biological systems, in particular, cellular systems. As Bellomo (2008) [1], Bellouquid and Delitala (2006) [2], suggest " The modeling of living systems is not an easy task, it requests technically complex mathematical methods to deal with the inner complexity of biological systems which exhibit features and behaviors very different from those of inert matter".

Biology today is at a crossroads. The molecular paradigm has run its course. Engineering discipline holds the promise of making biology an even more fundamental science, one that, along with physics, probes and defines the nature of reality [3].

In complex biological systems, such as the propagation of an infection, or in the anomalous proliferation of tumor cells, the early stage is mainly stochastic while at large times, by some law of large numbers, the predominant effects are deterministic, and the behavior can be described by deterministic equations with random initial data. Before embarking on this topic, we will offer a concise concept about what is the biological system under consideration and how it can be modeled. What interests us in this thesis is the focus on modeling of complex multicellular systems by a mathematical approach related to mathematical kinetic theory.

"Darwinian" Evolution is a theory that transcends all of biology. Any observation of a living system must ultimately be interpreted in the context of its evolution. Because of the tremendous advances over the last half-century, evolution has become a discipline that is based on precise mathematical foundations [4]. Evolution is a change in the heritable characteristics of biological populations of successive generations [5]. There are three basic building blocks of evolutionary dynamics: replication, selection, and mutation. These are the fundamental principles of biological systems. They apply to any biological organization anywhere in our or other universes and do not depend on the particular details of which chemistry was recruited to embody life. Any living organism is contin-

uously modified by these three principles. An individual organism's phenotype results from both its genotype and the influence from the environment it has lived in. A substantial part of the phenotypic variation in a population is caused by genotypic variation [4].

Variation comes from mutations in the genome, reshuffling of genes through sexual reproduction and migration between populations (gene flow). Despite the constant introduction of new variation through mutation and gene flow, most of the genome of a species is identical in all individuals of that species [6]. However, even relatively small differences in genotype can lead to dramatic differences in phenotype.

Darwinian evolution is truly relevant in cancer-immune system competition because it provides a description of the changes of the successive generations of immune cells, adapting to the specific antigens they fight.

In this thesis, the dynamics that the model presented in Chapters 3 and 4 should take into account is a Darwinian-type evolution of cell phenotypes contrasted with the immune system. The phenotypes correspond to the immune-hallmarks of cancer, while the immune system develops a learning process from innate immunity to acquired immunity. Generally, this contrast action is sufficient to prevent the indefinite proliferation of cancer cells. However, for some specific mutations, the Darwinian selections can generate highly aggressive cell phenotypes that progress and proliferate with a speed that cannot be contrasted by the learning process of the immune system [7].

The value of an evolutionary approach to medicine has become increasingly recognized. There are several ways in which an evolutionary perspective can enrich medical education and improve medical practice [8]. For instance, evolutionary modelling approaches led to the proposal of a new therapeutic strategy that aims to maintain a stable tumour population instead of trying to achieve maximal cell kill. According to the strategy, killing clones is a resistance to treatment in a competitive manner. A basic assumption of this strategy is that resistant clones have a lower fitness than sensitive clones because they commit more resources to maintain the resistant phenotype. This strategy has been tested in animal models of ovarian cancer but proof of principle in humans is not yet available [9]. Cancer therapy selects for cancer cells resistant to treatment, a process that is fundamentally evolutionary [10].

As we know, the immune system works to protect the body from all threats, and eliminate malignant cells during initial transformation in a process termed immune surveillance, but after cancer exposure, the process will become somewhat complicated, because cancer has the ability to escape immune recognition and subsequent destruction. This will require a therapeutic intervention using the strategies of immunotherapy, which includes cancer vaccines, adoptive cellular

immunotherapy, immune checkpoint blockade, and oncolytic viruses. Scientists have known for decades that cancer cells are particularly effective in suppressing the body's natural immune response, which is why most treatments exploit other means, such as surgery, radiation therapy and chemotherapy, to eliminate neoplastic cells. Cancer therapy has long relied on the strategy of attacking cancer cells directly to treat patients. Cancer immunotherapy, the treatment that harnesses the patient's immune system to treat cancer has become an important addition to conventional therapies. Immune checkpoint blockade therapy, in particular, has undoubtedly been one of the most impressive advancements made in cancer therapeutics in recent years [11]. The mathematical models help to design therapeutic strategies (external actions, therapeutical actions or other external agents). Many recent studies have been devoted to this field, for example, the paper by De Angelis and Jabin [12] consider different types of therapeutical actions such as the activation of the immune system, angiogenesis inhibition factors, and weakening of tumor cells by chemotherapeutical actions, while paper [13] considers a Boltzmann transport model for dose calculation in radiotherapy.

Here we deal with multicellular systems that experience cell proliferation, cell death and immune supervision. According to the mathematical approach, these cells are characterized by biological functions and the ability to organize their dynamics and interactions with other cells [1, 2]. Mathematical models are useful to describe the system under consideration using mathematical concepts and language. A model may help to explain a system and to study the effects of different components and to make predictions about behaviour.

The mathematical approach used in this dissertation is based on the *Kinetic Theory of Active Particles* (KTAP), that has been specifically developed to model a variety of complex systems [14–17], as for instance vehicular traffic flow [18], immune competition [7] and social systems [19], while the papers [20] and [21] present a model of virus mutations and evolution of epidemics in a system of interacting individuals. The approach to living systems was initiated by the pioneer paper [22] and developed and applied by various authors [2, 7, 17, 23–32]. 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, which is related to the intrinsic biological function of particles. The evolution of each functional subsystem is described by a distribution function whose time evolution is governed by interactions, while the overall state of the system is described by the probability distribution function over microscopic states.

The modeling of biological systems can be developed at the cellular scale (microscopic scale), where the physical state of each single object is individually described, or at the macroscopic scale when the model refers to the evolution of

quantities obtained by local averages of the microscopic state. The mathematical approach attempts to describe the statistical evolution of large systems of interacting particles by derivation of evolution equations.

The aim of this thesis is the detailed mathematical study of the immune competition with Darwinian dynamics, and its modeling and simulations. In particular, the competition between the immune system and cells carrier of a pathological state. As a theoretical background, we say that the immune system has the ability to activate a defence of immune cells against infectious agents and mutated cells. The derivation of models must deal with the analysis of microscopic interactions, due to the presence of proliferation, mutations and/or destruction of cells.

The thesis is made up of four chapters: Chapter 1 is the starting point to enlightening the topic under study. This chapter is focused on a general presentation of the mathematical tools of the kinetic theory of active particles and presents a concise description of the mathematical tools "concepts" and "definitions" used in this thesis. In Chapter 2, we provide a concise introduction to the immune system and cancer cells. This chapter provides a phenomenological description of some aspects of the biology of the system we are dealing with, while the following chapters are based on studying of a model describing the competition between the immune system and cancer cells. Chapter 3, deals with the modeling of interactions between the immune system and cancer cells. The model was proposed in the paper by Bellouquid et al. (2013) [7], which assumed discrete values of the activity of cancer and immune cells. Further, in this chapter, we have made a number of simulations with the aim to investigate how the state of the various cell populations evolves in time depending on the choice of the free parameters. In addition, we present a proposal for modify the parameter that characterizes the probability density function. In Chapter 4, we present a generalization of the model proposed by Bellouquid et al. (2013) [7]. The model is obtained by replacing the discrete activity values by continuous values, choosing suitable relations to describe the interactions between active particles. This chapter also deals with the derivation from the model at the cellular scale of a model at the macroscopic scale, that considers as variables quantities obtained by local averages of the microscopic state.

In the introduction of each chapter, we explain the specific motivations for such analysis, and we discuss the state of the art in research. During each chapter, we make some remarks, that are recalled in the final discussions of this thesis.

Chapter 1

Mathematical Tools of the Kinetic theory of Active Particles

This chapter provides an introduction to the mathematical tools that will be used in this thesis. The approach is based on a suitable generalization of methods of classical kinetic theory. So the mathematical tools offer a conceptual framework to modeling the complex system under consideration and allow modeling the dynamics of large systems of interacting particles. These interactions are ruled not only by laws of classical mechanics but also by biological functions. The presentation is organized into three parts corresponding to the following three sections. Section 1.1 provides a brief description of the complex living system object of the modeling as well as the strategy to derive the mathematical structures needed by the modeling approach. Section 1.2 deals with the derivation of mathematical structures suitable to model the microscopic interactions in the internal system and derivation of the structure for a closed system. Finally, Section 1.3 shows how these structures can be modified to include external actions such as therapeutical actions.

1.1 From Multiscale Features and Evolution to Mathematical Structures

In this section, we begin by presenting the concept of (biological) system. In general, a biological system is a complex network of several biologically relevant entities. The microscopic entities in biology, said cells in a multicellular system, are characterized by biological functions and the ability to organize their dynamics and interactions with other cells [33]. So these systems of the real world consist of a very large number of interacting elements, whose state is described by a set

of microscopic variables, and the overall system is defined by an extremely large number of evolution equations corresponding to the dynamics of their elements. These equations are linked together owing to the interactions. For instance, the kinetic theory of active particles has been applied to ensembles of bees, of birds, of fishes,... considered as self-propelled particles, with some rules relating their speed and direction of motion to their mutual respective distances. Impressive successes have been achieved in reproducing the collective motion of such animals, which in some occasions may exhibit very strong fluctuations in local density and local speed, whereas in some other situations it has a very regular and efficient pattern of motion. This is in contrast with the motion of usual atoms or molecules, which are not self-propelled, and shows that the techniques of kinetic theory are much more powerful than its classical use in the kinetic theory of gases.

The first conceptual step in the mathematical distribution of biological system is the choice of the representation scale of the observed phenomena. So the mathematical models can be derived at the microscopic scale when the evolution of each element is individually described, or at the macroscopic scale when the model refers to the evolution of quantities obtained by local averages of the microscopic state. The first kind of approach leads to a large number of equations due to a large number of particles involved in the system, while their numerical solution needs a very large computational time, making the approach too cumbersome and expensive. The above modeling approach can be replaced by a macroscopic description, typical of continuum mechanics, which reduces the complexity by dealing with quantities which are averaged locally in space.

Now we consider that the overall behavior of complex systems of many interacting entities is determined by the dynamics of their interactions. Specifically, in the large systems of interacting elements, the microscale refers to individual entities, while the macro-scale is related to observable, locally averaged, quantities corresponding to the overall dynamics. Many studies that examine the models of biological systems have relied on the paper of Hartwell, et al. (1999), where a conceptual framework for the mathematical approach to biological system was proposed. They wrote: "Biological systems are very different from the physical or chemical systems analyzed by statistical mechanics or hydrodynamics. Statistical mechanics typically deals with systems containing many copies of a few interacting components, whereas cells contain from millions to a few copies of each of thousands of different components, each with very specific interactions. ... In addition, the components of physical systems are often simple entities, whereas in biology each of the components is often a microscopic device in itself, able to transduce energy and work far from equilibrium" [2].

So, for the large system described above, the microscopic description of the biological system is more complicated than that in a physical system. Therefore

it is necessary to move from a higher level of analysis to view this complexity. At the same time, a biological system cannot simply be observed and interpreted at a macroscopic level, where it shows only the output of the cooperative and organized behaviors which instead may not be apparent at the cellular scale.

From the above, the following technical definitions can be given:

Definition 1.1.1. ***Micro-scale*** *is the scale at which the entities of the interacting system are identified.*

Definition 1.1.2. ***Micro-state*** *is the variable that identifies the biological state of each interacting entity, while the collective behavior is that observed, at the macro-scale, on the overall system.*

Definition 1.1.3. ***Macro-scale*** *is the scale where variable sets of activated individuals interact. It is characterized by the evolution of the activity from one state to another.*

Since the micro-scale and the macro-scale change during the development process, we need to define a distribution function for each set of interacting elements.

Definition 1.1.4. *The* ***distribution function*** *is the function which describes the activity of cells at a given time. It is defined as the number of cells that at a time t is in a specific microscopic state.*

The features of a general modeling approach, as mentioned in the paper [26], are as follows:

- understanding the links between the dynamics of living systems and their complexity features;
- derivation of a general mathematical structure, consistent with the aforesaid features, with the aim of offering the conceptual framework toward the derivation of specific models;
- design of specific models corresponding to well-defined classes of systems according to a detailed interpretation of the dynamics at the micro-scale;
- validation of models by comparison of the dynamics predicted by them with that resulting from empirical data;
- analysis of the gap between modeling and mathematical theory.

Modeling biological systems need to understand the multi-scale, where the dynamics of the cell is ruled by sub-cellular entities, while most phenomena can be observed effectively only at the macroscopic scale. So the multi-scale approach shows how macroscopic equations can be obtained from the microscopic descriptions given by the underlying mathematical kinetic theory for multicellular systems.

The mathematical kinetic theory for multicellular systems is defined by a system of integro-differential equations which describes the evolution in time and space of the distribution functions over the microscopic state of cells of each population.

Based on the above system, the following nomenclatures will be proposed, which will be addressed in the next sections:

- The system is said to be **closed** if it cannot exchange material.
- The system is said to be **open** if it can share material with abroad.

Remark 1.1.1. *In this work, we study closed systems. This does not mean that our analysis is unable to incorporate the action of medical drugs. Such action will be reflected through the modification of the internal parameters of immune cells* $(\beta_2, \varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28})$ *(In the case that the drugs are aimed to stimulate them) or of the internal parameters of the cancer cells* (β_1, ε_1) *(If the drugs are aimed at weakening the resistance of cancer cells). When we refer to closed systems, we mean: a) no new immune cells are incorporated from the outside to the system; b) no cancer cells are removed from the systems in a direct way, i.e. without the action of medical drugs. Thus, the "closed-system hypothesis" applies to the different kinds of cells (which are the particles considered in our analysis) but not to the drugs because they are not described by an evolution equation, but through the values of the parameters.*

1.2 Derivation of a Structure for Closed System

This section deals with the mathematical approach which is based on the development of a mathematical kinetic theory of large systems of active particles. It is a quite natural approach considering that classical models of the kinetic theory, for example, the Boltzmann and Vlasov equations, lead to models which describe the collective behavior of classical particles which cannot be individually identified in a large system, while single interactions are modeled within the framework of classical mechanics [32].

The kinetic theory of active particles, KTAP, has been developed in the last two decades to model complex systems constituted by a large number of interacting particles (called **active particles**), whose microscopic state includes not only geometrical and mechanical variables (typically position and velocity) but also biological functions called activities which are related to the intrinsic biological function of particles. According to KTAP, the overall system is divided into a number of subsystems each of them composed of particles that collectively express the same biological function (**functional subsystems**). The evolution of each functional subsystem is described by a distribution function over the microscopic state of the particles, and the time evolution of the subsystem is governed by interaction, which changes both the microscopic state (conservative interaction) and the number of particles (non-conservative interaction). Essentially, complex biological closed systems are composed of a large number of interacting individuals, in the absence of any effective external action. The mathematical kinetic theory methods describe the system by identifying the microscopic state of the entities interacting within a large system, and the distribution function over this state.

Remark 1.2.1. *The biological microscopic state of the active particles is a scalar variable $u \in D_u$, (D_u is the domain of existence of the variable u), which defines the physical state of active particles. The same variable is used for all particles, yet this variable attains different values for each particle.*

In accordance with what has been mentioned above, the following assumptions can be made:

Assumption 1.2.1. *The system consists of a large number of interacting entities called active particles, each one belonging to several different populations. whose state, called microscopic state, includes not only geometrical and mechanical variables, typically position and velocity, but also an additional variable called activity, which represents the biological functions expressed by suitable collections of active particles.*

Assumption 1.2.2. *Active particles are subdivided into functional subsystems identified by the specific activity they express.*

Assumption 1.2.3. *The state of each functional subsystem is defined by a suitable, time-dependent, distribution function over the microscopic state.*

Assumption 1.2.4. *The evolution of the distribution of each functional subsystem is obtained by a balance of particles within an elementary volume of the space of the microscopic states, where the dynamics of inflow and outflow of particles is related to interactions at the microscopic scale.*

Assumption 1.2.5. *Interactions are modeled by games, more precisely stochastic games, where the state of the interacting particles and the output of the interactions are deduced from probability laws. Only binary interactions are possible.*

Assumption 1.2.6. *The effect of drugs will be reflected as a change in the parameters describing the internal state of the cells. Because of our assumption of closed systems, we cannot describe the time evolution of the cells as a consequence of a supply of drugs implying a change of internal parameters, but we may compare the evolution of systems with different values of the internal parameters, and thus to explore which kind of medical actions would be the most promising ones.*

This section is organized in four subsections. The first subsection deals with the mathematical representation of an isolated system (closed system). The second subsection is devoted to modeling the microscopic interactions between individuals. The third one shows the general mathematical structure for the evolution equation of the distribution function. The forth subsection deal with the spatially homogeneous model that will be used in the Chapters 3 and 4.

1.2.1 Mathematical Representation

A large system of objects, or individuals, is constituted by some differential populations of interacting entities called **active particles**.

Definition 1.2.1. *The physical variable denoting the state of each active particle is called the* ***microscopic state****, and is denoted by* $\mathbf{w}$*, which is formally written as follows:*

$$\mathbf{w} = (\mathbf{x}, \mathbf{v}, u) \in D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u,$$

where $\mathbf{x} \in D_{\mathbf{x}}$ *is the* ***geometrical microscopic variable*** *(position),* $\mathbf{v} \in D_{\mathbf{v}}$ *is the* ***microscopic mechanical variable*** *(velocity), and* $u \in D_u$ *characterizes the* ***biological microscopic internal state****, of each subject. Moreover,* $D_{\mathbf{x}}$*,* $D_{\mathbf{v}}$*, and* D_u *refer to the domains of existence of these variables, while the space* $D_{\mathbf{w}} = D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u$ *of microscopic states is called the* ***state space****.*

Definition 1.2.2. *The dependent variable*

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}, u) = f_i(t, \mathbf{w}) : [0, T] \times D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u \to \mathbb{R}^+$$

for $i = 1, 2, \ldots, M$*, defines the distribution at the time* t*, of individuals of the* i*-th functional subsystem, over the microscopic state* $\boldsymbol{w}$*.*

Each distribution function $f_i(t, \mathbf{w})d\mathbf{w}$ *denotes the number of particles, whose state at time* t*, is in the elementary volume of the space of the microscopic states* $[\mathbf{w}, \mathbf{w} + d\mathbf{w}]$*, defined as* $[\mathbf{w}, \mathbf{w} + d\mathbf{w}] = [\mathbf{x}, \mathbf{x} + d\mathbf{x}] \times [\mathbf{v}, \mathbf{v} + d\mathbf{v}] \times [u, u + du]$.

If the distribution functions f_i are known, then macroscopic quantities can be computed, under suitable integrability assumptions, as moments weighted of the above distribution functions [2] and [26]. For instance, the zero-th order moments of the functions f_i provide information on the number density of each population.

According to KTAP, the following definitions are used:

- The number density or local size of the i^{th} population at time t and position $\mathbf{x}$ in the domain D_x is given by

$$n_i[f_i](t,\mathbf{x}) = \int\int_{D_u \times D_{\mathbf{v}}} f_i(t,\mathbf{x},\mathbf{v},u)d\mathbf{v}du. \tag{1.1}$$

  The total size of the whole population n is given by the sum of all n_i. The local initial size of the i^{th} population at t_0 is denoted by n_{i0}, while the local size for the whole population at t_0 and position $\mathbf{x}$ is denoted by n_0 and is given by

$$n_0(\mathbf{x}) = n(t_0,\mathbf{x}) = \sum_{i=1}^{n} n_{i0}(\mathbf{x}) \tag{1.2}$$

- The total number of individuals of the i^{th} population at time t in a domain $D_{\mathbf{x}}$ is given by

$$N_i[f_i](t) = \int_{D_{\mathbf{x}}} n_i(t,\mathbf{x})d\mathbf{x}, \tag{1.3}$$

  which may depend on time due to proliferation or destruction phenomena that occur. The total size of all population N is given by the sum of all N_i, so

$$N(t) = \sum_{i=1}^{n} N_i(t)$$

  and the total size at the time t_0 denoted by N_0. In all practical cases, it may be appropriate to normalize the distribution functionf_i taking into account the total size N_0 at t_0, so that each size is related to an initial condition.

Using the previous quantities, one can calculate the following classical mechanical quantities:

- Local momentum is obtained by the first order momenta as follows

$$\mathbf{q}[f_i](t,\mathbf{x}) = \frac{1}{n_i(t,\mathbf{x})}\int_{D_u \times D_{\mathbf{v}}} \mathbf{v}f(t,\mathbf{x},\mathbf{v},u)d\mathbf{v}du. \tag{1.4}$$

- The local energy is given by

$$e[f_i](t,\mathbf{x}) = \frac{1}{n_i(t,\mathbf{x})}\int_{D_u\times D_{\mathbf{v}}} \mathbf{v}^2 f(t,\mathbf{x},\mathbf{v},u)d\mathbf{v}du; \tag{1.5}$$

- The global quantities of the local momentum and energy are given respectively by

$$\begin{aligned} Q[f_i](t) &= \int_{D_{\mathbf{x}}} \mathbf{q}[f_i](t,\mathbf{x})d\mathbf{x} \\ \varepsilon[f_i](t) &= \int_{D_{\mathbf{x}}} e[f_i](t,\mathbf{x})d\mathbf{x} \end{aligned} \tag{1.6}$$

- Moreover, according to the quantities with a relevant local momentum, one can define the activation at time t and position $\mathbf{x}$ of the i^{th} population, as follows:

$$A_i[f_i](t,\mathbf{x}) = \int_{D_v\times D_u} uf(t,\mathbf{x},\mathbf{v},u)d\mathbf{v}du \tag{1.7}$$

- and the quadratic activation is given by

$$E_i[f_i](t,\mathbf{x}) = \int_{D_{\mathbf{v}}\times D_u} u^2 f(t,\mathbf{x},\mathbf{v},u)d\mathbf{v}du \tag{1.8}$$

- while the corresponding activation density and quadratic activation density are given respectively by

$$\mathcal{A}_i[f_i](t,\mathbf{x}) = \frac{A_i[f_i](t,\mathbf{x})}{n_i[f_i](t,\mathbf{x})} \tag{1.9}$$

$$\mathcal{E}_i[f_i](t,\mathbf{x}) = \frac{E_i[f_i](t,\mathbf{x})}{n_i[f_i](t,\mathbf{x})} \tag{1.10}$$

The above description of a large system refers to the general model of the kinetic theory, where all components of the microscopic state (geometric, mechanical and biological) are important in the description of the system. The special cases where the microscopic state is identified only by the activity variable will be presented later.

1.2.2 Modeling Microscopic Interactions

The KTAP is a new mathematical approach that develops methods of mathematical kinetic theory to deal with active particles (cells, for example) rather than with classical particles. Thus, according to the modeling of microscopic interactions, particles are classified into three types [26]:

- *Test particles* of i^{th} functional subsystem with microscopic state, at time t, delivered by the variable $\mathbf{w} = (\mathbf{x}, \mathbf{v}, u)$, whose distribution function is

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}, u) = f_i(t, \mathbf{w}).$$

  The test particle is assumed to be representative of the whole system.

- *Field particles* of the k^{th} functional subsystem with microscopic state, at time t, defined by the variable $\mathbf{w}^* = (\mathbf{x}^*, \mathbf{v}^*, u^*)$, whose distribution function is

$$f_k = f_k(t, \mathbf{x}^*, \mathbf{v}^*, u^*) = f_k(t, \mathbf{w}^*).$$

- *Candidate particles*, of the h^{th} functional subsystem, with microscopic state, at time t, defined by the variable $\mathbf{w}_* = (\mathbf{x}_*, \mathbf{v}_*, u_*)$, whose distribution function is

$$f_h = f_h(t, \mathbf{x}_*, \mathbf{v}_*, u_*) = f_h(t, \mathbf{w}_*).$$

The above definitions depend upon modeling of microscopic interactions based on binary interactions involving test or (candidate) particles and field particles, where the field particles enter into the action domain of the test particles. In this modeling, there are two types of microscopic interactions for derivation the mathematical framework [1] and [2]:

Definition 1.2.3. *The **short-range binary interactions** refer to the mutual actions between test and field cells, when the test cell enters into the action domain $\Sigma \subset D_{\mathbf{x}}$ of the field cell; Σ is relatively small with respect to $D_{\mathbf{x}}$ and only binary encounters are assumed to be relevant.*

Definition 1.2.4. ***Long range mean-field interactions** refer to the action over the test active particles applied by all field active particles which are in the long-range action domain $D_{\mathbf{x}} \subseteq \mathbb{R}^3$ of the field particle. The action is still of the type of binary encounters.*

For both types of interactions, we consider the following classifications:

- **Conservative interactions** which modify the state, mechanical and/or activity, of the interacting active particles, but not their number.

- **Non-Conservative** (Proliferative or Destructive) **interactions** which generate birth or death of active particles respectively due to pair interactions.

Assumption 1.2.7. *Microscopic state of individuals is going to change after the interaction between individuals. Each interaction depends on the microscopic state of interacting individuals and can generate changes in the population of different species too. They do not preserve the total number of individuals of each population because proliferation or destruction of individuals are both possible.*

1.2.3 Mathematical Structures

This subsection deals with the derivation of a general structure for the evolution of the distribution functions.

The features of the approach to derive the aforesaid mathematical structures according to what has been mentioned above, can be summarized as follows [26]:

- The overall system is divided into a number of functional subsystems, where each subsystem contains a number of active particles that develop the strategy by interactions;
- The activity defines the overall action expressed by the cells, and it describes the biological function of each functional subsystem;
- Active particles interact within the same functional subsystem and with particles of other subsystems. The interactions can be non-local and nonlinearly additive, and are modeled by theoretical tools of stochastic games;
- The evolution of the distribution function is obtained by a balance of particles within an elementary volume of the space of microscopic states, the inflow and outflow of particles being related to the aforementioned interactions.

Let us consider a large system of interacting active particles subdivided into M functional subsystems labeled by the subscript i. The evolution equation for each distribution function f_i, is obtained by balance of particles within the microscopic state $\mathbf{w}$ in the elementary volume $[\mathbf{w}, \mathbf{w} + d\mathbf{w}]$, that means, equating the rate of variation of the distribution functions in the elementary volume of the state space to the net flux of the active particles which reach the state $\mathbf{w}$ (due to the conservative interactions, proliferations and mutations), minus that leaving the state $\mathbf{w}$ (due to conservative interactions, destructive interactions and natural cells death); all this in the absence of fluxes from the outer environment,

namely, no external action is influencing the particles, recall that the effect of drugs here may be taken into account through different initial sets of values of the parameters describing the internal state of the different kinds of cell. Thus, we have

Variation rate of the number of active particles
= inflow rate caused by conservative interactions
- outflow rate caused by conservative interactions
+ inflow rate caused by proliferative interactions
- outflow rate caused by destructive interactions
+ inflow rate caused by mutations
- outflow rate caused by natural death .

We will remember that, the microscopic state $\mathbf{w}$ is defined as $\mathbf{w} = (\mathbf{x}, \mathbf{v}, u)$ as indicated in Def. 1.2.1.

The evolution equation of the distribution function of the i-th population can be written similarly as the Boltzmann equation, as follows:

$$(\frac{\partial}{\partial t} + \mathbf{v} \cdot \bigtriangledown_{\mathbf{x}}) f_i(t, \mathbf{x}, \mathbf{v}, u) = J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u), \qquad \forall\, i = 1, 2, ..., M, \tag{1.11}$$

where $\nabla_{\mathbf{x}}$ is the gradient operator, and where

$$J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u) = (C_i + P_i + M_i - D_i - L_i)[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u), \qquad \forall i = 1, 2, ..., M. \tag{1.12}$$

The equation (1.11) refers to the general equation that describes the evolution for each f_i specifically, the operators appearing in equation (1.12), will be described as follows.

- $J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u)$ models the flow, at time $t \in [t_0, T]$, of particles that fall into the state $\mathbf{w}$ of the functional subsystem i;

- $C_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u)$ is the net flux, at time $t \in [t_0, T]$, into the state $\mathbf{w} \in D_{\mathbf{w}}$ of the functional subsystem i, due to conservative interactions. These only modify the micro-state, but not the number of particles, and include the flux rate C_i^+ and C_i^- of particles which enter or leave the elementary volume $d\mathbf{w}$ of the state space, therefore:

$$C_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u) = C_i^+[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u) - C_i^-[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u). \tag{1.13}$$

- $P_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u)$ is the inflow, at time $t \in [t_0, T]$, into the state $\mathbf{w} \in D_{\mathbf{w}}$ of the functional subsystem i, due to proliferative events that occur within the same functional subsystem, and generate the birth or gain of particles due to pair interactions;

- $M_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u)$, refers to the inflow, at time $t \in [t_0, T]$, into the state $\mathbf{w} \in D_{\mathbf{w}}$ of the functional subsystem i, due to mutation events, where daughter particles occur in a subsystem different from that of the mother cell;

- $D_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u)$ is the outflow, at time $t \in [t_0, T]$, into the state $\mathbf{w} \in D_{\mathbf{w}}$ of the functional subsystem i, due to destructive events that generate the death or the loss of particles due to pair interactions;

- $L_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u)$, refers to the natural cell death (apoptosis, necrosis, mitotic catastrophe).

The modeling of interactions at the micro-scale is based on the knowledge of the following quantities:

- ***Interaction rates*** (Encounter rates), $\eta_{hk}[\mathbf{f}](\mathbf{w}_*, \mathbf{w}^*)$ and $\mu_{hk}[\mathbf{f}](\mathbf{w}_*, \mathbf{w}^*)$; these are parameters which model the frequency of the interactions between a candidate h-particle with state $\mathbf{w}_*$ and a field k-particle with state $\mathbf{w}^*$. So the encounter rate depends both on the states and on the type of populations of the interacting pairs. In general, different rates η and μ are used corresponding to conservative and proliferative/mutation/destructive interactions, respectively;

- ***Transition probability density*** $\mathcal{B}^i_{hk}[\mathbf{f}]\,(\mathbf{w}_* \to \mathbf{w}; \mathbf{w}^*)$, which denotes the probability density that a candidate h-particle ends up into the state of the test particle of the i^{th} functional subsystem after an interaction (with rate η_{hk}) with a field k-particle, while test i-particles interact with field particles and lose their state;

- ***Proliferative term events*** $\mathcal{P}^i_{hk}[\mathbf{f}](\mathbf{w}_* \to \mathbf{w}; \mathbf{w}^*)$, which models the proliferative events for a candidate h-particle into the i-th functional subsystem after interaction (with rate μ_{hk}) with a field k-particle;

- ***Mutation term events*** $\mathcal{M}^i_{hk}[\mathbf{f}](\mathbf{w}_* \to \mathbf{w}; \mathbf{w}^*)$, which models the mutation events for a candidate h-particle into the functional subsystem $i \neq h$ after interaction (with rate μ_{hk}) with a field k-particle;

- ***Destructive term events*** $\mathcal{D}_{ik}[\mathbf{f}]\,(\mathbf{w}; \mathbf{w}^*)$, which models the rate of destruction for a candidate i-particle in its own functional subsystem after an interaction (with rate μ_{ik}) with a field k-particle.

- ***Relaxation and cell death events*** $\mathcal{L}_i[\mathbf{f}]\,(\mathbf{w})$, which models the natural loss of activity and death (apoptosis, necrosis, mitotic catastrophe) of the cells, due to their damage or age.

Remark 1.2.2. *In the above expressions* $\mathbf{f}$ *denotes the set of all distribution functions:* $\mathbf{f} = \{f_i\}, \quad i = 1, \cdots M$.

Remark 1.2.3. *The encounter rate depends both on the states and on the type of populations of the interacting pairs.*

The first quantities can be viewed in terms of rates by multiplying their interaction rate with the terms modeling transition, proliferative, mutation and destructive events. Therefore, one has:

- *Transition rate*: $C^i_{hk}[\mathbf{f}] = \eta_{hk}[\mathbf{f}]\, \mathcal{B}^i_{hk}[\mathbf{f}]$;
- *Proliferation rate*: $P^i_{hk}[\mathbf{f}] = \mu_{hk}[\mathbf{f}]\, \mathcal{P}^i_{hk}[\mathbf{f}]$;
- *Destruction rate*: $D_{ik}[\mathbf{f}] = \mu_{ik}[\mathbf{f}]\, \mathcal{D}_{hk}[\mathbf{f}]$;
- *Mutation rate*: $M^i_{hk}[\mathbf{f}] = \mu_{hk}[\mathbf{f}]\, \mathcal{M}_{ik}[\mathbf{f}]$.

The modeling of these terms can take advantage of suitable elaboration of the concept of distance between particles for the encounter rate, and of game theory for the transition probability density, while proliferative and destructive terms occur with the said encounter rate with an intensity depending on the properties, namely state and functional subsystem, of the interacting active particles.

Finally, the rate of relaxation and cell death events is modeled as:

- *Relaxation and cell death rate*: $L_i[\mathbf{f}] = \mathcal{L}_i[\mathbf{f}]$, where $\mathcal{L}_i[\mathbf{f}](\mathbf{w}) = \lambda_i[f_i(t, \mathbf{w}) - f_i(t_0, \mathbf{w}_0)]$, $\mathbf{w}_0$ is the microscopic state in the time t_0 and λ_i is a positive constant, refer to the relaxation time related to the normalized density.

Remark 1.2.4. *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.*

$$\eta_{hk}[\mathbf{f}] = \eta_{hk}(d_{hk}[\mathbf{f}]).$$

In general the encounter rate depends on the distance between the interacting particles. There are different concepts of distance can play an important role in the interaction dynamics [26].

In some situations one expects that the encounter rate decays with the distance $d_{hk}(u_*, u^*) = |u_* - u^*|$ *between the activity state of the interacting particles.*

In other cases d_{hk} *may depend on distribution function* $f_h(t)$ *and* $f_k(t)$*. A simple possibility is to consider the distance induced by the norm* L^1*:*

$$d_{hk}[\mathbf{f}](t) = \|f_h(t) - f_k(t)\|\,. \tag{1.14}$$

Remark 1.2.5. *The function $\mathcal{B}^i_{hk}$ has the structure of a probability density function with respect to the variable* $\mathbf{w}$*:*

$$\int_{D_{\mathbf{w}}} \mathcal{B}^i_{hk}(\mathbf{w}_*, \mathbf{w}^*; \mathbf{w})\mathbf{dw} = \mathbf{1} \tag{1.15}$$

In the equation (1.13), $C_i = C_i^+ + C_i^-$; C_i^+ refers to the gain term, which is the number of test particles of the i^{th} population appearing in the state $\mathbf{w}$, after interactions between candidate particles of the same population with microscopic state $\mathbf{w}_*$, and field particles of the i^{th} population with microscopic state $\mathbf{w}^*$. The term C_i^+ can be written as follows:

$$\begin{aligned} C_i^+[f](\mathbf{x}, \mathbf{v}, u) &= \sum_{h,k=1}^{M} \int_{(\Omega \times D_u^2 \times D_{\mathbf{v}}^2)[\mathbf{f}]} \eta_{hk}[\mathbf{f}](\mathbf{x}, \mathbf{x}^*, \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) \\ &\cdot \quad \mathcal{B}^i_{hk}[\mathbf{f}](\mathbf{v}_* \to \mathbf{v}, u_* \to u; \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) \\ &\cdot \quad f_h(t, \mathbf{x}, \mathbf{v}_*, u_*) f_k(t, \mathbf{x}^*, \mathbf{v}^*, u^*) d\mathbf{x}^* d\mathbf{v}_* d\mathbf{v}^* du_* du^*. \end{aligned} \tag{1.16}$$

The term C_i^- refers to the **loss** term which is the number of test particles which leave the state $\mathbf{w}_*$, per unit of time and volume, after having interacted with field particles with state $\mathbf{w}^*$, the **loss** term is defined as:

$$\begin{aligned} C_i^-[\mathbf{f}](\mathbf{x}, \mathbf{v}, u) &= f_i(t, \mathbf{x}, \mathbf{v}, u) \sum_{k=1}^{M} \int_{(\Omega \times D_u \times D_{\mathbf{v}})[f]} \eta_{ik}[\mathbf{f}](\mathbf{x}, \mathbf{x}^*, \mathbf{v}, \mathbf{v}^*, u, u^*) \\ &\cdot \quad f_k(t, \mathbf{x}^*, \mathbf{v}^*, u^*) d\mathbf{x}^* d\mathbf{v}^* du^*, \end{aligned} \tag{1.17}$$

while the terms P_i, M_i, D_i and L_i, corresponding to proliferation, mutation, destruction, and relaxation are defined respectively as:

$$\begin{aligned} P_i[\mathbf{f}](\mathbf{x}, \mathbf{v}, u) &= \sum_{h,k=1}^{M} \int_{(\Omega \times D_u^2 \times D_{\mathbf{v}}^2)[\mathbf{f}]} \mu_{hk}[\mathbf{f}](\mathbf{x}, \mathbf{x}^*, \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) \mathcal{P}^i_{hk}[f](u_* \to u; u^*) \\ &\cdot \quad f_h(t, \mathbf{x}, \mathbf{v}_*, u_*) f_k(t, \mathbf{x}^*, \mathbf{v}^*, u^*) d\mathbf{x}^* d\mathbf{v}_* d\mathbf{v}^* du_* du^* \end{aligned} \tag{1.18}$$

$$\begin{aligned} M_i[\mathbf{f}](\mathbf{x}, \mathbf{v}, u) &= \sum_{h,k=1}^{M} \int_{(\Omega \times D_u^2 \times D_{\mathbf{v}}^2)[\mathbf{f}]} \mu_{hk}[\mathbf{f}](\mathbf{x}, \mathbf{x}^*, \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) \mathcal{M}^i_{hk}[f](u_* \to u; u^*) \\ &\cdot \quad f_h(t, \mathbf{x}, \mathbf{v}_*, u_*) f_k(t, \mathbf{x}^*, \mathbf{v}^*, u^*) d\mathbf{x}^* d\mathbf{v}_* d\mathbf{v}^* du_* du^*, \quad i \neq h \end{aligned} \tag{1.19}$$

$$\begin{aligned} D_i[\mathbf{f}](\mathbf{x}, \mathbf{v}, u) &= f_i(\mathbf{x}, \mathbf{v}, u) \sum_{k=1}^{M} \int_{(\Omega \times D_u \times D_{\mathbf{v}})[\mathbf{f}]} \mu_{ik}[\mathbf{f}](\mathbf{x}, \mathbf{x}^*, \mathbf{v}, \mathbf{v}^*, u, u^*) \mathcal{D}_{ik}[\mathbf{f}](u, u^*) \\ &\cdot \quad f_k(t, \mathbf{x}^*, \mathbf{v}^*, u^*) d\mathbf{x}^* d\mathbf{v}^* du^* \end{aligned} \tag{1.20}$$

$$L_i[\mathbf{f}](\mathbf{x},\mathbf{v},u) \;=\; \lambda_i\,[f_i(t,\mathbf{x},\mathbf{v},u) - f_i(t_0,\mathbf{x}_0,\mathbf{v}_0,u_0)] \tag{1.21}$$

The system of evolution equations is obtained substituting the formal expressions given in equations (1.16)– (1.21) into the equation (1.11).

1.2.4 Spatially Homogeneous Models

Now we will consider a simplified model related to the previous mathematical framework, which will be used in Chapters 3 and 4. This simplification corresponds to the spatially homogeneous case, in which the space and velocity variables are not significant or they are constant in time. In other words, in this case the microscopic state is given by the main biological function u. So the state of the system is identified by the distribution function:

$$f_i = f_i(t,u) : [t_0,T]\times D_u \;\to\; \mathbb{R}^+, \quad \text{for} \quad i\in\{1,2,\ldots,M\}, \tag{1.22}$$

Therefore, the suitable balance equation to describe this case is obtained by writing the evolution equation of the distribution function as:

$$\begin{aligned}
\partial_t f_i(t,u) \;&=\; J_i[\mathbf{f}](t,u) = (C_i^+ - C_i^- + P_i + M_i - D_i - L_i)[\mathbf{f}](t,u)\\
&=\; \sum_{h,k=1}^{M}\int_{D_u^2}\eta_{hk}[\mathbf{f}](u_*,u^*)\,\mathcal{B}_{hk}^i[\mathbf{f}](u_*\to u;u_*,u^*)\,f_h(t,u_*)f_k(t,u^*)du_*du^*\\
&-\; f_i(t,u)\sum_{k=1}^{M}\int_{D_u}\eta_{ik}[\mathbf{f}](u,u^*)f_k(t,u^*)du^*\\
&+\; \sum_{h,k=1}^{M}\int_{D_u^2}\mu_{hk}[f](u_*,u^*)\,\mathcal{P}_{hk}^i[\mathbf{f}](u_*\to u;u_*,u^*)\,f_h(t,u_*)f_k(t,u^*)du_*du^*\\
&+\; \sum_{h,k=1}^{M}\int_{D_u^2}\mu_{hk}[f](u_*,u^*)\,\mathcal{M}_{hk}^i[\mathbf{f}](u_*\to u|u_*,u^*)\,f_h(t,u_*)\,f_k(t,u^*)\,du_*\,du^*\\
&-\; f_i(t,u)\sum_{k=1}^{M}\int_{D_u}\mu_{ik}[\mathbf{f}](u,u^*)\mathcal{D}_{ik}[\mathbf{f}](u,u^*)\,f_k(t,u^*)du^*\\
&-\; \lambda_i[\mathbf{f}](u)\,[f_i(t,u) - f_i(t_0,u_0)].
\end{aligned} \tag{1.23}$$

1.3 Derivation of a Mathematical Structure for Open Systems

The above mathematical structure delivered by the equations (1.11)–(1.21) refers to an isolated system, in other words, it is valid in the absence of external actions. As we have said before, the action of external drugs is here introduced by modification of the parameters describing the internal state of the cells. Once the choice of these parameters is made, the biological system evolves without interaction with the environment. In this section, we introduce a more general model, where the interaction with the environment is not limited to fix the cell internal parameters but is sustained over time, modifying the dynamics of the biological system. An external action may be applied on the biological system, by the outer environment and/or by specific therapeutical actions. We will limit to consider the spatially homogeneous case, which had already been addressed in the equation (1.23).

When an external therapeutical action is applied on a biological system, this action will have an impact on the development of the system, so modifying its dynamics. For example, a therapeutic treatment could stimulate (activate) the proliferation rate of normal cells or destroy the abnormal cells. In other words, the aim of therapeutical treatment will be to lead the distribution functions of the functional subsystems towards the higher or lower states of the activation.

Here we will assume that the modeling of the interplay between the system and its environment follows hallmarks similar to those introduced for closed systems. A useful reference is offered by [2, 34, 35]. In particular, we suppose that the external system is constituted by active agents (for example a chemical of a biological substance) [36]. The system is subdivided into agents functional subsystems, each one labeled by the subscript $j = 1, ..., M$ and each identified by a different action corresponding to the ability to interact with the activity of each functional subsystem of the inner system. The state of each external functional subsystem corresponding to a definite drug substance is represented, in probability, by the distribution function

$$g_j(t, \alpha) : [t_0, T] \times D_\alpha \to \mathbb{R}^+$$

where α is the variable describing the activity of the external system that here is supposed defined in the same domain of the activity variable: $D_\alpha \equiv D_u$. To incorporate the drug-cell interaction, we model the biological of chemical substance as that constitute the external system in a form similar to that used for modeling closed systems. The approach is basically the same of that of the preceding subsection, therefore, the corresponding mathematical structure is as

follows:

$$\partial_t g_j(t,\alpha) = Y_j[\mathbf{g}](t,\alpha) = (C_j^e + P_j^e - D_j^e)[\mathbf{g}](t,\alpha) \tag{1.24}$$

where the terms C_j^e, P_j^e and D_j^e correspond respectively to the conservative, proliferative and destructive events in the external system (and this has been inferred using the variable e, to distinguish from those that have been used in a closed system. We will assume:

$$\begin{aligned} C_j^e[\mathbf{g}](t,\alpha) &= \sum_{k=1}^{M} \int_{D_u^2} \eta_{jk}^e[\mathbf{g}](\alpha_*,\alpha^*)\, \mathcal{B}_{jk}^e[\mathbf{g}](\alpha_* \to \alpha;\alpha_*,\alpha^*)\, g_j(t,\alpha_*) g_k(t,\alpha^*) d\alpha_* d\alpha^* \\ &- g_j(t,\alpha) \sum_{k=1}^{M} \int_{D_u} \eta_{jk}^e[\mathbf{g}](\alpha,\alpha^*) g_k(t,\alpha^*) d\alpha^* \end{aligned}$$

$$P_j^e[\mathbf{g}](t,\alpha) = \sum_{k=1}^{M} \int_{D_u^2} \mu_{jk}^e[\mathbf{g}](\alpha_*,\alpha^*)\, \mathcal{P}_{jk}^e[\mathbf{g}](\alpha_* \to \alpha;\alpha_*,\alpha^*)\, g_j(t,\alpha_*) g_k(t,\alpha^*) d\alpha_* d\alpha^*$$

$$D_j^e[\mathbf{g}](t,\alpha) = g_j(t,\alpha) \sum_{k=1}^{M} \int_{D_u} \mu_{jk}^e[\mathbf{g}](\alpha,\alpha^*) \mathcal{D}_{jk}^e[\mathbf{g}](\alpha,\alpha^*)\, g_k(t,\alpha^*) d\alpha^*$$

In previously equations we have introduced the following quantities, whose meaning is identical to those introduced for closed systems:

- $[\mathbf{g}]$ denotes the set of all distribution functions of the agents functional subsystems of the external system. It is: $\mathbf{g} = \{g_j\}, \quad j = 1, \cdots M$.
- $\eta_{jk}^e[\mathbf{g}](\alpha_*,\alpha^*)$ and $\mu_{jk}^e[\mathbf{g}](\alpha_*,\alpha^*)$ are parameters which model the encounter rate between the populations in the outer system, related to the conservative and the proliferative/destructive interactions, respectively;
- $\mathcal{B}_{jk}^e[\mathbf{g}](\alpha_* \to \alpha;\alpha_*,\alpha^*)$ is the transition probability density due to encounters between particles of a given agents functional subsystem, the definition of this function is similar to that referred in the previous subsection;
- $\mathcal{P}_{jk}^e[\mathbf{g}](\alpha_* \to \alpha;\alpha_*,\alpha^*)$ and $\mathcal{D}_{jk}^e[\mathbf{g}](\alpha,\alpha^*)$ model the birth-death rate related to proliferative/destructive interactions, respectively;

In the open system model, it is assumed that the effect of external force or therapy does not cause a mutation in the cells, nor is there a relaxation rate that leads the system to a state of equilibrium.

According to the previous two systems (closed and open systems), we can modeling the interplay between the internal and the external system, and include the interactions between them. Therefore, the general mathematical structure can be written as follows:

$$\begin{cases} \partial_t f_i(t,u) = \mathcal{H}_i[\mathbf{f},\mathbf{g}](t,u) = J_i[\mathbf{f}](t,u) + C_i[\mathbf{f},\mathbf{g}](t,u) + P_i[\mathbf{f},\mathbf{g}](t,u) \\ -D_i[\mathbf{f},\mathbf{g}](t,u) - L_i[\mathbf{f},\mathbf{g}](t,u), \\ \\ \partial_t g_i(t,\alpha) = \mathcal{K}_i[\mathbf{g},\mathbf{f}](t,\alpha) = Y_i[\mathbf{g}](t,\alpha) + C_i^e[\mathbf{g},\mathbf{f}](t,\alpha) + P_i^e[\mathbf{g},\mathbf{f}](t,\alpha) \\ -D_i^e[\mathbf{g},\mathbf{f}](t,\alpha), \end{cases}$$

where $J_i[\mathbf{f}](t,u)$ and $Y_i[\mathbf{g}](t,\alpha)$ are delivered by the equations (1.12) and (1.24) respectively, the other terms characterize the drug-cell interaction between the considered system and its environment.

1- $C_i[\mathbf{f},\mathbf{g}](t,u)$ and $C_i^e[\mathbf{f},\mathbf{g}](t,\alpha)$ refer to the conservative interactions,

2- $P_i[\mathbf{f},\mathbf{g}](t,u)$ and $P_i^e[\mathbf{f},\mathbf{g}](t,\alpha)$, refer to the proliferative interactions,

3- $D_i[\mathbf{f},\mathbf{g}](t,u)$, $D_i^e[\mathbf{f},\mathbf{g}](t,\alpha)$ refer to the destructive interactions,

4- $L_i[\mathbf{f},\mathbf{g}](t,u)$ refer to the relaxation rate, which occurs after excitation caused by external force or therapy. In other words, the restoration of equilibrium following disturbance.

In detail, the above terms can be delivered by the technical calculation as follows:

$$\begin{aligned} C_i[\mathbf{f},\mathbf{g}](t,u) &= \sum_{h,k=1}^{M} \int_{D_u^2} \eta_{hk}^e[\mathbf{f},\mathbf{g}](u_*,\alpha^*)\, \mathcal{B}_{hk}^i[\mathbf{f},\mathbf{g}](u_* \to u; u_*,\alpha^*)\, f_h(t,u_*) g_k(t,u^*) du_* du^* \\ &- f_i(t,u) \sum_{k=1}^{M} \int_{D_u} \eta_{ik}^e[\mathbf{f},\mathbf{g}](u,\alpha^*) g_k(t,\alpha^*) d\alpha^* \end{aligned}$$

$$P_i[\mathbf{f},\mathbf{g}](t,u) = \sum_{h,k=1}^{M} \int_{D_u^2} \mu_{hk}^e[\mathbf{f},\mathbf{g}](u_*,\alpha^*)\, \mathcal{Q}_{hk}^i[\mathbf{f},\mathbf{g}](u_* \to u; u_*,\alpha^*)\, f_h(t,u_*) g_k(t,\alpha^*) du_* d\alpha^*$$

$$D_i[\mathbf{f},\mathbf{g}](t,u) = f_i(t,u) \sum_{k=1}^{M} \int_{D_u} \mu_{ik}^e[\mathbf{f},\mathbf{g}](u,\alpha^*) \mathcal{R}_{ik}^i[\mathbf{f},\mathbf{g}](u,\alpha^*)\, g_k(t,\alpha^*) d\alpha^*$$

$$L_i[\mathbf{f},\mathbf{g}](t,u) = \lambda_i \left[g_i(t,\alpha) - g_i(t_0,\alpha_0) \right]. \tag{1.25}$$

In a similar way, the results on the external agents of the interaction with the system can be modeled as:

$$\begin{aligned} C_j^e[\mathbf{g},\mathbf{f}](t,\alpha) &= \sum_{k=1}^{M} \int_{D_u^2} \eta_{jk}^e[\mathbf{g},\mathbf{f}](\alpha_*,u^*)\, \mathcal{B}_{jk}^e[\mathbf{g},\mathbf{f}](\alpha_* \to \alpha;\alpha_*,u^*)\, g_j(t,\alpha_*) f_k(t,u^*) du_* d\alpha^* \\ &- g_j(t,\alpha) \sum_{k=1}^{M} \int_{D_u} \eta_{jk}^e[\mathbf{g},\mathbf{f}](\alpha,u^*) f_k(t,u^*) du^* \end{aligned}$$

$$P_j^e[\mathbf{g},\mathbf{f}](t,\alpha) = \sum_{k=1}^{M} \int_{D_u^2} \mu_{jk}^e[\mathbf{g},\mathbf{f}](\alpha_*,u^*)\, \mathcal{Q}_{jk}^e[\mathbf{g},\mathbf{f}](\alpha_* \to \alpha;\alpha_*,u^*)\, g_j(t,\alpha_*) f_k(t,u^*) d\alpha_* du^*$$

$$D_j^e[\mathbf{g},\mathbf{f}](t,\alpha) = f_j(t,\alpha) \sum_{k=1}^{M} \int_{D_u} \mu_{jk}^e[\mathbf{g},\mathbf{f}](\alpha,u^*) \mathcal{R}_{jk}^e[\mathbf{g},\mathbf{f}](\alpha,u^*)\, f_k(t,u^*) du^*$$

In this briefly subsection, we have outlined the mathematical structure able to describe the interplay between the system and external therapeutical action. In the future this model could be applied to specific medical situations.

Chapter 2

Immune System and Cancer Cell: Basic Concepts and Clarifications

This chapter is devoted to present a concise idea of the immunology. Also, it is about cells of the immune system and their interactions with cancer cells. In addition, it provides some of the basic concepts of some of the terminology used in the next chapters. The fundamental point in this chapter heading towards the identification of immune system and the ways have taken by this system to protect the body from all threats. In this chapter, we will stand on what has been taken from the Interpretations in the paper presented by Steven A. Hofmeyr [37] and the Book [38]. The article of Bellomo et al.([39], pp.188-190) has offered a good and inclusive introduction to the immune system and the biology of cancer. This chapter is organized into four sections which follow this introduction. Specifically: In Section 2.2 we will look briefly at the immune system, its features, its components and the mechanism of the work. Section 2.3 is devoted to viewing a simple background about cancer, hallmark of cancer cells and the main strategies in cancer immunotherapy. Section 2.4 refers to the interactions among cells which are needed to be used in the next chapters.

2.1 Introduction

Firstly we go to define the cell as the basic structural, functional, and biological unit in living organisms, all living organisms are composed of one or more cells. A cell is the smallest unit of life that can replicate independently producing cells of cell division after the growth process. The cell consists of cytoplasm enclosed within a membrane, which contains many biomolecules such as proteins and nucleic acids.

The human body consists of billions of different functional cells, among these

cells, there are a large number of cells involved in the immune response. These cells are distributed throughout the body in the blood, lymph and epithelial. In other words, the immune cell system is composed of all parts of the body that help in the recognition and destruction of foreign materials. The immune system is almost more complicated than every part of the body, where it can recognize a very large number of enemies, and at the same time, it can produce several secretions and cells to eliminate pathogens. The immune system is involved in the autoimmune diseases and this happens when occurs mistakenly in the immune system which leads to recognizing own body's cells as foreign or dangerous. The ability to recognize "self" fails. The cause of immune dysfunction is unclear but genetics, environment, and long-term chronic inflammation state can all cause autoimmune diseases.

2.2 The Immune System

This section provides a brief introduction to the immune system and the techniques that are used to measure its status. Firstly, we define the **immunology** as the science that deals with the immune system and its responses to invading pathogens. The **immune system**, in multicellular organisms, is a very complex system, and it is made up of a network of cells, tissues, and organs that work together to protect the body from pathogens and other foreign substances such as bacteria, parasites, and fungi that can cause infections. A phenomenological description of the immune system is presented in the book of Cooper and Hausman [40], from the view point of theoretical biologists.

The **immune response** can be considered as an organizer of the substances between the cells, and consists in the coordinate reaction of these cells to infectious microbes.

2.2.1 Features of the Immune System

The most important features of the immune system are the capability to distinguish between host entities (self) and foreign components (non-self), by reacting against everything different to itself (Antigens). The immune system has the amazing ability to respond to any reaction from the foreign molecule, different to its own structure, even if this molecule is very small. However, it does not react against its own components. In addition, the immune system usually recognizes and get rid of the self-cells and tissue that has changed due to infection or disease (such as cancer cells that have become ineffective) by means of an apoptosis process (programmed cell death).

To recognize pathogens, the immune system reacts through two different types of response, that differ in how they do this:

1- **Innate immune system** (Innate response): Is the immunity that inherits the organism of his parents. It grows and develops naturally with the evolution of human life. The innate response is the first line of defence, occurs immediately and quickly activated after pathogen exposure or when circulating innate cells recognize a problem. This type of host defence is always present in healthy individuals, prepared to block the entry of microbes and to rapidly eliminate those that succeed in entering host tissues. The innate response provides an immediate response, but it is non-specific. This response is carried out by epithelial barriers and by specialized cells and natural antibiotics present in epithelium; if microbes do breach epithelium and enter the tissues or circulation, they are attacked by phagocytes (specialized lymphocytes called natural killer cells), and several plasma proteins, including the proteins of the complement system.

   The **complement system** is so named because it is complementary to the antibody response of the adaptive immune system, and it **is** defined as a set of distinct plasma proteins that act together to attack extracellular forms of pathogens and induce a series of inflammatory responses that help to fight infection. A number of complement proteins are proteases that are themselves activated by proteolytic cleavage. Such enzymes are called zymogens and were first found in the gut. The innate immune system provides defence against the invading pathogens until the adaptive immune system develops.

2- **Adaptive immune system** (Acquired response): It starts to act after repeated exposures to a given infection. Here the immune system adapts its response during an infection to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, in the form of an immunological memory, and allows the acquired response to load faster and stronger attacks each time this pathogen is encountered. The adaptive immune responses are carried out by white blood cells (called lymphocytes) and their products, such as antibodies responses (humoral immunity) and cell-mediated immune responses (or cellular immunity). Lymphocytes **are** express receptors that can identify different types of substances that **are** produced by the microbes. These substances are called antigens. The antibodies responses and cell-mediated immune responses are carried out by different classes of lymphocytes, called B-lymphocytes and T-lymphocytes, respectively.

Immune memory is a feature of the adaptive immune response. After B-cells or T-cells are activated, they expand rapidly. As the problem resolves, cells stop dividing and are retained in the body as memory cells. The next time this same pathogen enters the body, a memory cell is already poised to react and can clear away the pathogen before it establishes itself.

Both types of the immune system response are working together against the infection, but in both cases, the defence starts from the recognition of the pathogen agents.

Through the series of steps carried out by the immune response, the immune system can destroy infected and malignant cells, and removes cellular debris, although the innate immune system eliminates the infection, but many of the disease-causing microbes have evolved to resist innate immunity. Defence against these infectious agents is the task of adaptive immunity, the adaptive immune responses are specialized to combat different types of infections and they are triggered only if the microbes are able to penetrate the epithelial barriers and are delivered to the lymph organs that can recognize them by lymphocytes.

Definition 2.2.1. ***Antigen****: A substance (usual proteins)that is found on the surface of the pathogen: bacteria, viruses, or fungi that cause infection and disease. The antigen that is able to provoke an immune response.*

Definition 2.2.2. ***Antigen-presenting cells****: are a heterogeneous group of immune cells that mediate the cellular immune response by processing and presenting antigens for recognition by certain lymphocytes such as T cells. Classical antigen-presenting cells include dendritic cells, macrophages and B-cells.*

Definition 2.2.3. ***Antibodies****: are a special type of proteins which attacks antigens.*

2.2.2 Cells of the Immune System(Components)

The immune system involves different populations of cells. Among them: white blood cells, phagocytes and lymphocytes, bone marrow, lymph nodes, tonsils, thymus, and spleen are all part of the immune system. One of the most important cells involved are the **white blood cells** or *leukocytes*. The white blood cells are the key players in the immune system. They are responsible for much of the work of the immune system as they are involved in protecting the body against both infectious disease and foreign invaders. The white blood cells are grouped into two basic types: **Phagocytes** and **Lymphocytes**, each of which carries out somewhat different functions. All white blood cells are produced and derived from multipotent cells in the bone marrow known as hematopoietic stem

cells.

- **Phagocytes**: These cells have the ability to travel throughout the body to the pursuit of the invasion of pathogens, these cells are those chew up invading organisms.
- **Lymphocytes**: These cells have a variety of different functions. They attack viruses and other pathogens. They also make antibodies which help to destroy bacteria. The lymphocytes can be divided into three classes T-cells, B-cells and natural killer cells. Each B-cell and T-cell is specific for a particular antigen, but their function is under the control of dendritic cells.

1 - **B cells (bursa-derived cells)**: are the only cells that produce antibodies against antigens that can bind to pathogens, block pathogen invasion, activate the complement system, and enhance pathogen destruction.

2 - **T cells (thymus cells)**: are a subtype of white blood cells; they originate in bone marrow and mature in the thymus, and circulate around the body, scanning for abnormal cells and infections. T-cells play a central and important role in cell-mediated immunity. They help to recognize and destroy infected or cancerous cells. They attack body cells themselves when they have been taken over by viruses or have become cancerous. T-cells can be distinguished by the presence of a T-cell receptor on the cell surface. T-cells multiply and divided into helper, regulatory, cytotoxic T-cells or become memory T-cells.

   - T-helper cells: are a type of T-cell that plays an important role in the immune system, as they are required for almost all adaptive immune response, and help to activate the immune system. They not only help activate B-cells to secrete antibodies and macrophages to destroy ingested microbes, but they also help activate cytotoxic T-cells to kill infected target cells. More accurately, without helper T-cells, we cannot defend ourselves even against many microbes that are normally harmless.
   - Regulatory T-cells: inhibit immune response and resolve inflammation.
   - Cytotoxic T-cells: kill cells that produce foreign antigens, such as cells infected by viruses and other intracellular microbes.
   - Memory T-Cells: These cells are derived from normal T-cells specific for antigens that can respond rapidly to subsequent encounter with that antigen and differentiate into effector cell to eliminate the antigen.

Remark 2.2.1. *Naïve T-cells are those cells that have not yet encountered foreign antigen and have not yet been activated.*

3 - **Natural killer cells** are a type of lymphocyte, that function as both cytotoxic effectors and regulators of immune responses, they play a major role in defending the host from both tumors and virally infected cells, and kill any type of host cells that are harbouring infectious microbes in the cytoplasm.

4 - **Dendritic cells**: they are the type of antigen-presenting cell and they are phagocytes in tissues that are in contact with the external environment such as the skin and the inner lining of the nose, lungs and stomach. They are professional antigen processing cells. They have a number of receptors that enhance the uptake of antigens. However, the dendritic cells present antigens to T-cells to help them to recognize foreign antigens. They activate helper T-cells and killer T-cells as well as B-cells by presenting them with antigens derived from the pathogen. They control responses by T-cells and by all other types of lymphocytes. Dendritic cells also influence the type or quality of the response.

2.2.3 Mechanisms of the Immune System

When an antigen enters the body, several types of cells work together to recognize it and respond. It may be partially neutralized by components of the innate immune system. It may be attacked by phagocytes which recognize the pathogens and differentiate them, and then they inform T-helper cells to open up the immune system and operated to trigger the B-lymphocytes to produce antibodies, as well as killer T-cells to get rid of foreign cells. All of them will work together with the complement system. The lymphocytes of the adaptive immune system are brought into play. If lymphocytes encounter an antigen trapped by the antigen-presenting cells of the lymphoid organs, lymphocytes with receptors specific to that antigen stop their migration and settle to mount an immune response locally. After the pathogens have been eliminated, the regulatory T-cells play a central role in the immune system by potently controlling the responses of other immunocytes. Their activity appears to be essential not only for the maintenance of immunological tolerance but also in the control of all physiological immune responses whether against normal self-proteins, microbes or cancerous cells.

In addition, all the cells in the human body, carry signs or markers on the cell membrane of certain chemical compounds called Major Histocompatibility Complex (MHC). This is a set of cell surface proteins that are essential for the acquired immune system to recognize foreign molecules or tumor cells. In fact,

they have the propriety of bind oneself to the antigens which are typical of a pathogen and to display them on the surface of the infected cell, thus allowing its identification by the appropriate T-cells.

2.3 The Cancer and the Hallmark of Cancer Cells

The human cells grow and divide to form new cells as the body needs them. The evolution of cells is regulated by the genes contained inside its nucleus, that controls the cell's functions, especially how they grow and divide. Normal cells have many controls on their growth. They only grow when stimulated by growth factors. They can divide only a limited number of times. If they are damaged, a molecular brake stops them from dividing until they are repaired. If they can't be repaired, they commit cell suicide (apoptosis). They are part of a tissue structure and remain where they belong. If the aforementioned genes mutate, **Cancer** can occur.

Cancer is a large class of very different cellular diseases, all of which characterized by uncontrollable growth. Cancer cells generally have severe chromosomal abnormalities, which worsen as the disease progresses. Cancer cells have defects in the control mechanisms that govern how often they divide, and in the feedback systems that regulate these control mechanisms, and start to proliferate in a non controlled way [41]. They have ability to thrive in a chronically inflamed microenvironment. They have the capability of evading the immune system, by invade local tissue and spread, or metastasize, to distant sites. They have ability to suppress immune reactivity [42]. Local chronic inflammation has an important role in inducing many types of cancer. Cancers historically and evolutionary theory for understanding this disease, have been viewed in [10, 43] respectively. Furthermore the dynamics of cancer progressions is documented in [44]

The immune system also plays a role in cancer. The immune system can find and attack tumor cells, but when this function breaks down it can cause cancers and tumors to develop. There are also cancers of the immune system (Leukemias and lymphomas), that cause immune cells to grow uncontrolled. In fact, the immune system has a major role in cancer suppression, it can eliminate oncogenic pathogens (a gene that has the potential to cause cancer), and it can also inhibit tumor growth and progression through the recognition and rejection of malignant cells, through a process called immuno-surveillance. In other hand, the tumor when become more clinically and biologically aggressive over time. This has been termed 'tumor progression', which can be invasion and metastasis, as well as more efficient escape from host immune regulation [45].

Definition 2.3.1. *Cancer cells are the foundation of the disease that can occur in a variety of organs. They grow and divide at a rapid and unregulated pace. The disease, that is known as cancer, only occurs when immune cells (particularly natural killer cells) fail to recognize and/or destroy cancer cells. Thus, the cancer cells initiate tumors and drive tumor progression forward.*

Definition 2.3.2. *A tumor (neoplasm) is an abnormal mass of tissue which may be solid or fluid-filled. Tumors can be benign (not cancerous), or malignant (cancerous).*

Remark 2.3.1. *The tumor progression refers to the formation of a tumor, and its development.*

2.3.1 Distinctive Capabilities of Tumor Cells

As documented in the seminal paper by Hanahan and Weinberg [46] and [47], there are six hallmarks essential for tumor growth: They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis.

More precisely, following Hanahan and Weinberg [46], the essential traits in cell physiology that possibly dictate malignant growth are the following:

- **Self-sufficiency in growth signals, insensitivity to anti-growth signals and indefinite cell replication.** Tumor cells do not need stimulation from external signals (in the form of growth factors) to multiply, but 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 [48]. In a similar way, tumor cells proliferate owing of their capacity to produce their own growth factors.

  The growth of normal cells is kept under control by growth-inhibitors or signals. These inhibitors act on the cell cycle clock, by interrupting cell division. If a normal cell is damaged, they interrupt its cycle of life, until the damage is repaired. Tumor cells are resistant to anti-proliferative signals and can divide uncontrollably. Non-cancer cells die after a certain number of divisions. Cancer cells have damaged chromosomes and are able of multiply indefinitely.

- **Evasion of Programmed Cell Death (Apoptosis)**. An important feature of organogenesis is the apoptosis, a mechanism by which cells are programmed to die in the event they become damaged (cell suicide). Follow-

ing [46], cancer cells are characteristically able to overcome apoptosis to progress. This lead to an uncontrolled cell proliferation, such as cancer.

Criticisms are leveled at the inference that the ability to evade programmed cell death can be linked to the initiation and progression of cancer. During carcinogenesis, indeed, explaining a net local accrual of cells requires either an increased cell proliferation rate and/or inhibition of cell death. Enderling and Hahnfeldt [49] using mathematical modeling and computer simulation found that increasing the rate of apoptosis, while obviously reducing tumor size in the short-time, actually enhances growth in the long-time. They show that tumors can remain dormant for a long time while stimulation of apoptosis can cause the tumor cell population to aggressively invade.

- **Sustained angiogenesis (Tissue invasion and metastasis)**. Angiogenesis is the process by which new blood vessels are formed. Cancer cells stimulate the growth of blood vessels to supply nutrients to tumors. Cancer cells can move away from their site of origin to invade adjacent tissue or travel to distant sites.

2.3.2 The Main Strategies in Cancer Immunotherapy

After the discovery of the six hallmarks of tumor growth, that have already mentioned in the previous subsection, the idea of exploiting the host's immune system to treat cancer began with the idea that the immune system could eliminate malignant cells during the initial transformation in a process called immune surveillance. Immunotherapy has become a clinically validated treatment for many types of cancer. For decades, cancer has been known to suppress the body's natural immune response. For this reason, most treatments use other methods, such as surgery, radiation therapy and chemotherapy, to eliminate neoplastic cells.

It has been established that the various components of the immune system play a pivotal role in protecting humans. After many disappointing efforts and clinical failure, the area of immunotherapy with cancer has recently received a significant boost, primarily encouraged by the approval of autologous cellular immunotherapy. Immunotherapy against existing cancers includes different approaches, ranging from stimulating the responder mechanisms to counteracting inhibitory and suppressive mechanisms. The main strategies in cancer immunotherapy are cancer vaccines, adoptive cellular immunotherapy, immune checkpoint blockade, and oncolytic viruses. Cancer therapy has long depended on these strategies that directly attack tumor cells to treat patients. Cancer immunotherapy is the treatment that harnesses the patient's immune system to fight cancer, and is now emerging as an important addition to conventional therapies. Immune

checkpoint blockade therapy, in particular, has undoubtedly been one of the most impressive advancements made in cancer therapeutics in recent years [11].

2.4 Interacting Among Cells

In this section, we have intensified attention to the researches provided by [7, 50].

In general, all multicellular systems are constituted by a large number of interacting cells that interact in an amazing form and non-linear ways. These interactions play a crucial role in the development and function of multicellular organisms. Understanding the roles of non-linear interactions is very complicated and is included among the challenges in the study of complex systems. These interactions allow cells to communicate with each other in response to changes in their microenvironment. In the interactions, each entity has a certain action. This action depends on the strategy that can develop through the interaction, which is often related to surviving and adaptation ability. In general, when studying this kind of complex systems, it is needed to simplify the interaction occurring between two entities.

In the next chapters,three classifications will be used: conservative interactions, proliferative interactions, and destructive interactions. The following three figures illustrate these three types of actions.

1 - Conservative interactions: This type of interactions refers to modifying the state of reactive cells from one state to another without change in the size of the populations. See Figure 2.1.

2 - Proliferative interaction: In this event, antigens are presented to the naïve T-lymphocyte by dendritic cells, after the activation of T-cells, they proliferate rapidly. See Figure 2.2.

3 - Destructive interactions: Is a term that refers to the death of exotic material and antigens that enter the body or cancer cells. This is the task of the cytotoxic T-cells and natural killer cells. See Figure 2.3

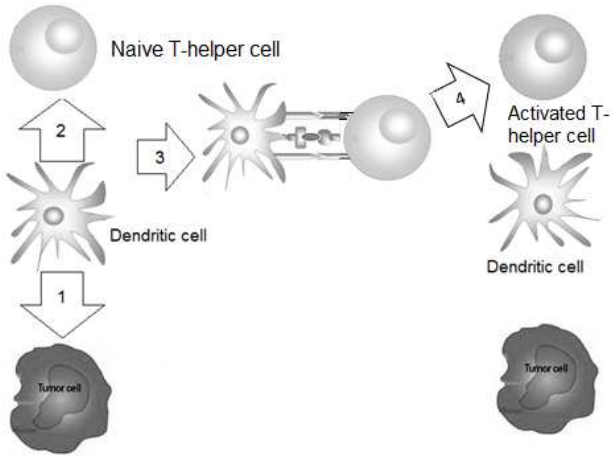

Figure 2.1: *Conservative interaction between T cell and dendritic cell, dendritic cell process antigens and present them to T-cells to activate them.*

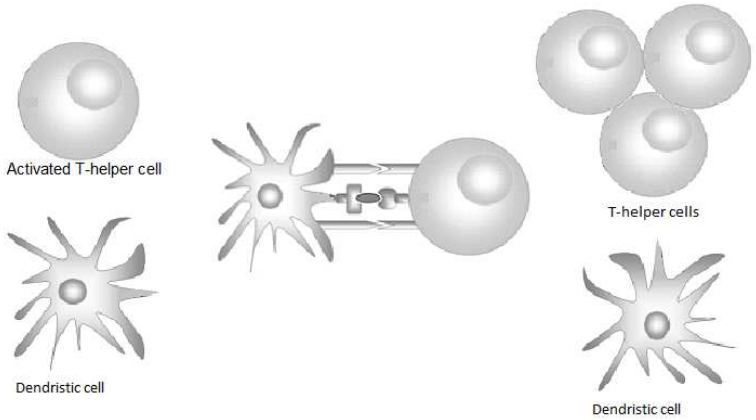

Figure 2.2: *Proliferative interaction,*

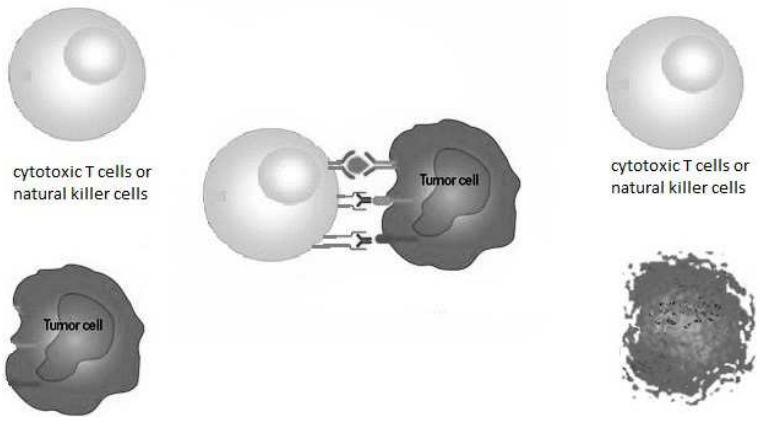

Figure 2.3: *Destructive interactions*

Chapter 3

Spatially Homogeneous Discrete Model

As already said, Hanahan and Weinberg [46, 47] suggested that the complexity of cancer can be reduced to a small number of underlying principles: cancer cells have defects in the control mechanisms that govern how often they divide and are able to stimulate their own growth. They are able to overcome apoptosis to progress. They have the capacity to evade the immune recognition. The immune system plays an important role in these dynamics. As said in Chapter 2, 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 [51].

Mathematical models may be useful for a better understanding of the mechanisms that govern the interaction between immune system and cancer cells, to develop cancer immunotherapies. Applied mathematicians are involved in this research activity as documented in review papers [52, 53] and [54]. In [7] 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*, which has been systematically developed in Chapter 1. To model the immune competition according to KTAP, the overall system is divided into different populations (functional subsystems). The time evolution of each functional subsystem is described by a distribution function and is governed by interactions [35].

This chapter deals with the model proposed in [7], which was formulated by A. Bellouquid, E. De Angelis and D. Knopoff (2013) [7], to describe the competition between cancer cells and immune system, where the scalar variable is

characterized by a discrete activity. A detailed analysis of this model is made, and a number of simulations are 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 chapter will be divided into four sections which follow this introduction. Specifically: Section 3.1, briefly outlines the paper of Bellouquid, De Angelis and Knopof [7], which is the starting point of this study. Section 3.2 presents a variety of simulations to investigate how the different parameters influence the dynamical behavior of the system. In Section 3.3, the results of the previous section will be discussed. In Section 3.4 a modification of Bellouquid *et al.* [7] model is made, to better investigate the results of conservative interactions. An Appendix reports the Matlab code used.

3.1 Modeling Immune-Cancer Competition

This section provides a concise description of the model proposed by Bellouquid et al.(2013) [7]. The overall 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.

As we have said, the cancer is a kind of cellular disorder which allows certain cellular populations to manifest deviant characteristics. 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. When abnormal cells are recognized by immune cells, a competition starts and may end up either with the suppression of cancer cells or with their indefinite growth, with aggregation into tumor structures.

To put in a mathematical framework this process, Bellouquid *et al.* (2013) [7] identify 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 to suppress 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 to contrast 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:

$$n_i[\mathbf{f}](t) = \sum_{j=1}^{m} f_{ij}(t), \quad i = 1, \cdots, 8 \tag{3.1}$$

3.1.1 Dynamics of Cellular Interactions

In the KTAP, the interactions involve three types of particles: test, field and candidate. As said in Chapter 1, 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:

$$\frac{df_{ij}(t)}{dt} = C_{ij}[\mathbf{f}](t) + M_{ij}[\mathbf{f}](t) + P_{ij}[\mathbf{f}](t) - D_{ij}[\mathbf{f}](t) - L_{ij}[\mathbf{f}](t) \tag{3.2}$$

for $i = 1, \cdots, 8$ and $j = 1, \cdots, m$, where C_{ij}, M_{ij}, P_{ij}, D_{ij} and L_{ij} are 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 microstate;
- $P_{ij}[\mathbf{f}](t)$ 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. The mathematical structure is written as follows:

$$\begin{aligned}
\frac{df_{ij}(t)}{dt} = J_{ij}[\mathbf{f}](t) &= \sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{ik}[\mathbf{f}]\mathcal{B}_{ik}^{pq}(j)[\mathbf{f}]f_{ip}f_{kq} - f_{ij}\sum_{k=1}^{8}\sum_{q=1}^{m}\eta_{ik}f_{kq} \\
&+ \sum_{h=1}^{8}\sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{hk}[\mathbf{f}]\mathcal{P}_{hk}^{pq}(ij)f_{hp}f_{kq} \\
&+ \sum_{h=1}^{8}\sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{hk}[\mathbf{f}]\mathcal{M}_{hk(h=i+1)}^{pq}(ij)f_{hp}f_{kq} \\
&- f_{ij}\sum_{k=1}^{8}\sum_{q=1}^{m}\eta_{ik}[\mathbf{f}]\mathcal{D}_{ik}^{jq}f_{kq} - \lambda_i(f_{ij} - f_{ij}^0) \qquad (3.3)
\end{aligned}$$

Briefly, the addends in (3.3) are modeled as follows:

$$C_{ij}[\mathbf{f}] = \sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{ik}[\mathbf{f}]\,\mathcal{B}_{ik}^{pq}(j)[\mathbf{f}]\,f_{ip}f_{kq} - f_{ij}\sum_{k=1}^{8}\sum_{q=1}^{m}\eta_{ik}f_{kq}, \tag{3.4}$$

$$P_{ij}[\mathbf{f}] = \sum_{h=1}^{8}\sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{hk}[\mathbf{f}]\mathcal{P}_{hk}^{pq}(ij)f_{hp}f_{kq}, \tag{3.5}$$

$$M_{ij}[\mathbf{f}] = \sum_{h=1}^{8}\sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{hk}[\mathbf{f}]\mathcal{M}_{hk(h=i+1)}^{pq}(ij)f_{hp}f_{kq}, \tag{3.6}$$

$$D_{ij}[\mathbf{f}] = f_{ij}\sum_{k=1}^{8}\sum_{q=1}^{m}\eta_{ik}[\mathbf{f}]\mathcal{D}_{ik}^{jq}f_{kq}, \qquad (i=2,3,4), \tag{3.7}$$

$$L_{ij}[\mathbf{f}] = \lambda_i(f_{ij} - f_{ij}^0), \qquad (i=5,6,7,8). \tag{3.8}$$

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:

$$\sum_{i=1}^{8}\sum_{k=1}^{8}\sum_{p=1}^{m}\sum_{q=1}^{m}\mathcal{B}_{ik}^{pq}[\mathbf{f}](u_p \to u|u_p,u^q) = 1, \quad \forall\, u_p, u^q \in D_u. \tag{3.9}$$

- $\mathcal{P}_{hk}^{pq} = \mathcal{P}_{hk}^{pq}[\mathbf{f}](ij)$ 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.

3.1.2 Modeling 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: $\eta_{hk}[\mathbf{f}] = \eta^0_{hk}[\mathbf{f}](d_{hk})$. Different distances can be chosen depending on the system in consideration [15]. Bellouquid *et al.* (2013) [7] 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:

$$\eta_{hk}[\mathbf{f}] = \eta^{(0)}_{hk}[\mathbf{f}]\, d_{hk}[\mathbf{f}], \tag{3.10}$$

where

$$d_{hk}[\mathbf{f}] = \begin{cases} \exp\left(-\tau \dfrac{\|f_h - f_k\|}{\|f_h\| + \|f_k\|}\right), & \|f_h\|, \|f_k\| \neq 0, \tau > 0, \\ 0, & \|f_h\| = \|f_k\| = 0, \end{cases} \tag{3.11}$$

and τ is a positive real constant.

The function $\eta^{(0)}_{hk}$ 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 $\eta_0 > 0$), in sense that the encounters between epithelial and cancer cells increases with the hallmark h, as progressive hallmarks correspond to increasing activation to search nutrients for increasing proliferation, while is assumed constant for the encounters between immune and cancer cells ($\eta_{hk}[\mathbf{f}] = \eta_0 \sigma\, d_{hk}[\mathbf{f}]$, with $\sigma > 0$), for each pair $(h, k) = (5, 2), (6, 2)$, $(6, 3)$,$(7, 2)$, $(7, 3), (7, 4)$, $(8, 2)$, $(8, 3)$, $(8, 4)$, in sense that immune cells have the ability to identify cancer cells only if they have acquired this specific ability after a learning process.

The dimensionless parameter η_0 corresponds to the 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:

$$\eta_{hk} = \begin{pmatrix} d_{11} & 2d_{21} & 3d_{31} & 4d_{41} & 0 & 0 & 0 & 0 \\ 2d_{21} & 0 & 0 & 0 & \sigma d_{52} & \sigma d_{62} & \sigma d_{72} & \sigma d_{82} \\ 3d_{31} & 0 & 0 & 0 & 0 & \sigma d_{63} & \sigma d_{73} & \sigma d_{83} \\ 4d_{41} & 0 & 0 & 0 & 0 & 0 & \sigma d_{74} & \sigma d_{84} \\ 0 & \sigma d_{52} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma d_{62} & \sigma d_{63} & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma d_{72} & \sigma d_{73} & \sigma d_{74} & 0 & 0 & 0 & 0 \\ 0 & \sigma d_{82} & \sigma d_{83} & \sigma d_{84} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.12}$$

In accordance with (4.12), we can formulate the following remarks:

Remark 3.1.1. *Encounter rates are symmetric:* $\eta_{hk} = \eta_{kh}, \quad \forall h, k, p, q.$

Now in accordance with the matrix above, we can be set the following assumption:

Remark 3.1.2. *The encounter rate is assumed to be equal to zero in the following cases:*

1 - for encounters involving only cancer cells, $\eta_{hk}[\mathbf{f}] = 0$, $\forall h, k = 2, 3, 4$.

2 - For encounters involving only immune cells.

3 - For encounters between the epithelial cell $h = 1$ and the immune cells $k = 5, 6, 7, 8$.

4 - When the immune cells do not have ability to identify cancer cells, for example for each couples $(h, k) = (5, 3)$, $(5, 4)$, $(6, 4)$.

3.1.3 Modeling 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 the 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.

Remark 3.1.3. *It is assumed that the transition probability density is zero when the encounter rate is zero.*

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. [7], we assume the structure for the matrix whose elements express the transition probability densities to be given by:

$$\mathcal{B}_{ik}^{pq} = \begin{pmatrix} \mathcal{B}_{11}^{pq} & 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ \mathcal{B}_{21}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{B}_{31}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{B}_{41}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{B}_{52}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{B}_{62}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \mathcal{B}_{73}^{pq} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mathcal{B}_{84}^{pq} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.13}$$

where in particular the nonzero elements are given as follows:

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

$$\mathcal{B}_{1k}^{pq}(p) = 1. \tag{3.14}$$

- *Interactions involving the functional subsystems $h = 1, 2, 3, 4$ (epithelial and cancer cells) and the epithelial subsystem $k = 1$.* In this case, epithelial cells are assumed to feed progression in the activity of epithelial $h = 1$ and cancer cells $h = 2, 3, 4$ after interactions. For this, 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 get:

$$\mathcal{B}_{h1}^{pq}(j) = \begin{cases} \alpha\,(1 - u_p)\,, & j = p + 1,\ \alpha \in (0, 1], \\ 1 - \alpha\,(1 - u_p)\,, & j = p, \\ 0 & \text{otherwise.} \end{cases} \tag{3.15}$$

- *Interactions involving the functional subsystems $h = 5, 6, 7, 8$ (immune cells) with functional subsystems involving cancer cells $k = 2, 3, 4$.* Immune cells acquire progressively the ability to identify cancer cells of successive hallmarks. As a consequence, immune cells may increase their state and the probability of progression of cancer cells decreases with increasing p-th-state: Thus, we have:

$$\mathcal{B}_{52}^{pq}(j) = \mathcal{B}_{62}^{pq}(j) = \mathcal{B}_{73}^{pq}(j) = \mathcal{B}_{84}^{pq}(j) = \begin{cases} \alpha\,(1 - u_p)\,, & j = p + 1,\ \alpha \in (0, 1], \\ 1 - \alpha\,(1 - u_p)\,, & j = p, \\ 0, & \text{otherwise.} \end{cases} \tag{3.16}$$

- Interactions between cancer cells ($h = 2, 3, 4$) with immune system cells ($k = 5, 6, 7, 8$). It is assumed that these types of interactions do not induce biological events to cancer cells. Therefore, the result of these interactions gives zero.

In accordance to all mentioned in subsections 3.1.2 and 3.1.3, the conservative interactions are modelled by substituting the equations (3.10)–(3.16) in the term $C_{ij}[\mathbf{f}]$ in the equation (3.4), one gets:

$$\begin{aligned} \mathcal{C}_{1j}[\mathbf{f}] &= d_{11}[\mathbf{f}]\alpha(1 - u_{j-1})\,(1 - \delta_{1j})\,f_{1(j-1)}n_1[\mathbf{f}] \\ &+ d_{11}[\mathbf{f}]\,[1 - \alpha(1 - u_j)]\,f_{1j}n_1[\mathbf{f}] - d_{11}[\mathbf{f}]f_{1j}n_1[\mathbf{f}] \end{aligned} \tag{3.17}$$

$$\begin{aligned}
\mathcal{C}_{2j}[\mathbf{f}] &= d_{21}[\mathbf{f}]\alpha(1-u_{j-1})\,(1-\delta_{1j})\,f_{2(j-1)}n_1[\mathbf{f}] \\
&+ d_{21}[\mathbf{f}]\,[1-\alpha(1-u_j)]\,f_{2j}n_1[\mathbf{f}] - d_{21}[\mathbf{f}]f_{2j}n_1[\mathbf{f}] \\
&- \sigma d_{52}f_{2j}n_5[\mathbf{f}] - \sigma d_{62}f_{2j}n_6[\mathbf{f}] - \sigma d_{72}f_{2j}n_7[\mathbf{f}] \\
&- d_{82}f_{2j}n_8[\mathbf{f}], \qquad (3.18)
\end{aligned}$$

$$\begin{aligned}
\mathcal{C}_{3j}[\mathbf{f}] &= d_{31}[\mathbf{f}]\alpha(1-u_{j-1})\,(1-\delta_{1j})\,f_{3(j-1)}n_1[\mathbf{f}] \\
&+ d_{31}[\mathbf{f}]\,[1-\alpha(1-u_j)]\,f_{3j}n_1[\mathbf{f}] - d_{31}[\mathbf{f}]f_{3j}n_1[\mathbf{f}] \\
&- \sigma d_{36}f_{3j}n_6[\mathbf{f}] - \sigma d_{37}f_{3j}n_7[\mathbf{f}] - \sigma d_{38}f_{3j}n_8[\mathbf{f}], \qquad (3.19)
\end{aligned}$$

$$\begin{aligned}
\mathcal{C}_{4j}[\mathbf{f}] &= d_{41}[\mathbf{f}]\alpha(1-u_{j-1})\,(1-\delta_{1j})\,f_{4(j-1)}n_1[\mathbf{f}] \\
&+ d_{11}[\mathbf{f}]\,[1-\alpha(1-u_j)]\,f_{4j}n_1[\mathbf{f}] - d_{41}[\mathbf{f}]f_{4j}n_1[\mathbf{f}] \\
&- \sigma d_{41}f_{4j}n_7[\mathbf{f}] - \sigma d_{48}f_{4j}n_8[\mathbf{f}], \qquad (3.20)
\end{aligned}$$

$$\begin{aligned}
\mathcal{C}_{5j}[\mathbf{f}] &= \sigma d_{52}[\mathbf{f}]\alpha(1-u_{j-1})\,(1-\delta_{1j})\,f_{5(j-1)}n_2[\mathbf{f}] \\
&+ \sigma d_{52}[\mathbf{f}]\,[1-\alpha(1-u_j)]\,f_{5j}n_2[\mathbf{f}] - \sigma d_{52}[\mathbf{f}]f_{5j}n_2[\mathbf{f}], \qquad (3.21)
\end{aligned}$$

$$\begin{aligned}
\mathcal{C}_{6j}[\mathbf{f}] &= \sigma d_{62}[\mathbf{f}]\alpha(1-u_{j-1})\,(1-\delta_{1j})\,f_{6(j-1)}n_2[\mathbf{f}] \\
&+ \sigma d_{62}[\mathbf{f}]\,[1-\alpha(1-u_j)]\,f_{6j}n_2[\mathbf{f}] - \sigma d_{62}[\mathbf{f}]f_{6j}n_2[\mathbf{f}] \\
&- \sigma d_{63}[\mathbf{f}]f_{6j}n_3[\mathbf{f}], \qquad (3.22)
\end{aligned}$$

$$\begin{aligned}
\mathcal{C}_{7j}[\mathbf{f}] &= \sigma d_{73}[\mathbf{f}]\alpha(1-u_{j-1})\,(1-\delta_{1j})\,f_{7(j-1)}n_3[\mathbf{f}] \\
&+ \sigma d_{73}[\mathbf{f}]\,[1-\alpha(1-u_j)]\,f_{7j}n_3[\mathbf{f}] - \sigma d_{72}[\mathbf{f}]f_{7j}n_2[\mathbf{f}] \\
&- \sigma d_{73}[\mathbf{f}]f_{7j}n_3[\mathbf{f}] - \sigma d_{74}[\mathbf{f}]f_{7j}n_4[\mathbf{f}], \qquad (3.23)
\end{aligned}$$

$$\begin{aligned}
\mathcal{C}_{8j}[\mathbf{f}] &= \sigma d_{84}[\mathbf{f}]\alpha(1-u_{j-1})\,(1-\delta_{1j})\,f_{8(j-1)}n_4[\mathbf{f}] \\
&+ \sigma d_{84}[\mathbf{f}]\,[1-\alpha(1-u_j)]\,f_{8j}n_4[\mathbf{f}] - \sigma d_{83}[\mathbf{f}]f_{8j}n_3[\mathbf{f}] \\
&- \sigma d_{84}[\mathbf{f}]f_{8j}n_4[\mathbf{f}], \qquad (3.24)
\end{aligned}$$

Remark 3.1.4. *We recall that δ_{ij} denotes the Kronecker delta defined as follows:*

$$\delta_{ij} = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases}$$

3.1.4 Modeling Proliferative Events

The proliferative events dynamics is modeled as follows: A candidate-cell (mother cell) of subsystem h with a state p, by interacting with a field-cell from subsystem k, with the state q, proliferate a daughter cell of the same subsystem, and with the same activity. Following Bellouquid et al. (2013), these events are modeled by the following matrix expression:

$$\mathcal{P}_{hk} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{P}_{21}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{P}_{31}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{P}_{41}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{P}_{62}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{P}_{72}^{pq} & \mathcal{P}_{73}^{pq} & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{P}_{82}^{pq} & \mathcal{P}_{83}^{pq} & \mathcal{P}_{84}^{pq} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.25}$$

In particular, one has:

- *Proliferations in cancer subsystems* $h = 2, 3, 4$. They are related to the encounters with particles of the first functional subsystem $k = 1$. In this case, the proliferation increases with the hallmarks of cancer cells, due to the increasing proliferation program which is an acquired capability of tumor cells. So, we assume:

$$\mathcal{P}_{h1}^{pq}(hj) = \begin{cases} \beta_1 h u_p, & \text{with } j = p,\ \beta_1 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.26}$$

  where β_1 is a positive coefficient that models the proliferation rate in cancer subsystems.

- *Proliferations 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:

$$\mathcal{P}_{hk}^{pq}(hj) = \begin{cases} \beta_2, & \text{with } j = p,\ \beta_2 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.27}$$

  for each pair $(h, k) = (6, 2), (7, 2), (7, 3), (8, 2), (8, 3), (8, 4)$. Coefficient β_2 model the proliferation rate for immune cells.

The dynamics of the proliferation is obtained substituting the equations (3.26) and (3.27) in the term $P_{ij}[\mathbf{f}]$ in the equation (3.5), together with the equations in the Section 3.1.2. We found:

$$P_{2j}[\mathbf{f}] = 4d_{21}[\mathbf{f}]\beta_1 u_j f_{2j} n_1[\mathbf{f}], \tag{3.28}$$

$$P_{3j}[\mathbf{f}] = 9d_{31}[\mathbf{f}]\beta_1 u_j f_{3j} n_1[\mathbf{f}], \tag{3.29}$$

$$P_{4j}[\mathbf{f}] = 16d_{41}[\mathbf{f}]\beta_1 u_j f_{4j} n_1[\mathbf{f}], \tag{3.30}$$

$$P_{6j}[\mathbf{f}] = \sigma d_{62}[\mathbf{f}]\beta_2 f_{6j} n_2[\mathbf{f}], \tag{3.31}$$

$$P_{7j}[\mathbf{f}] = \sigma d_{72}[\mathbf{f}]\beta_2 f_{7j} n_2[\mathbf{f}] + \sigma d_{73}[\mathbf{f}]\beta_2 f_{7j} n_3[\mathbf{f}], \tag{3.32}$$

$$P_{8j}[\mathbf{f}] = \sigma d_{82}[\mathbf{f}]\beta_2 f_{8j} n_2[\mathbf{f}] + \sigma d_{83}[\mathbf{f}]\beta_2 f_{8j} n_3[\mathbf{f}] + \sigma d_{84}[\mathbf{f}]\beta_2 f_{8j} n_4[\mathbf{f}], \tag{3.33}$$

While $P_{1j}[\mathbf{f}] = P_{5j}[\mathbf{f}] = 0$.

3.1.5 Modeling Mutation Events

Mutation events refer to changes 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:

$$\mathcal{M}_{hk}^{pq} = \begin{pmatrix} \mathcal{M}_{11}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{M}_{21}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{M}_{31}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{M}_{52}^{pq} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \mathcal{M}_{63}^{pq} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mathcal{M}_{74}^{pq} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.34}$$

with the following assumptions [7]:

- *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:

$$\mathcal{M}_{h1}^{pq}(ij) = \begin{cases} \varepsilon_1 u_p, & \text{with } i = h + 1, j = 1, \varepsilon_1 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.35}$$

  where coefficient ε_1 models the mutation rate for cancer cells.

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

$$\mathcal{M}_{52}^{pq}(6j) = \begin{cases} \varepsilon_{26} u_p, & \text{with } j = 1, \varepsilon_{26} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.36}$$

$$\mathcal{M}_{63}^{pq}(7j) = \begin{cases} \varepsilon_{27} u_p & \text{with } j = 1, \varepsilon_{27} > 0 \\ 0 & \text{otherwise.} \end{cases} \tag{3.37}$$

$$\mathcal{M}_{74}^{pq}(8j) = \begin{cases} \varepsilon_{28} u_p & \text{with } j = 1, \varepsilon_{28} > 0 \\ 0 & \text{otherwise.} \end{cases} \tag{3.38}$$

  Coefficients $\varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28}$ characterize the mutation rate for immune cells.

The dynamics of mutation is obtained substituting the equations (3.35), (3.36), (3.37) and (3.38) in the term $M_{ij}[\mathbf{f}]$ in the equation (3.6), together with the equations written in Section 3.1.2. It follows:

$$M_{1j}[\mathbf{f}] = d_{11}[\mathbf{f}] \varepsilon_1 \delta_{1j} n_1[\mathbf{f}] \sum_{p=1}^{m} u_p f_{1p}, \tag{3.39}$$

$$M_{2j}[\mathbf{f}] = 2 d_{21}[\mathbf{f}] \varepsilon_1 \delta_{1j} n_1[\mathbf{f}] \sum_{p=1}^{m} u_p f_{2p}, \tag{3.40}$$

$$M_{3j}[\mathbf{f}] = 3 d_{31}[\mathbf{f}] \varepsilon_1 \delta_{1j} n_1[\mathbf{f}] \sum_{p=1}^{m} u_p f_{3p}, \tag{3.41}$$

$$M_{5j}[\mathbf{f}] = \sigma d_{52}[\mathbf{f}] \varepsilon_{26} \delta_{1j} n_2[\mathbf{f}] \sum_{p=1}^{m} u_p f_{5p}, \tag{3.42}$$

$$M_{6j}[\mathbf{f}] = \sigma d_{63}[\mathbf{f}] \varepsilon_{27} \delta_{1j} n_3[\mathbf{f}] \sum_{p=1}^{m} u_p f_{6p}, \tag{3.43}$$

$$M_{7j}[\mathbf{f}] = \sigma d_{74}[\mathbf{f}] \varepsilon_{28} \delta_{1j} n_4[\mathbf{f}] \sum_{p=1}^{m} u_p f_{7p}, \tag{3.44}$$

while $M_{4j}[\mathbf{f}] = M_{8j}[\mathbf{f}] = 0$.

3.1.6 Modeling Destructive Events

Destructive events refer to the loss dynamics. The dynamics of the destructive interactions follow 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 increased activity of immune cells. For the rate $\mathcal{D}_{hk}^{pq}$, we assume the following matrix:

$$\mathcal{D}_{hk}^{pq} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \mathcal{D}_{26}^{pq} & \mathcal{D}_{27}^{pq} & \mathcal{D}_{28}^{pq} \\ 0 & 0 & 0 & 0 & 0 & 0 & \mathcal{D}_{37}^{pq} & \mathcal{D}_{38}^{pq} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mathcal{D}_{48}^{pq} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.45}$$

where

$$\mathcal{D}_{26}^{pq} = \mathcal{D}_{27}^{pq} = \mathcal{D}_{28}^{pq} = \mathcal{D}_{37}^{pq} = \mathcal{D}_{38}^{pq} = \mathcal{D}_{48}^{pq} = \gamma u_q \;\; and \;\; \gamma > 0. \tag{3.46}$$

and γ refers to suppression rate.

The destruction dynamics is obtained substituting the equations in the Section 3.1.2 and the equation (3.46) in the term $D_{ij}[\mathbf{f}]$ in equation (3.7). It follows:

$$D_{2j}[\mathbf{f}] = \sigma\gamma f_{2j} \sum_{q=1}^{m} u_q \left(d_{26}[\mathbf{f}] f_{6q} + d_{27}[\mathbf{f}] f_{7q} + d_{28}[\mathbf{f}] f_{8q} \right), \tag{3.47}$$

$$D_{3j}[\mathbf{f}] = \sigma\gamma f_{3j} \sum_{q=1}^{m} u_q \left(d_{37}[\mathbf{f}] f_{7q} + d_{38}[\mathbf{f}] f_{8q} \right), \tag{3.48}$$

$$D_{4j}[\mathbf{f}] = \sigma\gamma f_{4j} \sum_{q=1}^{m} u_q d_{48}[\mathbf{f}] f_{8q}, \tag{3.49}$$

while $D_{1j}[\mathbf{f}] = D_{5j}[\mathbf{f}] = D_{6j}[\mathbf{f}] = D_{7j}[\mathbf{f}] = D_{8j}[\mathbf{f}] = 0$.

3.1.7 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 (3.8) $\lambda_i = 0$ for $i = 2, 3, 4$, and $\lambda_i = \lambda = constant$ for $i = 5, 6, 7, 8$. Thus we have:

$$L_{ij}[\mathbf{f}] = \lambda(f_{ij} - f_{ij}^0), \quad i = 5, 6, 7, 8. \tag{3.50}$$

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

3.2 Simulations and Emerging Behaviors

A general mathematical framework describing the overall state of the system has been proposed in system (3.3), characterized by $8 \times m$ ordinary differential equations in the unknown distribution function $f_{ij} : \mathbb{R}^+ \to \mathbb{R}^+$, where $i = 1, \cdots 8$ and $j = 1, \cdots m$. The dynamical equations can be obtained substituting the previous assumptions on the right-hand side of system (3.3), thus reducing the complexity of the large number of components. The model is characterized by the 11 unknown parameters: $\alpha, \sigma, \tau, \beta_1, \beta_2, \gamma, \lambda, \varepsilon_1, \varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28}$; these parameters are physically well-defined and are related with the interactions and the encounters among the cells, each one referring to a specific event, in order to clarify the phenomenon under consideration. In this section, we will make use of simulations for visualizing 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 (3.3) which can be written as follows:

$$\begin{cases} \dfrac{df_{ij}(t)}{dt} = J_{ij}[\mathbf{f}], \\ \\ f_{ij}(0) = f_{ij}^0, \end{cases} \tag{3.51}$$

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

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

for $i = 1, \cdots, 8$ and $j = 1, \cdots, m$

To begin the Simulations, firstly, 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 $n_8 = n_{81} + n_{82} + n_{83}$.

3.2.1 Primary 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: $\sigma = 0.5$, $\tau = 1$, $\gamma = 1$, $\alpha = 10^{-2}$, $\lambda = 0.02$, $\beta_1 = 10^{-3}$, $\beta_2 = 10^{-1}$, $\varepsilon_1 = 10^{-3}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$, and different values of $\varepsilon_{28} = 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}$, that are those which had considered in paper [7]. The results are shown in the Figure 3.1.

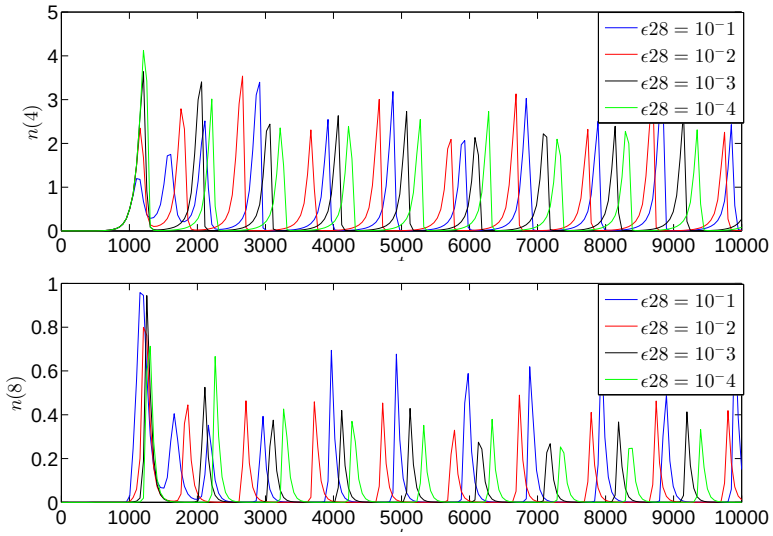

Figure 3.1: *Plot n(4) and n(8). The two figures are obtained with different values of parameter* ε_{28} *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

As one sees in the Figure 3.1, the plots show aperiodic oscillations with 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.

3.2.2 Modify the Parameters to Improve the Overall State of the System

- Firstly, in the figure 3.2 we can seen that the number density of cancer (abnormal cells) of the last hallmark rapidly proliferate for $\varepsilon_{28} = 0$, as the immune system is not able to deplete the cancer cells.

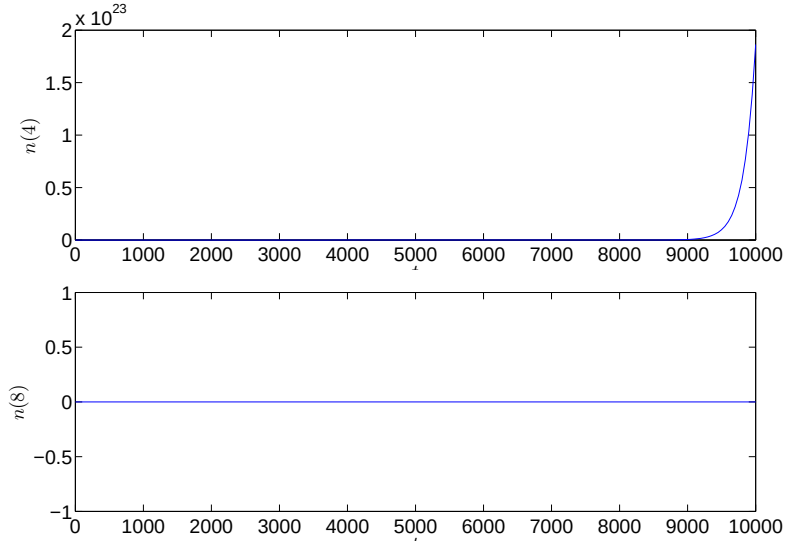

Figure 3.2: *Plot of* $n_4 = n_{41} + n_{42} + n_{43}$ *and of* $n_8 = n_{81} + n_{82} + n_{83}$ *obtained with* $\varepsilon_{28} = 0$*, and with initial condition* $f_1^0 = (1, 0, 0)$*,* $f_5^0 = (0.2, 0, 0)$

- We first modify the parameters β_1 and β_2 that characterize the proliferation rate of cancer and immune system cells of the various hallmarks. The best result is shown in Figure 3.3, it corresponds to $\tau = 1$, $\gamma = 1$, $\varepsilon_1 = 10^{-3}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$, $\varepsilon_{28} = 10^{-2}$, $\alpha = 10^{-2}$, $\beta_1 = 10^{-4}$, $\beta_2 = 10^{-1}$ and $\lambda = 0.02$. Compared with $n(4)$ and $n(8)$ in Figure 3.1, the plot in Figure 3.3 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.

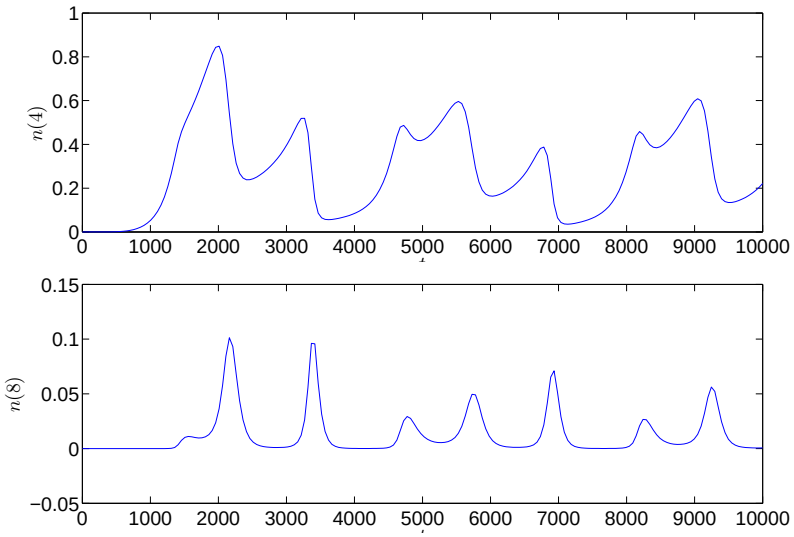

Figure 3.3: *Modify* β_1 *and* β_2*. Plot n(4) and n(8), obtained with* $\beta_1 = 10^{-4}$ *and* $\beta_2 = 10^{-1}$*, with initial conditions* $f_1^0 = (1, 0, 0)$*,* $f_5^0 = (0.2, 0, 0)$*, at the time* $t = 10000$

- 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 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 3.4. One sees beginning diminishing oscillations of n_4 and n_8.

- 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 3.5, 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 $\beta_2 = 10^{-1}$.

- 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 3.6. 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.

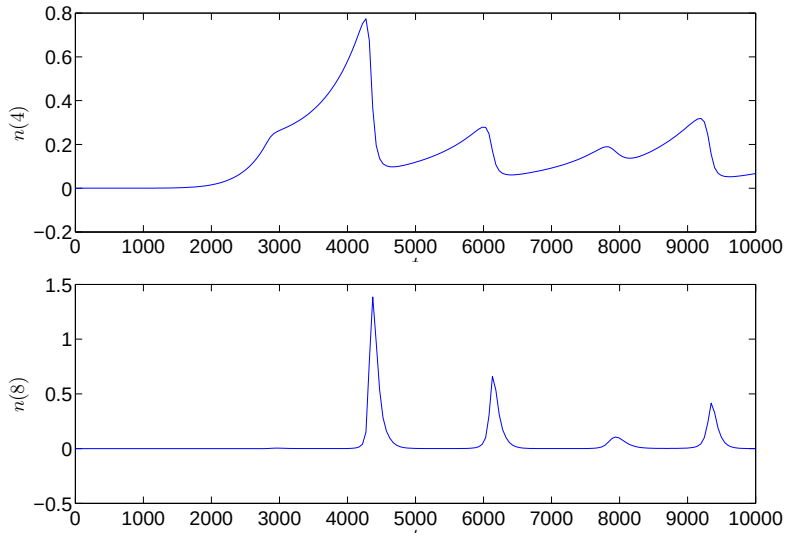

Figure 3.4: *Modify* α*. Plot* $n(4)$ *and* $n(8)$*, obtained with* $\alpha = 10^{-3}$*, with initial conditions* $f_1^0 = (1, 0, 0)$*,* $f_5^0 = (0.2, 0, 0)$*, at the time* $t = 10000$*.*

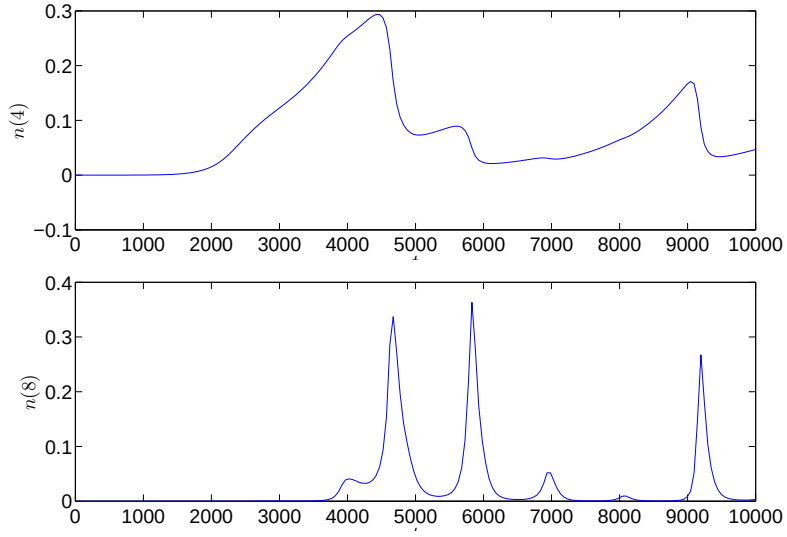

Figure 3.5: *Modify* σ*. Plot* $n(4)$ *and* $n(8)$*, obtained with* $\sigma = 0.9$*, and with initial conditions* $f_1^0 = (1, 0, 0)$*,* $f_5^0 = (0.2, 0, 0)$*, at the time* $t = 10000$*.*

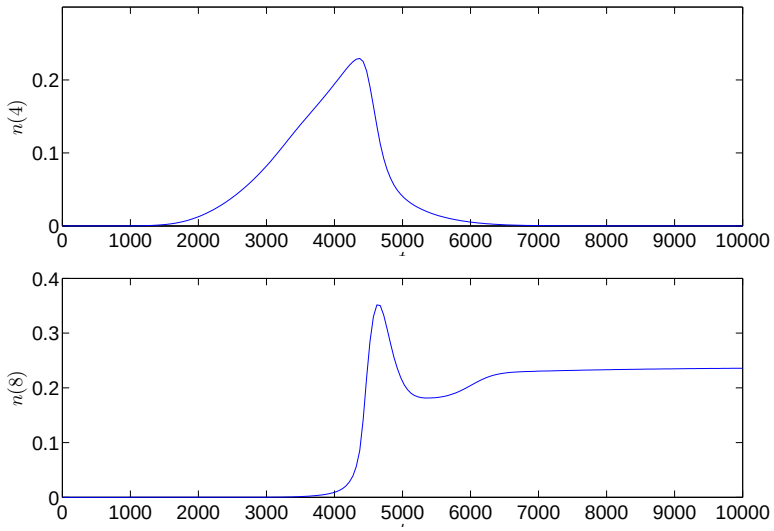

Figure 3.6: *Modify* λ. *Plot* $n(4)$ *and* $n(8)$, *obtained with* $\lambda = 0.01$, *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

After the satisfactory results that are shown in Figure 3.6, 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 3.7. 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.

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 3.8 and 3.9.

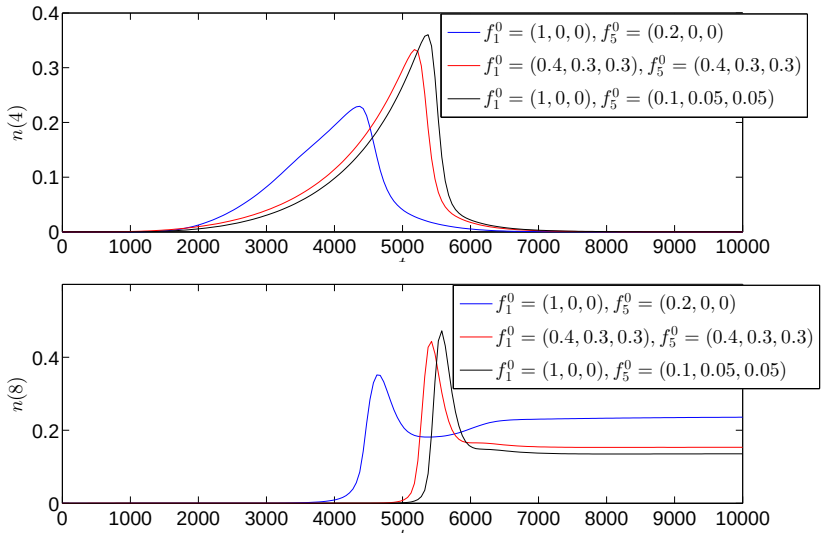

Figure 3.7: *Modify the initial conditions. Plot* $n(4)$ *and* $n(8)$ *obtained varying the initial conditions.*

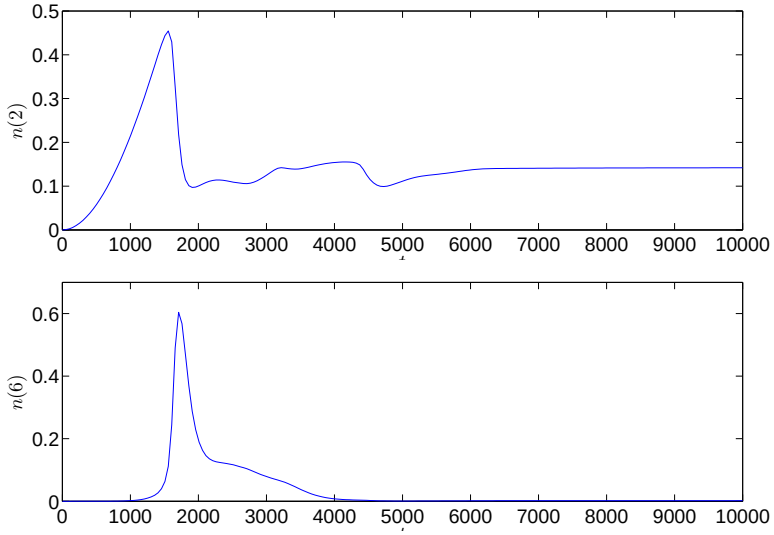

Figure 3.8: *Plot of* $n(2)$ *and* $n(6)$*, with initial conditions* $f_1^0 = (1,0,0)$*,* $f_5^0 = (0.2,0,0)$*, at the time* $t = 10000$*.*

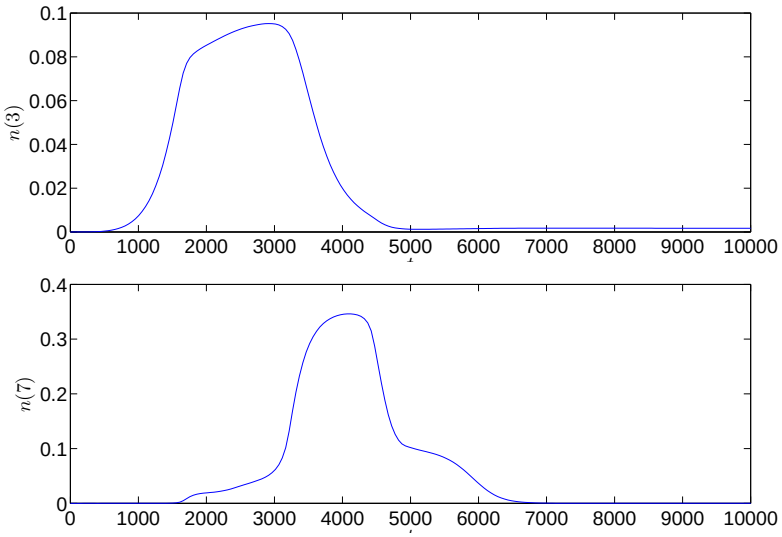

Figure 3.9: *Plot* $n(3)$ *and* $n(7)$*, with initial conditions* $f_1^0 = (1, 0, 0)$*,* $f_5^0 = (0.2, 0, 0)$*, at the time* $t = 10000$*.*

3.2.3 Secondary Numerical Analysis

The results we have obtained in Section 3.2.2 showed that the immune cell population is able to suppress cancer cells by selecting the parameters $\tau = 1$, $\gamma = 1$, $\alpha = 10^{-3}$, $\beta_1 = 10^{-4}$, $\beta_2 = 10^{-1}$, $\sigma = 0.9$, $\lambda = 0.01$, $\varepsilon_1 = 10^{-3}$, $\varepsilon_{28} = 10^{-2}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$. Now we go back to make some changes (one parameter at a time) on these final values for the free parameters with the aim to observe the effect of these changes on the behavior of the system.

1. $\beta_2 = 10^{-1}$. This is the appropriate value we have chosen for the parameter that characterizes the rate of production of immune system cells. We want to see what happens when we choose values of this parameter lesser or greater than that previously obtained. The results are illustrated in Figure 3.10.

   From the simulation, we note that values of β_2 lesser than 10^{-1} do not give improved results.

2. $\beta_1 = 10^{-4}$ is the value we have obtained for the proliferation rate of cancer cells. Modifying this value, one sees that β_1 should not exceed 10^{-4}, while values of lesser than 10^{-4} would give good results. The plots in Figure 3.11 support our conclusions.

3. $\lambda = 10^{-2}$ is the last parameter we have modified in the previous section

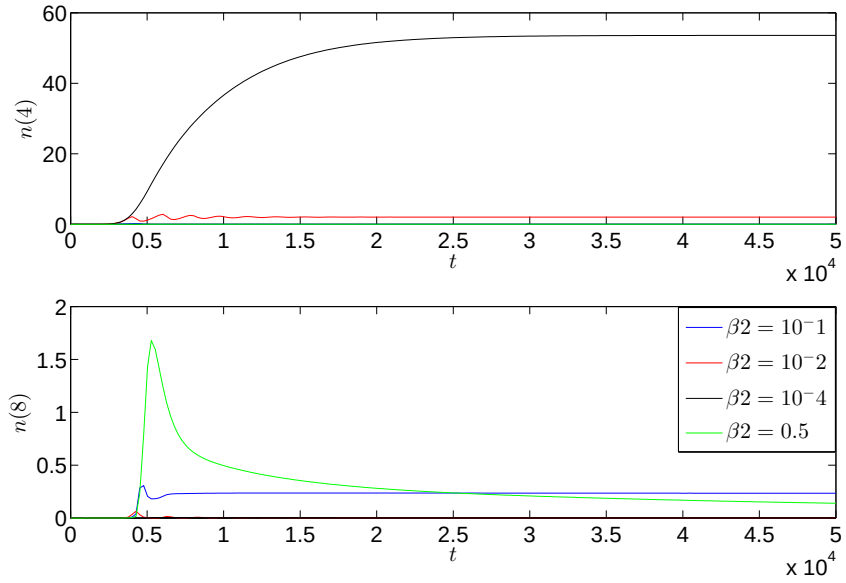

Figure 3.10: *Modify* $\beta_2 = 10^{-1}$. *Plot n(4) and n(8), obtained with* $\beta_2 = 10^{-1}$, $\beta_2 = 10^{-2}$, $\beta_2 = 10^{-4}$ *and* $\beta_2 = 0.5$, *with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 50000$.

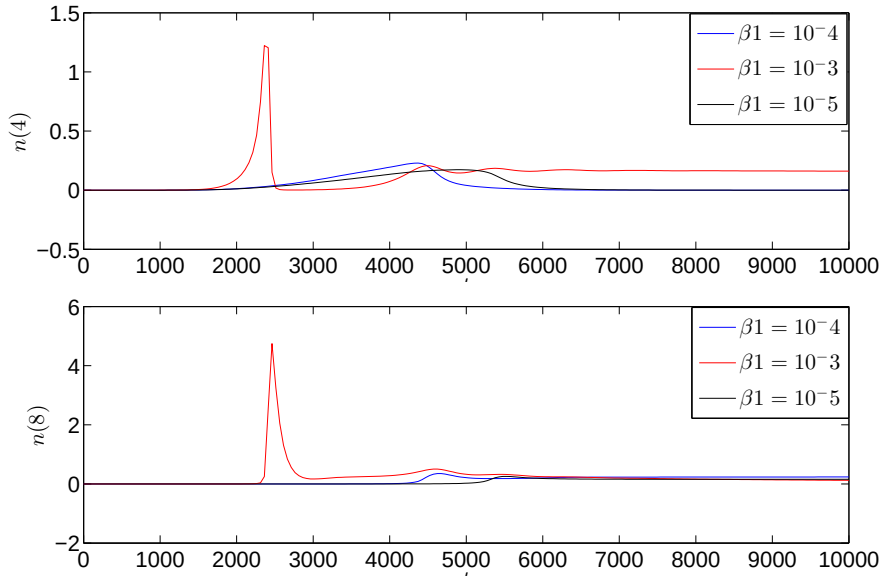

Figure 3.11: *Modify* $\beta_1 = 10^{-4}$. *Plot n(4) and n(8), obtained with* $\beta_1 = 10^{-3}$ *and* $\beta_1 = 10^{-5}$, *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

and played an active role in the stability of the behavior of the system as shown in Figure 3.6. In the simulations, we chose for it values lesser and greater than 0.01. The results are illustrated in Figure 3.12.

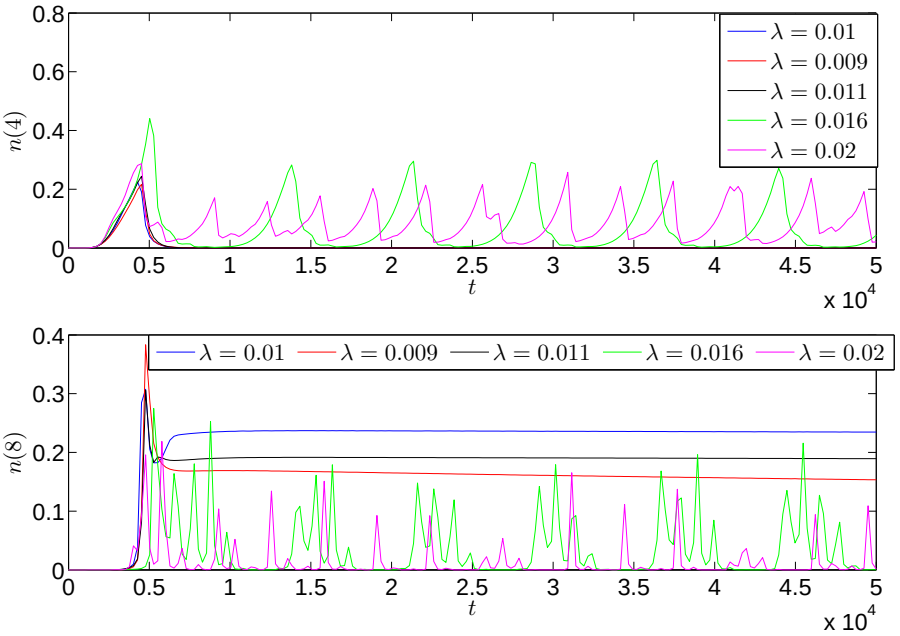

Figure 3.12: *Modify* $\lambda = 10^{-2}$. *Plot n(4) and n(8), obtained with different values of* λ, *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t =$ 50000.

As one can see, the immune cell population remains in its active state, unlike cancer cells that tend to decay to 0. One observes that the behavior of the system began to change for $\lambda = 0.016$.In fact, values for λ greater than 0.016 lead to the growth of cancer cells which start to oscillate dramatically.

4. $\alpha = 10^{-3}$ is the value that we considered among the values of satisfactory results. We will see the effect of selecting larger and smaller values than 10^{-3} on the behavior of the system. Figure 3.13 illustrates a comparison between $\alpha = 10^{-3}$, with $\alpha = 10^{-2}$ and $\alpha = 10^{-4}$. As noted, the results are good when $\alpha = 10^{-4}$ (values smaller than 10^{-3}), but when we select $\alpha = 10^{-2}$ (values greater than 10^{-3}) one gets persistent oscillations of tumor and immune cells.

5. $\sigma = 0.9$. In the previous section, we have selected for σ one of the values in the interval $[0.5, 1]$. Now we shall see the effect of smaller values on the

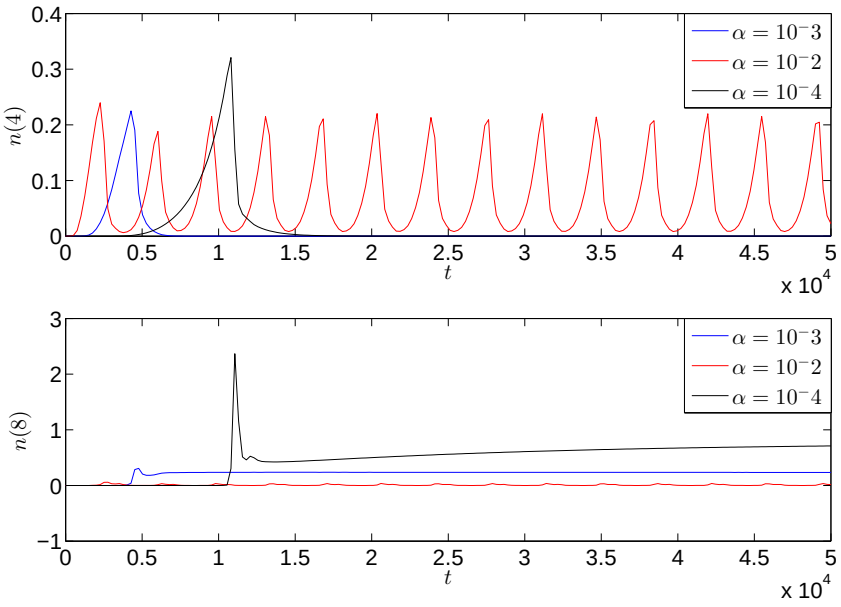

Figure 3.13: *Modify* $\alpha = 10^{-3}$. *Plot n(4) and n(8), obtained with* $\alpha = 10^{-2}, 10^{-3}, 10^{-4}$, *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 50000$.

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 Figure 3.14. One sees persistent oscillations of tumor and immune cells when $\sigma = 0.3$ and $\sigma = 0.2$ (values less than 0.5). We deduce therefore that a critical value of σ is 0.5.

6. $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$ and $\varepsilon_{28} = 10^{-2}$ are the selected values for the parameters that characterize the rate of mutations in the immune system. We make some changes in these parameters to determine the effect of the change on the behavior of the system, see Figure 3.15.

   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.

7. $\varepsilon_1 = 10^{-3}$: Now we test the effect of a 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 Figure 3.16.

   One notes that the immune system is not able to suppress cancer cells for

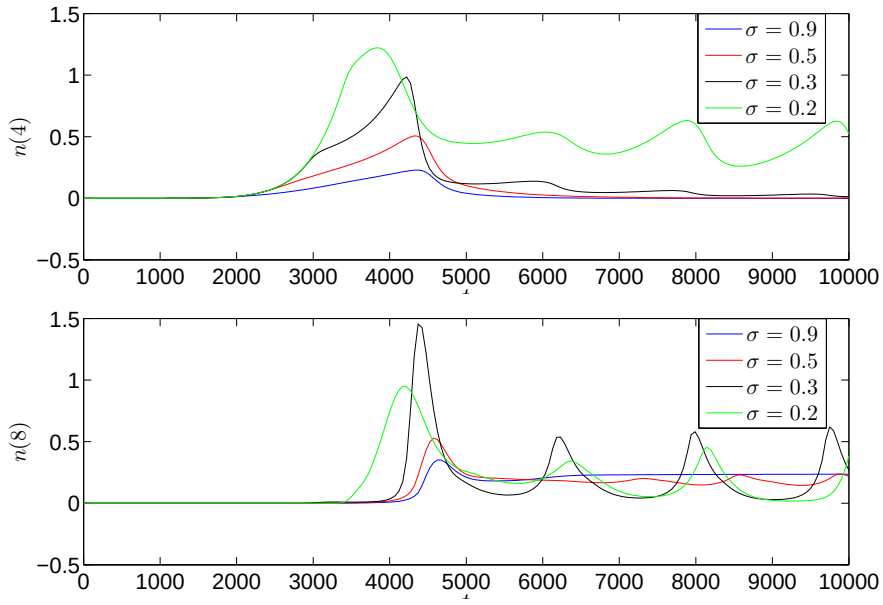

Figure 3.14: *Modify* $\sigma = 0.9$. *Plot n(4) and n(8), obtained with* $\sigma = 0.2, 0.3, 0.5, 0.9$, *and with an initial condition* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

$\varepsilon_1 = 10^{-4}$ and $\varepsilon_1 = 10^{-5}$, i.e. when the rate of mutations in the cancer cells is very small. This unexpected result deserves some considerations. Why the immune system is not able to suppress definitely the cancer cells when they have a very little rate 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 3.16. This could be due to the fact that in this situation the immune system relaxes too quickly to recognize malignant cancer cells.

8. $\gamma = 1$ is the parameter that characterizes the destruction rate of cancer cells proposed in paper [7], and that we have left unmodified in our search for the best parameter in Section 3.2.1. Naturally, the destruction rate plays a fundamental role in the immune system's ability to suppress cancer cells, as the increasing in the destruction rate, give an increasing activity of immune cells enough to repel any hostile attack. From simulations, we see that the value 0.1 did not furnish the immune system's ability to resist cancer cells. See Figure 3.17.

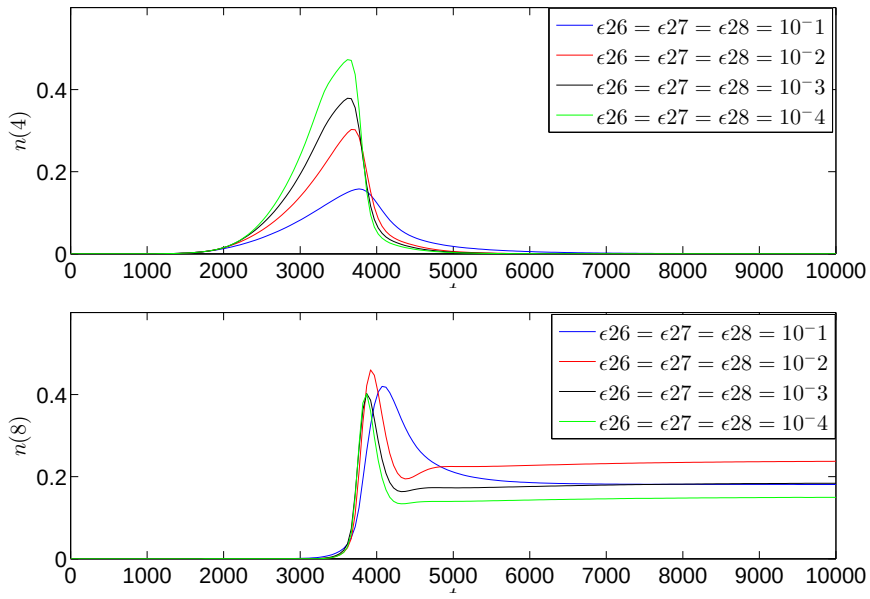

Figure 3.15: *Modify* $\varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28}$. *Plot n(4) shows evolution of the number density of cancer cells of the last hallmark* $n_4 = n_{41} + n_{42} + n_{43}$ *and n(8) shows evolution of the number density of immune cells* $n_8 = n_{81} + n_{82} + n_{83}$, *obtained 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* $t = 10000$.

3.3 Discussion of The Results and Concluding Remarks

In this section we have followed the paper of Bellouquid, De Angelis and Knopoff [7], 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 role 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

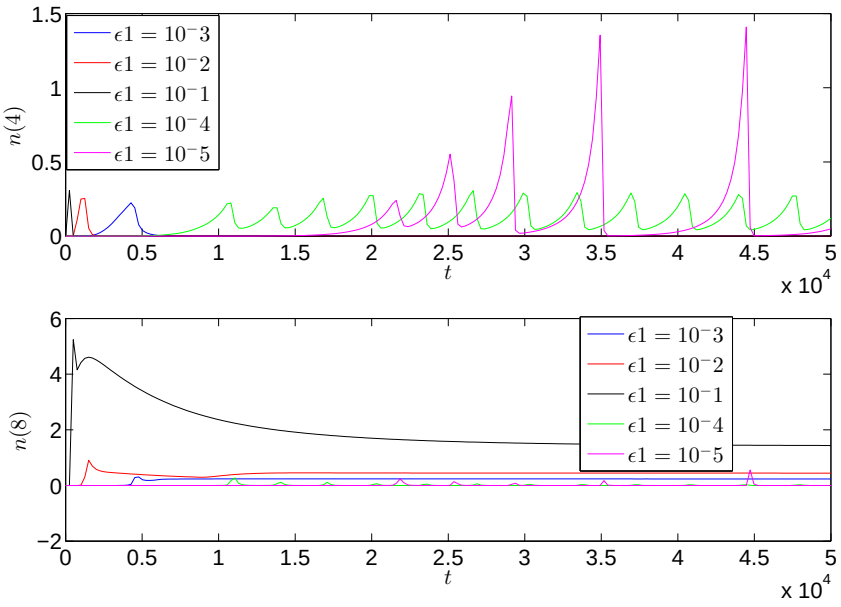

Figure 3.16: *Modify* ε_1. *Plot n(4) and n(8), obtained with different values of* ε_1, *and with an initial condition* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 50000$.

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 an the upper limit for it $\lambda_c = 0.016$.

3.4 Proposal to Develop the Model

In this section, we will go to explore the possibility of developing the above model by modifying the parameter α, that model the probability density in conservative interaction in the progression phenomena. So, we will assume different values for this parameter α_1 and α_2, where α_1 characterizes the probability of transition in the cancer cell populations, and α_2 characterizes the probability of transition in the immune system cell populations. Therefore, the equations, (3.17) and (3.16)

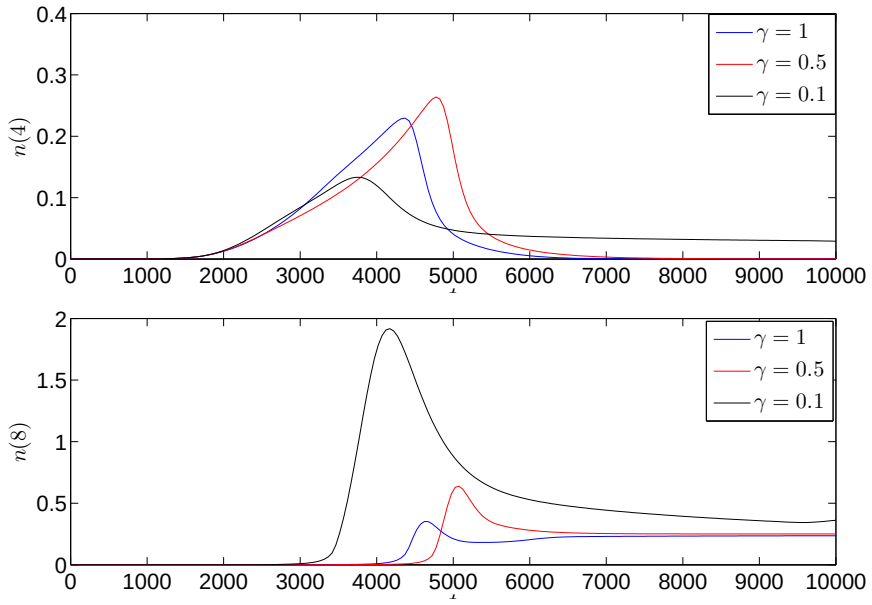

Figure 3.17: *Modify γ . Plot n(4) and n(8), obtained with different values of γ, and with initial conditions $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, at the time $t = 10000$.*

are modified as follows:

$$\mathcal{B}_{21}^{pq}(j) = \mathcal{B}_{31}^{pq}(j) = \mathcal{B}_{41}^{pq}(j) = \begin{cases} \alpha_1 (1 - u_p), & j = p + 1, \ \alpha_1 \in (0, 1], \\ 1 - \alpha_1 (1 - u_p), & j = p, \\ 0 & \text{otherwise.} \end{cases} \tag{3.52}$$

$$\mathcal{B}_{52}^{pq}(j) = \mathcal{B}_{62}^{pq}(j) = \mathcal{B}_{73}^{pq}(j) = \mathcal{B}_{84}^{pq}(j) = \begin{cases} \alpha_2 (1 - u_p), & j = p + 1, \ \alpha_2 \in (0, 1], \\ 1 - \alpha_2 (1 - u_p), & j = p, \\ 0, & \text{otherwise.} \end{cases} \tag{3.53}$$

Now, we need to introduce some different values for these two parameters for investigating their influence on the behavior of the system. Figure 3.18 shows different behavior of n_4 and n_8 with different values of α_1 and α_2.

As expected, Figure 3.18 show results analogous to those of the Figure 3.4: the results are good in the case when $\alpha_1 = \alpha_2 = 10^{-4}$, which values smaller than 10^{-3}, but when we selected values of $\alpha_1 = \alpha_2$ greater than 10^{-3} the result gave persistent oscillations of tumor and immune cells.

Now, we must investigate the role played by changing the parameter α_1 with fix $\alpha_2 = 10^{-3}$ and show how it modifies the behavior of the system. This will be illustrated in Figure 3.19.

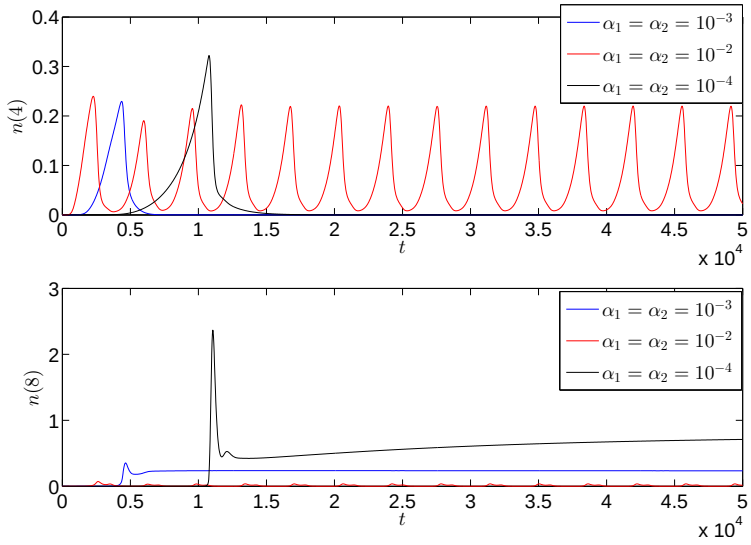

Figure 3.18: *Plot n(4) shows evolution of the number density of cancer cells of the last hallmark and n(8) shows evolution of the number density of immune cells, obtained with* $\alpha_1 = 10^{-3}, 10^{-2}, 10^{-4}$, $\alpha_2 = 10^{-3}, 10^{-2}, 10^{-4}$ *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

As noted, the immune system cells are not able to deplete cancer cells completely at $\alpha_1 = 10^{-2}$ and at $\alpha_1 = 10^{-1}$, this means that the coefficient α_1 that characterizes the probability density in the cancer cell populations, should not take greater values than 10^{-3}, because these high values increase the possibility of cancer cells to escape immune recognition, as we have seen in the Figure 3.19,.

On the other hand, we will show what happens if we change the parameter α_2, with fix $\alpha_1 = 10^{-3}$, in order to show how this parameter influences the behavior of the system. This will be illustrated in Figure 3.20.

One sees that the persistent oscillations of tumor look clearly that, when we selected values greater than 10^{-3}, the cancer cells become most aggressive.

Naturally, the model studied in this chapter does not describe phenomena as the angiogenesis, the tissue invasion and metastasis. However, the results of our simulation show that the importance of the activity of 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.

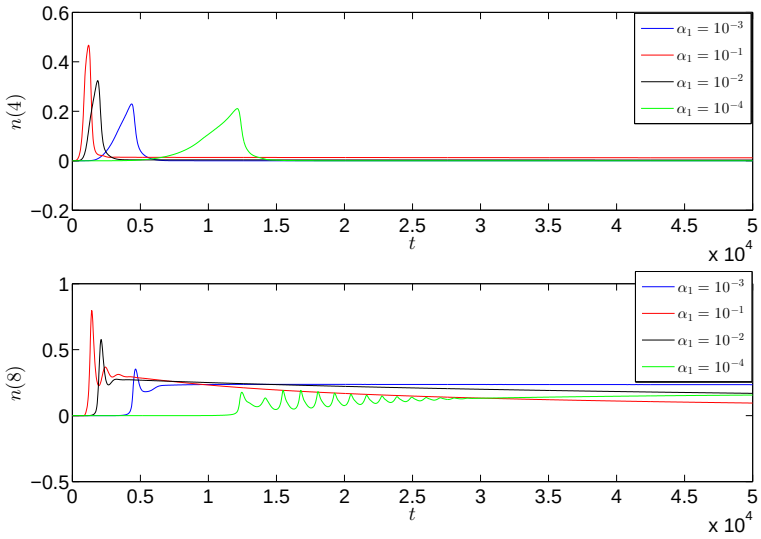

Figure 3.19: *Plot n(4) shows evolution of the number density of cancer cells of the last hallmark and n(8) shows evolution of the number density of immune cells, obtained with* $\alpha_1 = 10^{-3}, 10^{-1}, 10^{-2}, 10^{-4}$ *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

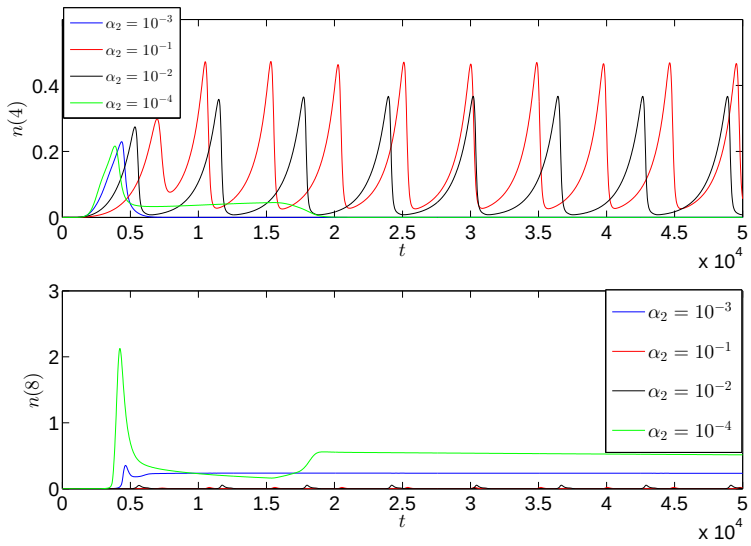

Figure 3.20: *Plot n(4) shows evolution of the number density of cancer cells of the last hallmark and n(8) shows evolution of the number density of immune cells , obtained with* $\alpha_2 = 10^{-3}, 10^{-1}, 10^{-2}, 10^{-4}$ *and with initial conditions* $f_1^0 = (1, 0, 0)$, $f_5^0 = (0.2, 0, 0)$, *at the time* $t = 10000$.

3.5 Appendix 3.A: The Code Used by Matlab to Obtain Simulations of the Spatially Homogeneous Discrete Model

In Matlab, we can use numerical integration techniques to solve the system of ordinary differential equations 3.51. In order to solve these, we use the inbuilt MATLAB command ode45, that is suitable for a wide variety of this initial value problem. We have got all last simulations that viewed in chapter 3 by using the following Matlab code, this code would make a number of m.files or script files (all well be function files, other than the first file, which contains all parameters and the initial conditions used in this model).

Consequently, the MATLAB code that used to simulate this model appears below.

- At the first, we create one file contains all necessary parameters and initial conditions.

```
alpha=10^-3;
epsilon1=10^-3;
epsilon26=10^-1;
epsilon27=10^-1;
epsilon28=10^-2;
tau=1;
eta0=1;
sigma=0.9;
lambda=0.01;
beta1=10^-4;
beta2=10^-1;
gamma=1;
up=[0 0.5 1.0];
Npart=3;
%%SET INITIAL CONDITION%%
clear Fin;
Fin=0*ones(8,Npart);
Fin(1,1)=1.0;
Fin(1,2)=0.0;
Fin(1,3)=0.0;
Fin(5,1)=0.2;
```

```
Fin(5,2)=0.0;
Fin(5,3)=0.0;
initz=Fin(:);
%%%%%%%%%%%%%%
timeSTEPs=200;
finalTIME=10000;
tspan=linspace(0,finalTIME,timeSTEPs);
[T,F,n]=rigid(Npart,alpha,up,epsilon1,epsilon26,epsilon27,epsilon28,
tau,eta0,sigm,lambda,beta1,beta2,gamma,initz,tspan);
for jt=1:timeSTEPs
    ndensity(:,jt)=n(:,jt)/sum(n(:,jt));
end
figure;
plot(tspan,n(4,:));
set(gca,'Fontsize',18);
xlabel('$t$','interpreter','latex','fontsize',18);
ylabel('$n(4)$','interpreter','latex','fontsize',18);
 %%%%%%%%%%%%%%%%
figure;
plot(tspan,n(8,:));
set(gca,'Fontsize',18);
xlabel('$t$','interpreter','latex','fontsize',18);
ylabel('$n(8)$','interpreter','latex','fontsize',18);
```

- Now create another file called 'rigid', that is the main m.file which contain the inbuilt MATLAB command ode45. In this file also calculates the encounter rate between the particles 'eta(h,k)', and compute Jfunction by recall the functions Bfile,C,P,M,D,L, which will be defined in the next m.files.

```
function [T,F,n]=rigid(Npart,alpha,up,epsilon1,epsilon26,
epsilon27,epsilon28,tau,eta0,sigma,lambda,beta1,beta2,gamma,initz,
tspan)
[B,mu,ni]=Bfile(Npart,alpha,up,epsilon1,epsilon26,epsilon27,
epsilon28,beta1,beta2,gamma);
[T,f1] = ode45(@(t, z) Jfunction(Npart,t,z,initz,B,mu,ni,alpha,
tau,eta0,sigma,lambda,up),tspan,initz);
size(f1)
  for jx=1:length(tspan)
f(:,:,jx)=reshape(f1(jx,:),8,Npart);
 for i=1:8
```

```
      n(i,jx)=sum(f(i,:,jx));
 end
  for ii=1:8
      for jj=1:Npart
     F{ii,jj}(jx)=f(ii,jj,jx);
      end
  end
  end
function Jfunction=Jfunction(Npart,t,f,fin,B,mu,ni,alpha,tau,
eta0,sigma,lambda,up)
t
F=reshape(f,8,Npart);
Fin=reshape(fin,8,Npart);
J(8,Npart)=0;
C(8,Npart)=0;
P(8,Npart)=0;
D(8,Npart)=0;
L(8,Npart)=0;
eta(8,8)=0;
d(8,8)=0;
%
for h=1:8
    for k=1:8
        q1=sum(abs((F(h,:)-F(k,:))));
        q2=sum(abs(F(h,:)))+sum(abs(F(k,:)));
        if ((sum(abs(F(h,:)))>0)&&(sum(abs(F(k,:)))>0))
         %if ((sum(abs(F(h,:)))+sum(abs(F(k,:))))>0)
       d(h,k)=exp(-tau*(q1/q2));
        else
       d(h,k)=0;
        end
    end
end
eta(1,1)=eta0*d(1,1);eta(2,1)=2*eta0*d(2,1);
eta(3,1)=3*eta0*d(3,1);eta(4,1)=4*eta0*d(4,1);
eta(1,2)=2*eta0*d(2,1);eta(1,3)=3*eta0*d(3,1);
eta(1,4)=4*eta0*d(4,1);eta(5,2)=sigma*eta0*d(5,2);
eta(2,5)=sigma*eta0*d(5,2);eta(6,2)=sigma*eta0*d(6,2);
eta(6,3)=sigma*eta0*d(6,3);eta(2,6)=sigma*eta0*d(6,2);
eta(3,6)=sigma*eta0*d(6,3);eta(7,2)=sigma*eta0*d(7,2);
```

```
eta(7,3)=sigma*eta0*d(7,3);eta(7,4)=sigma*eta0*d(7,4);
eta(2,7)=sigma*eta0*d(7,2);eta(3,7)=sigma*eta0*d(7,3);
eta(4,7)=sigma*eta0*d(7,4);eta(8,2)=sigma*eta0*d(8,2);
eta(8,3)=sigma*eta0*d(8,3);eta(8,4)=sigma*eta0*d(8,4);
eta(2,8)=sigma*eta0*d(8,2);eta(3,8)=sigma*eta0*d(8,3);
eta(4,8)=sigma*eta0*d(8,4);
%%%%%%%%%%%%%
C=computeC(eta,alpha,up,F);
P=computeP(eta,mu,F);
D=computeD(eta,ni,F);
%%%%
for i=1:8
    for j=1:Npart
        if (i>4)
        L(i,j)=lambda*(F(i,j)-Fin(i,j));
        end
        J(i,j)=C(i,j)+P(i,j)-D(i,j)-L(i,j);
    end
end
Jfunction=J(:);
```

- Bfile: this function compute the translation probability density 'B', contain also proliferation, mutation events 'mu', and the destructive events 'ni'.

```
function [B,mu,ni]=Bfile(Npart,alpha,up,epsilon1,epsilon26,
epsilon27,epsilon28,beta1,beta2,gamma)
for jj1=1:Npart
for jj2=1:Npart
   B{jj1,jj2}(8,8,Npart) =0;
end
end
  for h=1:4
      for p=1:Npart
           for q=1:Npart
               for j=1:Npart
                   B{p,q}(h,1,j)=0;
                   if (j==p+1)
                        B{p,q}(h,1,j)=alpha *(1-up(p));
                    end
                      if (j==p)
```

```
                              B{p,q}(h,1,j)=1-alpha *(1-up(p));
                          end
                  end
              end
        end
   end
     for h=1:1
       for k=2:4
         B{p,q}(h,k,p)=1;
           II=[5 2;6 2; 7 3; 8 4];
             for hII=1:4
               for j=1:Npart
                 if (j==p+1)
                  B{p,q}(II(hII,1),II(hII,2),j)=alpha *(1-up(p));
                 end
               if (j==p)
                 B{p,q}(II(hII,1),II(hII,2),j)=1-alpha *(1-up(p));
                                        end
                                     end
                                 end
                            end
                        end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
for jj1=1:Npart
    for jj2=1:Npart
        mu{jj1,jj2}(8,8,8,Npart)=0;
    end
end
for p=1:Npart
    for q=1:Npart
        for h=1:3
            mu{p,q}(h,1,h+1,1)=epsilon1*up(p);
        end
        mu{p,q}(5,2,6,1)=epsilon26*up(p);
        mu{p,q}(6,3,7,1)=epsilon27*up(p);
        mu{p,q}(7,4,8,1)=epsilon28*up(p);
         for h=2:4
             mu{p,q}(h,1,h,p)=beta1*h*up(p);
         end
         mu{p,q}(6,2,6,p)=beta2;
```

```
          mu{p,q}(7,2,7,p)=beta2;
          mu{p,q}(7,3,7,p)=beta2;
          mu{p,q}(8,2,8,p)=beta2;
          mu{p,q}(8,3,8,p)=beta2;
          mu{p,q}(8,4,8,p)=beta2;
    end
end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
for jj1=1:Npart
    for jj2=1:Npart
        ni{jj1,jj2}(8,8)=0;
    end
end
for p=1:Npart
    for q=1:Npart
        ni{p,q}(2,6)=gamma*up(q);
        ni{p,q}(2,7)=gamma*up(q);
        ni{p,q}(2,8)=gamma*up(q);
        ni{p,q}(3,7)=gamma*up(q);
        ni{p,q}(3,8)=gamma*up(q);
        ni{p,q}(4,8)=gamma*up(q);
    end
end
```

- To compute the conservative interaction and the proliferative, mutation destructive interactions, the (rigid m.file) recall the m.files computeC, computeD, computeP respectively:

```
function C=computeC(eta,alpha,up,F)
Npart=size(F,2);
C(8,Npart)=0;
   %
    for h=1:4
    C(h,1)=C(h,1)+eta(h,1)*sum(F(1,:))*(-alpha*F(h,1));
     for j=2:Npart
    C(h,j)=C(h,j)+eta(h,1)*sum(F(1,:))*(alpha*(1-up(j-1))*F(h,j-1)
          -alpha1*(1-up(j))*F(h,j));
             end
         end
```

```
 %
for j=2:Npart
 C(5,j)=C(5,j) +eta(5,2)*sum(F(2,:))*(alpha*(1-up(j-1))*F(5,j-1)
        -alpha2*(1-up(j))*F(5,j));
 C(6,j)=C(6,j) +eta(6,2)*sum(F(2,:))*(alpha*(1-up(j-1))*F(6,j-1)
        -alpha2*(1-up(j))*F(6,j));
 C(7,j)=C(7,j) +eta(7,3)*sum(F(3,:))*(alpha*(1-up(j-1))*F(7,j-1)
        -alpha2*(1-up(j))*F(7,j));
 C(8,j)=C(8,j) +eta(8,4)*sum(F(4,:))*(alpha*(1-up(j-1))*F(8,j-1)
        -alpha2*(1-up(j))*F(8,j));
              end
 %
 for j=1
   C(5,j)=C(5,j)-alpha*eta(5,2)*sum(F(2,:))*F(5,1);
   C(6,j)=C(6,j)-alpha*eta(6,2)*sum(F(2,:))*F(6,1);
   C(7,j)=C(7,j)-alpha*eta(7,3)*sum(F(3,:))*F(7,1);
   C(8,j)=C(8,j)-alpha*eta(8,4)*sum(F(4,:))*F(8,1);
              end

function P=computeP(eta,mu,F)
Npart=size(F,2);
P(8,Npart)=0;

for i=1:8
  for j=1:Npart
    for h=1:8
      for k=1:8
        for q=1:Npart
          for p=1:Npart
            P(i,j)=P(i,j)+eta(h,k)*mu{p,q}(h,k,i,j)*F(h,p)*F(k,q);
                end
              end
          end
        end
    end
end

function D=computeD(eta,ni,F)
Npart=size(F,2);
D(8,Npart)=0;
```

```
for i=[2:4]
    for j=1:Npart
        for k=1:8
            for q=1:Npart
             D(i,j)=D(i,j)+F(i,j)*eta(i,k)*ni{j,q}(i,k)*F(k,q);
            end
        end
    end
end
```

3.6 Appendix 3.B: Table of the parameters

All parameters used in this model are summarized and shown in the Table 3.1:

Table 3.1:

Parameter	Biological meaning	The value of the parameter
η_0, τ, σ	Parameters modeling the encounter rate	$\eta_0 = 1$, $\tau = 1$, $\sigma \in [0.5, 1]$
α	Parameter characterizing the probability density in cancer and immune cells	$\alpha = 10^{-3}$
β_1	Parameter characterizing the proliferative rate in cancer cells	$\beta_1 = 10^{-4}$
β_2	Parameter characterizing the proliferative rate in immune system	$\beta_2 = 10^{-1}$
ε_1	Parameter characterizing the mutation rate in cancer cells	$\varepsilon_1 = 10^{-3}$
ε_{26}, ε_{27}, ε_{28}	Parameters modeling the mutation rate in immune system	$\varepsilon_{26} = 10^{-1}$, $\varepsilon_{27} = 10^{-1}$, $\varepsilon_{28} = 10^{-2}$
γ	Parameter characterizing the destructive rate in cancer cells	$\gamma = 1$
λ	Parameter characterizing the relaxation rate in immune system	$\lambda = 0.01$

Chapter 4

Spatially Homogeneous Continuous Model

In this chapter, we will deal with the study of the early stage of the immune cancer competition, following the line of thought traced in the previous chapter, but assuming that the activity variable u takes all values belonging to the interval $(0, \infty)$, as made in [55]. Furthermore, this chapter will be devoted to the derivation of a macroscopic model, in which evolution equations are obtained for some macroscopic quantities obtained by local averages of the microscopic state described by the kinetic Theory Approach.

According to KTAP presented in Chapter 1, the overall system is divided into eight ($M = 8$) different populations (functional subsystems) each of them consisting of cells (active particles), which collectively express the same function (the activity). The evolution of each functional subsystem is described by a distribution function and the time evolution of the subsystem is governed by interactions [35].

The chapter is organized as follows: in Section 4.1 the functional subsystems for the modeling of the competition between the immune system and cancer cells are identified and the dynamical model is built up, choosing suitable relations to describe the interactions between active particles. Section 4.2 deals with the derivation from the model at the cellular scale of a model at the macroscopic scale, that considers as variables the size, the activation and the quadratic activation of the different cells populations.

4.1 Dynamics of Immune-Cancer Competition

As mentioned in in Chapter 3, the first step of the modeling approach is the identification of the functional subsystems. Here, the functional subsystems are

the same as those mentioned in Section 3.1. Accordingly, the eight functional subsystems are as follows:

- $i = 1$ *Normal epithelial cells.*
- $i = 2$, $i = 3$, $i = 4$ *Cancer cells of the various hallmarks*, as specified in Section 3.1;
- $i = 5$ *Cells of the innate immune system*
- $i = 6$, $i = 7$, $i = 8$ *Cells of the adaptive immune system* which have the ability of contrasting the development of cancer cells of the various hallmarks, as specified in Section 3.1.

As already mentioned, the overall state of each functional subsystem is described by the one-cell generalized distribution function:

$$f_i = f_i(t, u) : [t_0, T] \times D_u \to \mathbb{R}^+, \quad \text{for} \quad i \in \{1, 2, \ldots, 8\}. \tag{4.1}$$

The domain D_u of the microscopic state, in view of the following applications, is assumed to coincide with interval $[u^{(0)}, +\infty)$, where $u^{(0)} > 0$ is the lowest value of the biological function of each active particle. We will assume also $f_i(t, u) = 0$, for $u < u^{(0)}$.

The time evolution of the distribution function f_i is obtained by a suitable balance of particles in the elementary interval $[u, u + du]$ of the microscopic state as follows:

$$\frac{\partial f_i}{\partial t}(t, u) = J_i[\mathbf{f}](t, u) \quad i \in \{1, 2, \ldots, 8\} \tag{4.2}$$

with $\mathbf{f} = (f_1, f_2, \ldots, f_8)$ the vector of the distribution functions, and where

$$J_i[\mathbf{f}](t, u) = C_i[\mathbf{f}](t, u) + M_i[\mathbf{f}](t, u) + P_i[\mathbf{f}](t, u) - D_i[\mathbf{f}](t, u) - L_i[\mathbf{f}](t, u). \tag{4.3}$$

The operators C_i, M_i, P_i, D_i and L_i, acting over the whole set of distribution functions, have been introduced in Chapter 1.

In the KTAP mentioned in Chapter 1, it is assumed that there are only interactions which modify the microscopic state of the particles. Interactions involve three type of particles: *candidate*, *test*, and *field*. 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.

In general, a different modeling approach has to be considered for cells of the various different functional subsystems. Briefly, we remember that the tumor cells

are distinguished according to their progressive hallmarks, while the immune cells are characterized by the capability to recognize specific hallmarks. The addends in $J_i[\mathbf{f}](t,u)$ are modeled as follows:

$$\begin{aligned} C_i[\mathbf{f}](t,u) &= \sum_{k=1}^{8} \int_{D_u \times D_u} \eta_{ik}[\mathbf{f}]\, \mathcal{B}_{ik}[\mathbf{f}]\, f_i(t,u_*)\, f_k(t,u^*)\, du_*\, du^* \\ &- f_i(t,u) \sum_{k=1}^{8} \int_{D_u} \eta_{ik}[\mathbf{f}]\, f_k(t,u^*)\, du^*, \end{aligned} \tag{4.4}$$

$$P_i[\mathbf{f}](t,u) = \sum_{k=1}^{8} \int_{D_u \times D_u} \eta_{ik}[\mathbf{f}]\, \mathcal{P}_{ik}[\mathbf{f}]\, f_i(t,u_*)\, f_k(t,u^*)\, du_*\, du^* \tag{4.5}$$

$$M_i[\mathbf{f}](t,u) = \sum_{h,k=1}^{8} \int_{D_u \times D_u} \eta_{hk}[\mathbf{f}]\, \mathcal{M}_{hk(h\neq i)}[\mathbf{f}]\, f_h(t,u_*)\, f_k(t,u^*)\, du_*\, du^* \tag{4.6}$$

$$D_i[\mathbf{f}](t,u) = f_i(t,u) \sum_{k=1}^{8} \int_{D_u} \eta_{ik}[\mathbf{f}]\, \mathcal{D}_{ik}[\mathbf{f}]\, f_k(t,u^*)\, du^* \tag{4.7}$$

$$L_i[\mathbf{f}](t,u) = \lambda_i[\mathbf{f}][f_i(t,u) - f_i(t_0,u_0)] \tag{4.8}$$

In these equations $\eta_{ik} = \eta_{ik}[\mathbf{f}](u_*,u^*)$ is the encounter rate between the candidate active particle, with state u_*, of the i-th functional subsystem and the field active particle, with state u^*, of the k-th functional subsystem; the other quantities model respectively the conservative interactions and the proliferation, mutation, destruction and relaxation events, as introduced in Chapter 1.

Remark 4.1.1. *In this model, we supposed that the encounter rate η_{ik} is the same for all events (conservative/proliferative/mutation/destructive interactions).*

4.1.1 Encounter Rate

In analogy with what we have said in Chapter 1, we will assume for the encounter rate the following expression:

$$\eta_{hk}[\mathbf{f}] = \overline{\eta}_{hk}\, d_{hk}[\mathbf{f}], \qquad \eta_{hk} = \eta_{kh} \tag{4.9}$$

with $\overline{\eta}_{hk}$ suitable constants and where $d_{hk}[\mathbf{f}]$ denotes the distance between the h-th and the k-th functional subsystems [15].

Only encounters which may lead to progression, mutations, proliferation or destructive events will be considered. In particular, the encounter rate between immune and epithelial cells is assumed to be equal to zero. Further, we make the following assumptions, specific to our model with continuous activity:

- The encounter between epithelial and tumor cells ($h = 1, 2, 3, 4$) with epithelial cells ($k = 1$) (which are the ones that can produce significant events) is assumed proportional to a constant $\overline{\eta}_{h1}$, which depends on the interacting cells: as progressive hallmarks corresponds to increasing activations to search nutrients for increasing proliferation, we will assume:

$$\eta_{h1}[\mathbf{f}] = \overline{\eta}_{h1}\, d_{h1}[\mathbf{f}], \tag{4.10}$$

  with $0 < \overline{\eta}_{11} \leq \overline{\eta}_{21} \leq \overline{\eta}_{31} \leq \overline{\eta}_{41}$.

- For the encounters between immune and cancer cells, only those corresponding to couples $(h, k) = (5, 2), (6, 2), (7, 2), (7.3), (7, 4), (8, 2), (8.3), (8, 4)$ are considered. Therefore, we assume

$$\eta_{hk}[\mathbf{f}] = \overline{\eta}_{hk}\, d_{hk}[\mathbf{f}], \tag{4.11}$$

  with $0 < \overline{\eta}_{5k} \leq \overline{\eta}_{6k} \leq \overline{\eta}_{7k} \leq \overline{\eta}_{8k}$. The modeling of the distance d_{hk} can be achieved in different ways assuming that increasing values of the distance corresponding to decreasing values of the encounter rate η_{hk}.

We summarize the previous assumptions in the following matrix expression for the encounter rate:

$$\eta_{hk} = \begin{pmatrix} \overline{\eta}_{11}d_{11} & \overline{\eta}_{21}d_{21} & \overline{\eta}_{31}d_{31} & \overline{\eta}_{41}d_{41} & 0 & 0 & 0 & 0 \\ \overline{\eta}_{21}d_{21} & 0 & 0 & 0 & \overline{\eta}_{52}d_{52} & \overline{\eta}_{62}d_{62} & \overline{\eta}_{72}d_{72} & \overline{\eta}_{82}d_{82} \\ \overline{\eta}_{31}d_{31} & 0 & 0 & 0 & 0 & \overline{\eta}_{63}d_{63} & \overline{\eta}_{73}d_{73} & \overline{\eta}_{83}d_{83} \\ \overline{\eta}_{41}d_{41} & 0 & 0 & 0 & 0 & 0 & \overline{\eta}_{74}d_{74} & \overline{\eta}_{84}d_{84} \\ 0 & \overline{\eta}_{52}d_{52} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \overline{\eta}_{62}d_{62} & \overline{\eta}_{63}d_{63} & 0 & 0 & 0 & 0 & 0 \\ 0 & \overline{\eta}_{72}d_{72} & \overline{\eta}_{73}d_{73} & \overline{\eta}_{74}d_{74} & 0 & 0 & 0 & 0 \\ 0 & \overline{\eta}_{82}d_{82} & \overline{\eta}_{83}d_{83} & \overline{\eta}_{84}d_{84} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{4.12}$$

4.1.2 Transition Probability Density

Conservative interactions refer to progression phenomena that lead to an increasing activity within the same subsystem. $C_i[\mathbf{f}](t, u)$ is the net flux, at time $t \in [0, T]$, into the state $u \in [u^{(0)}, +\infty)$ of the i-th population, due to conservative interactions that only modify the micro-state.

As already mentioned, $\mathcal{B}_{ik}$ represents the probability density that a candidate particle, with the state u_*, of the i-th functional subsystem ends up into the state u of the test particle of the same functional subsystem after the interaction with

the field particle, with the state u^*, of the k-th functional subsystem. $\mathcal{B}_{ik}$ satisfies, for all $i, k \in \{1, 2, \ldots, n\}$, the following condition:

$$\int_{D_u} \mathcal{B}_{ik}[\mathbf{f}](u_* \to u | u_*, u^*)\, du = 1, \quad \forall\, u_*, u^* \in D_u. \tag{4.13}$$

We model conservative events choosing for the probability density $\mathcal{B}_{ik}[\mathbf{f}](u_*, u^*, u)$ the following matrix expression:

$$\mathcal{B}_{ik} = \begin{pmatrix} \mathcal{B}_{11} & \mathcal{B}_{12} & \mathcal{B}_{13} & \mathcal{B}_{14} & 0 & 0 & 0 & 0 \\ \mathcal{B}_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{B}_{31} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{B}_{41} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{B}_{52} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{B}_{62} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \mathcal{B}_{73} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mathcal{B}_{84} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{4.14}$$

Different choices are possible for the transition probability density. In our case, we will assume that transition probability density does not depend on the activity u^* of the cell (field) that interacts with the candidate particle:

$$\mathcal{B}_{ik} = \mathcal{B}_{ik}(u_*, u). \tag{4.15}$$

The function $\mathcal{B}_{ik}(u_*, u)$ 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. Specifically we assume:

- Interaction that involve epithelial and cancer cells ($k = 1, 2, 3, 4$) and epithelial cells ($i = 1$). As in the discrete model, epithelial cells are assumed to feed progression of cancer cells without changing their activity. Thus, we assume:

$$\mathcal{B}_{1k}(u_*, u) = \delta(u_* - u) \qquad \text{for} \qquad k = 1, 2, 3, 4 \tag{4.16}$$

  Remark 4.1.2. *The function $\delta(u_* - u)$ denotes the Dirac distribution, having the fundamental property that*

$$\int_{D_u} f(u)\delta(u_* - u)du = f(u^*)$$

- Interactions that involve functional subsystem $k = 1$ and $i = 2, 3, 4$. The progression in the activity of cancer cells ($i = 2, 3, 4$) is due to the interaction

with epithelial cells ($k = 1$). In this case, we will assume that the probability of transition depends on the interacting populations and decrease with the activity state of the cancer cells. So we will assume

$$\mathcal{B}_{i1} = \alpha_i[1-(u_*+a_i)]\,\delta(u-(u_*+a_i))+[1-\alpha_i(1-(u_*+a_i)]\,\delta(u-u_*) \quad (4.17)$$

- Interactions that involve the innate immune system (functional subsystem $i = 5$) and the cancer cells. We assume that the innate immune system has the ability to recognize the cancer cell of the first hallmark (functional subsystem $k = 2$), without changing their activity. Thus, we assume:

$$\mathcal{B}_{52}(u_*, u) = \delta(u_* - u) \quad (4.18)$$

- Interactions that involve cells of the adaptive immune system. These cells acquire progressively the ability to identify the tumor cells. Thus for the pairs $(i, k) = (6, 2)$, (7.3), $(8, 4)$ we will assume

$$\mathcal{B}_{ik} = \alpha_i[1-(u_*+a_i)]\,\delta(u-(u_*+a_i))+[1-\alpha_i(1-(u_*+a_i))]\,\delta(u-u_*) \quad (4.19)$$

A more sophisticated expression consist of choosing coefficients α_i and a_i dependent on the interacting subsystems, but we will make here the simpler hypothesis (4.17)–(4.19).

The conservative events are expressed by the quantity (4.4). Substituting equations (4.16)–(4.19) in it, we get $C_1[\mathbf{f}](t, u) = 0$, $C_5[\mathbf{f}](t, u) = 0$, and for $i = 2, 3, 4$:

$$C_i[\mathbf{f}](t, u) = \overline{\eta}_{i1} d_{i1}\, n_1 \alpha_i (1 - u)\,[f_i(t, u - a_i) - (1 - (u + a_i)) f_i(t, u)]\,, \quad (4.20)$$

and for $i = 6, 7, 8$:

$$C_i[\mathbf{f}](t, u) = \overline{\eta}_{i(i-4)} d_{i(i-4)}\, n_{i-4} \alpha_i (1 - u)\,[f_i(t, u - a_i) - (1 - (u + a_i)) f_i(t, u)]\,. \quad (4.21)$$

4.1.3 Modeling Proliferative Events

$P_i[\mathbf{f}](t, u)$ is the gain, at time $t \in [0, T]$, into the state $u \in [u^{(0)}, +\infty)$ of the functional subsystem i, due to proliferative events. We model these events, in which a generation of a daughter cell occurs in the same functional subsystem

of the mother cell, choosing for the rate $\mathcal{P}_{hk}[\mathbf{f}](u_*, u^*, u)$ the following matrix expression:

$$\mathcal{P}_{hk} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{P}_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{P}_{31} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{P}_{41} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{P}_{62} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{P}_{72} & \mathcal{P}_{73} & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{P}_{82} & \mathcal{P}_{83} & \mathcal{P}_{84} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{4.22}$$

The proliferative events dynamics in the h-th functional subsystems are assumed to follow the following rules: A candidate particle (mother cell) of functional subsystem h with the state u_* by interacting with a cell (field) from subsystem k, with the state u^*, proliferate a daughter cell of the same functional subsystem, with the same activity $u = u_*$. More precisely:

- The proliferative events in the cancer subsystems $h = 2, 3, 4$, owing to their interaction with epithelial cells, increase with the hallmarks of cancer cells due to the increasing proliferation program, which is an acquired capability of tumor cells. So we assume:

$$\mathcal{P}_{h1} = \beta_h u_* \delta(u_* - u), \tag{4.23}$$

  with $0 < \beta_2 \leq \beta_3 \leq \beta_4$.

- The proliferative events in the immune subsystems $h = 6, 7, 8$ are due to the interactions with the cancer cells. Following [27], we assume, for each pair $(h, k) = (6, 2)$, (7,2), (7,3), (8,2), (8,3), (8,4):

$$\mathcal{P}_{hk} = \beta_h \delta(u_* - u), \tag{4.24}$$

  with $0 < \beta_6 \leq \beta_7 \leq \beta_8$.

The proliferative events are expressed by the quantity (4.5). Substituting

(4.23) and (4.24) in it, we get

$$\begin{aligned} P_2[\mathbf{f}](t,u) &= \overline{\eta}_{21} d_{21} \beta_2 n_1 u \, f_2(t,u) && (4.25)\\ P_3[\mathbf{f}](t,u) &= \overline{\eta}_{31} d_{31} \beta_3 n_1 u \, f_3(t,u) && (4.26)\\ P_4[\mathbf{f}](t,u) &= \overline{\eta}_{41} d_{41} \beta_4 n_1 u \, f_4(t,u) && (4.27) \end{aligned}$$

$$\begin{aligned} P_6[\mathbf{f}](t,u) &= \overline{\eta}_{62} d_{62} \beta_6 n_2 \, f_6(t,u) && (4.28)\\ P_7[\mathbf{f}](t,u) &= \overline{\eta}_{72} d_{72} \beta_7 n_2 \, f_7(t,u) + \overline{\eta}_{73} d_{73} \beta_7 n_3 \, f_7(t,u) && (4.29)\\ P_8[\mathbf{f}](t,u) &= \overline{\eta}_{82} d_{82} \beta_8 n_2 \, f_8(t,u) + \overline{\eta}_{83} d_{83} \beta_8 n_3 \, f_8(t,u) \\ &+ \overline{\eta}_{84} d_{84} \beta_8 n_4 f_8(t,u) && (4.30) \end{aligned}$$

4.1.4 Modeling Mutations

$M_i[\mathbf{f}](t,u)$ is the gain, at time $t \in [t_0, T]$, into the state $u \in [u^{(0)}, +\infty)$ of the functional subsystem i, due to mutation events, where a generation of a daughter cell occurs in a subsystem different from that of the mother cell. We model mutation events choosing for the rate $\mathcal{M}_{ik}[\mathbf{f}](u_*, u^*, u)$ the following matrix expression:

$$\mathcal{M}_{ik} = \begin{pmatrix} \mathcal{M}_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{M}_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \mathcal{M}_{31} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mathcal{M}_{52} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \mathcal{M}_{63} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mathcal{M}_{74} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{4.31}$$

The mutation events dynamics in the i-th functional subsystems are assumed to follow the following rules: A candidate particle (mother cell) of functional subsystem h with state u_*, by interacting with a cell (field) from subsystem k, with state u^*, proliferate a daughter cell belonging to the following functional subsystem $i = h + 1$ with the lowest activity values $u = u^{(0)}$.

Following [27], we will make the assumptions:

- The mutation events in the cancer subsystems $i = 2, 3, 4$ are related to the encounters of particles of the functional subsystems $h = 1, 2, 3$ respectively with the cells of the first functional subsystem, indeed, are the epithelial cells $k = 1$ that furnish to the mother cell the nutrient to create a mutated

daughter. So we assume, for $i = 2, 3, 4$:

$$M_i[\mathbf{f}](t,u) = \int_{D_u \times D_u} \overline{\eta}_{(i-1)1} d_{(i-1)1}[\mathbf{f}]\, \mathcal{M}_{(i-1)1}\, f_{i-1}(t,u_*)\, f_1(t,u^*)\, du_*\, du^* \tag{4.32}$$

where

$$\mathcal{M}_{(i-1)1} = \varepsilon_{(i-1)1} u_* \delta(u - u^{(0)}), \tag{4.33}$$

with $0 < \varepsilon_{11} \leq \varepsilon_{21} \leq \varepsilon_{31}$.

- The mutation events in the immune subsystems $i = 6, 7, 8$ are related to the increasing capability of the immune cells to recognize a specific cancer hallmark. Therefore, mutations in the immune system cells are due to the encounters of particles of the functional subsystems $h = 5, 6, 7$ with the cells of the subsystems $k = 2, 3, 4$ respectively. We assume, for $i = 6, 7, 8$:

$$M_i[\mathbf{f}](t,u) = \int_{D_u \times D_u} \overline{\eta}_{(i-1)(i-4)} d_{(i-1)(i-4)} \mathcal{M}_{(i-1)(i-4)} f_{i-1}(t,u_*) f_{i-4}(t,u^*) du_* du^* \tag{4.34}$$

where

$$\mathcal{M}_{(i-1)(i-4)} = \varepsilon_{(i-1)(i-4)} u_* \delta(u - u^{(0)}), \tag{4.35}$$

with $0 < \varepsilon_{52} \leq \varepsilon_{63} \leq \varepsilon_{74}$.

Substituting (4.33) in (4.32), we get for $i = 2, 3, 4$:

$$M_2 = \overline{\eta}_{11} d_{11}\, \varepsilon_{11}\, n_1\, A_1\, \delta(u - u^{(0)}), \tag{4.36}$$
$$M_3 = \overline{\eta}_{21} d_{21}\, \varepsilon_{21}\, n_1\, A_2\, \delta(u - u^{(0)}), \tag{4.37}$$
$$M_4 = \overline{\eta}_{31} d_{31}\, \varepsilon_{31}\, n_1\, A_3\, \delta(u - u^{(0)}). \tag{4.38}$$

Substituting (4.35) in (4.34), we get, for $i = 6, 7, 8$

$$M_6 = \overline{\eta}_{52} d_{52}\, \varepsilon_{52}\, n_2\, A_5\, \delta(u - u^{(0)}), \tag{4.39}$$
$$M_7 = \overline{\eta}_{63} d_{63}\, \varepsilon_{63}\, n_3\, A_6\, \delta(u - u^{(0)}), \tag{4.40}$$
$$M_8 = \overline{\eta}_{74} d_{74}\, \varepsilon_{74}\, n_4\, A_7\, \delta(u - u^{(0)}). \tag{4.41}$$

In equations (4.36)–(4.41) we have introduced the activity A_i defined in Chapter 1, that in this spatially homogeneous model is given by (4.49).

4.1.5 Modeling Destructive Events

$D_i[\mathbf{f}](t,u)$ is the loss, at time $t \in [t_0, T]$, in the state $u \in [u^{(0)}, +\infty)$ of the functional subsystem i, due to destructive events. The dynamics of the destructive

interactions follow the following rules. A candidate cell from functional subsystem i with state u_*, interacting with a field cell of the k-th functional subsystem with activity u^*, can undergo a destructive action. Only cancer cell can be destructed, owing to the interactions with the immune cells that are able to identify them. We assume that the ability of the immune cells is proportional to their activity u^*.

For the rate $\mathcal{D}_{ik}[\mathbf{f}](u, u^*)$ we obtain the following matrix:

$$\mathcal{D}_{ik} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_6 u^* & \gamma_7 u^* & \gamma_8 u^* \\ 0 & 0 & 0 & 0 & 0 & 0 & \gamma_7 u^* & \gamma_8 u^* \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_8 u^* \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{4.42}$$

Where, for each pair $(h, k) = (2, 6), (2, 7), (2, 8), (3, 7), (3, 8), (4, 8)$, the destructive rate $\mathcal{D}_{ik}[\mathbf{f}](u, u^*) = \gamma_k u^*$, with $0 < \gamma_6 \leq \gamma_7 \leq \gamma_8$. Consequently, by using the general expression (4.7), we obtain:

$$D_2[\mathbf{f}](t, u) = f_2(t, u) \left(\overline{\eta}_{26} d_{26} \gamma_6 A_6 + \overline{\eta}_{27} d_{27} \gamma_7 A_7 + \overline{\eta}_{28} d_{28} \gamma_8 A_8\right) \tag{4.43}$$

$$D_3[\mathbf{f}](t, u) = f_3(t, u) \left(\overline{\eta}_{37} d_{37} \gamma_7 A_7 + \overline{\eta}_{38} d_{38} \gamma_8 A_8\right) \tag{4.44}$$

$$D_4[\mathbf{f}](t, u) = f_4(t, u) \, \overline{\eta}_{48} d_{48} \gamma_8 A_8 \tag{4.45}$$

4.1.6 Modeling Relaxation and Apoptosis Events

The immune cells in the absence of tumor cells tend to return to their healthy initial state. We assume $\lambda_i = 0$ for $i = 2, 3, 4$, and for $i = 6, 7, 8$:

$$L_i[\mathbf{f}](t, u) = \lambda_i [f_i(t, u) - f_i(t_0, u_0)] \tag{4.46}$$

with $0 < \lambda_6 \leq \lambda_7 \leq \lambda_8$.

4.1.7 Evolution Equations at the Cellular Scale

Substituting in (4.2) the expressions of C_i, P_i, M_i, D_i and L_i found in previous section, we obtain the following system:

$$\begin{cases}
\frac{\partial f_1}{\partial t}(t,u) = 0 \\
\\
\frac{\partial f_2}{\partial t}(t,u) = \overline{\eta}_{21} d_{21} \alpha_2 n_1 (1-u)\left[f_2(t,u-a_2) - (1-(u+a_2)) f_2(t,u)\right] \\
\qquad +\overline{\eta}_{21} d_{21} \beta_2 n_1 u f_2(t,u) + \overline{\eta}_{11} d_{11} \varepsilon_{11} n_1 A_1 \delta(u-u^{(0)}) \\
\qquad -f_2(t,u)(\gamma_6 \overline{\eta}_{26} d_{26} A_6 + \gamma_7 \overline{\eta}_{27} d_{27} A_7 + \gamma_8 \overline{\eta}_{28} d_{28} A_8) \\
\\
\frac{\partial f_3}{\partial t}(t,u) = \overline{\eta}_{31} d_{31} \alpha_3 n_1 (1-u)\left[f_3(t,u-a_3) - (1-(u+a_3)) f_3(t,u)\right] \\
\qquad +\overline{\eta}_{31} d_{31} \beta_3 n_1 u f_3(t,u) + \overline{\eta}_{21} d_{21} \varepsilon_{21} n_1 A_2 \delta(u-u^{(0)}) \\
\qquad -f_3(t,u)(\gamma_7 \overline{\eta}_{37} d_{37} A_7 + \gamma_8 \overline{\eta}_{38} d_{38} A_8) \\
\\
\frac{\partial f_4}{\partial t}(t,u) = \overline{\eta}_{41} d_{41} \alpha_4 n_1 (1-u)\left[f_4(t,u-a_4) - (1-(u+a_4)) f_4(t,u)\right] \\
\qquad +\overline{\eta}_{41} d_{41} \beta_4 n_1 u f_4(t,u) + \overline{\eta}_{31} d_{31} \varepsilon_{31} n_1 A_3 \delta(u-u^{(0)}) - \gamma_8 \overline{\eta}_{48} d_{48} A_8 f_4(t,u) \\
\\
\frac{\partial f_5}{\partial t}(t,u) = 0 \\
\\
\frac{\partial f_6}{\partial t}(t,u) = \overline{\eta}_{62} d_{62} \alpha_6 n_2 (1-u)\left[f_6(t,u-a_6) - (1-(u+a_6)) f_6(t,u)\right] \\
\qquad +\overline{\eta}_{62} d_{62} n_2 \beta_6 f_6(t,u) + \overline{\eta}_{52} d_{52} \varepsilon_{52} n_2 A_5 \delta(u-u^{(0)}) - \lambda_6[f_6(t,u) - f_6(t_0,u_0)] \\
\\
\frac{\partial f_7}{\partial t}(t,u) = \overline{\eta}_{73} d_{73} \alpha_7 n_3 (1-u)\left[f_7(t,u-a_7) - (1-(u+a_7)) f_7(t,u)\right] + (\overline{\eta}_{72} d_{72} n_2 \\
\qquad +\overline{\eta}_{73} d_{73} n_3) \beta_7 f_7(t,u) + \overline{\eta}_{63} d_{63} \varepsilon_{63} n_3 A_6 \delta(u-u^{(0)}) - \lambda_7[f_7(t,u) - f_7(t_0,u_0)] \\
\\
\frac{\partial f_8}{\partial t}(t,u) = \overline{\eta}_{84} d_{84} \alpha_8 n_4 (1-u)\left[f_8(t,u-a_8) - (1-(u+a_8)) f_8(t,u)\right] \\
\qquad +(\overline{\eta}_{82} d_{82} n_2 + \overline{\eta}_{83} d_{83} n_3 + \overline{\eta}_{84} d_{84} n_4) \beta_8 f_8(t,u) + \varepsilon_{74} \overline{\eta}_{74} d_{74} n_4 A_7 \delta(u-u^{(0)}) \\
\qquad -\lambda_8[f_8(t,u) - f_8(t_0,u_0)]
\end{cases} \tag{4.47}$$

Remark 4.1.3. *The quantities $n_1, \cdots, n_8$ and $A_1, \cdots, A_8$, refereed to the size of the i-th population and the activation, respectively, which we will address in the next subsection.*

Remark 4.1.4. *System (4.47) is a highly nonlinear system of integro-differential equations in the unknown functions $f_1, \cdots, f_8$. Indeed, in it, the quantities d_{hk}, n_i and A_i may depend nonlinearly on the unknown functions: $d_{hk} = d_{hk}[\mathbf{f}]$, $n_i = n_i[\mathbf{f}]$ and $A_i = A_i[\mathbf{f}]$.*

4.2 Macroscopic Model

The mathematical model analyzed in the preceding subsections allows us to describe several interesting phenomena related to the several aspects of the immune-cancer competition. The dynamical evolutions of the unknown functions f_i can be obtained looking at solutions of a complicated system of integro-differential equations in the unknown functions f_i. A different approach is to work within a macroscopic framework, that gives us also important information on the evolution of the disease (cancer-immune system competition).

Our aim, in what follows, is to determine macroscopic equations by using a multiscale analysis. Thus, we shall derive from the underlying microscopic description macroscopic equations for the size, activation and quadratic activation of each cellular population.

As mentioned in chapter 1, if the distribution functions f_i are known, then macroscopic variables can be computed, under suitable integrability properties, as moments weighted by the above distribution function [1, 2]. For our purpose, we consider the following macroscopic variables:

- The *size* of the i-th population at time t, given by

$$n_i[\mathbf{f}](t) = \int_{D_u} f_i(t,u)\,du \quad \text{for} \quad i \in \{1,2,\ldots,8\}. \tag{4.48}$$

- The *activation* at time t of the i-th population, defined as:

$$A_i[\mathbf{f}](t) = \int_{D_u} u f_i(t,u)\,du \quad \text{for} \quad i \in \{1,2,\ldots,8\}, \tag{4.49}$$

- The *quadratic activation*:

$$E_i[\mathbf{f}](t) = \int_{D_u} u^2 f_i(t,u)\,du \quad \text{for} \quad i \in \{1,2,\ldots,8\}, \tag{4.50}$$

- The *cubic activation*:

$$Q_i[\mathbf{f}](t) = \int_{D_u} u^3 f_i(t,u)\,du \quad \text{for} \quad i \in \{1,2,\ldots,8\}. \tag{4.51}$$

Higher order moments can be also considered, but here we will deal only with first, second and third order moments, for the sake of simplicity.

4.2.1 Macroscopic Equations

By differentiating each of the both sides of the equations (4.48), (4.49), (4.50), with respect to t, and using the equations in the system (4.47), we can get the following equations for the averaged quantities n_i, A_i and E_i, $(i = 2, 3, 4, 6, 7, 8)$.

For $i = 2$ we get:

$$\begin{aligned}\frac{dn_2}{dt} &= \int_{D_u} [\overline{\eta}_{21} d_{21}\alpha_2 n_1(1-u)\,[f_2(t,u-a_2) - (1-(u+a_2))f_2(t,u)] \\ &+ \overline{\eta}_{21} d_{21}\beta_2 n_1 u f_2(t,u) + \overline{\eta}_{11} d_{11}\varepsilon_{11} n_1 A_1 \delta(u-u^{(0)})]du \\ &- \int_{D_u} f_2(t,u)(\overline{\eta}_{26} d_{26}\gamma_6 A_6 + \overline{\eta}_{27} d_{27}\gamma_7 A_7 + \overline{\eta}_{28} d_{28}\gamma_8 A_8)du \qquad (4.52)\end{aligned}$$

$$\begin{aligned}\frac{dA_2}{dt} &= \int_{D_u} [\overline{\eta}_{21} d_{21}\alpha_2 n_1(1-u)\,[f_2(t,u-a_2) - (1-(u+a_2))f_2(t,u)] \\ &+ \overline{\eta}_{21} d_{21}\beta_2 n_1 u f_2(t,u) + \overline{\eta}_{11} d_{11}\varepsilon_{11} n_1 A_1 \delta(u-u^{(0)})]udu \\ &- \int_{D_u} f_2(t,u)(\overline{\eta}_{26} d_{26}\gamma_6 A_6 + \overline{\eta}_{27} d_{27}\gamma_7 A_7 + \overline{\eta}_{28} d_8\gamma_{28} A_8)udu \qquad (4.53)\end{aligned}$$

$$\begin{aligned}\frac{dE_2}{dt} &= \int_{D_u} [\overline{\eta}_{21} d_{21}\alpha_2 n_1(1-u)\,[f_2(t,u-a_2) - (1-(u+a_2))f_2(t,u)] \\ &+ \overline{\eta}_{21} d_{21}\beta_2 n_1 u f_2(t,u) + \overline{\eta}_{11} d_{11}\varepsilon_{11} n_1 A_1 \delta(u-u^{(0)})]u^2du \\ &- \int_{D_u} f_2(t,u)(\overline{\eta}_{26} d_{26}\gamma_{26} A_6 + \overline{\eta}_{27} d_{27}\gamma_7 A_7 + \overline{\eta}_{28} d_{28}\gamma_8 A_8)u^2du \qquad (4.54)\end{aligned}$$

For $i = 3$ we get:

$$\begin{aligned}\frac{dn_3}{dt} &= \int_{D_u} [\overline{\eta}_{31} d_{31}\alpha_3 n_1(1-u)\,[f_3(t,u-a_3) - (1-(u+a_3))f_3(t,u)] \\ &+ \overline{\eta}_{31} d_{31}\beta_3 n_1 u f_3(t,u) + \overline{\eta}_{21} d_{21}\varepsilon_{21} n_1 A_2 \delta(u-u^{(0)})]du \\ &- \int_{D_u} f_3(t,u)(\overline{\eta}_{37} d_{37}\gamma_7 A_7 + \overline{\eta}_{38} d_{38}\gamma_8 A_8)du \qquad (4.55)\end{aligned}$$

$$\begin{aligned}\frac{dA_3}{dt} &= \int_{D_u} [\overline{\eta}_{31} d_{31}\alpha_3 n_1(1-u)\,[f_3(t,u-a_3) - (1-(u+a_3))f_3(t,u)] \\ &+ \overline{\eta}_{31} d_{31}\beta_3 n_1 u f_3(t,u) + \overline{\eta}_{21} d_{21}\varepsilon_{21} n_1 A_2 \delta(u-u^{(0)})]udu \\ &- \int_{D_u} f_3(t,u)(\overline{\eta}_{37} d_{37}\gamma_7 A_7 + \overline{\eta}_{38} d_{38}\gamma_8 A_8)udu \qquad (4.56)\end{aligned}$$

$$\begin{aligned}\frac{dE_3}{dt} &= \int_{D_u} [\overline{\eta}_{31} d_{31} \alpha_3 n_1 (1-u) \left[f_3(t, u-a_3) - (1-(u+a_3)) f_3(t,u) \right] \\ &+ \overline{\eta}_{31} d_{31} \beta_3 n_1 u f_3(t,u) + \overline{\eta}_{21} d_{21} \varepsilon_{21} n_1 A_2 \delta(u-u^{(0)})] u^2 du \\ &- \int_{D_u} f_3(t,u) (\overline{\eta}_{37} d_{37} \gamma_7 A_7 + \overline{\eta}_{38} d_{38} \gamma_8 A_8) u^2 du \end{aligned} \tag{4.57}$$

For $i = 4$ we get:

$$\begin{aligned}\frac{dn_4}{dt} &= \int_{D_u} [\overline{\eta}_{41} d_{41} \alpha_4 n_1 (1-u) \left[f_4(t, u-a_4) - (1-(u+a_4)) f_4(t,u) \right] \\ &+ \overline{\eta}_{41} d_{41} \beta_4 n_1 u f_4(t,u) + \overline{\eta}_{31} d_{31} \varepsilon_{31} n_1 A_3 \delta(u-u^{(0)})] du \\ &- \int_{D_u} f_4(t,u) (\overline{\eta}_{48} d_{48} \gamma_8 A_8) du \end{aligned} \tag{4.58}$$

$$\begin{aligned}\frac{dA_4}{dt} &= \int_{D_u} [\overline{\eta}_{41} d_{41} \alpha_4 n_1 (1-u) \left[f_4(t, u-a_4) - (1-(u+a_4)) f_4(t,u) \right] \\ &+ \overline{\eta}_{41} d_{41} \beta_4 n_1 u f_4(t,u) + \overline{\eta}_{31} d_{31} \varepsilon_{31} n_1 A_3 \delta(u-u^{(0)})] u du \\ &- \int_{D_u} f_4(t,u) (\overline{\eta}_{48} d_{48} \gamma_8 A_8) u du \end{aligned} \tag{4.59}$$

$$\begin{aligned}\frac{dE_4}{dt} &= \int_{D_u} [\overline{\eta}_{41} d_{41} \alpha_4 n_1 (1-u) \left[f_4(t, u-a_4) - (1-(u+a_4)) f_4(t,u) \right] \\ &+ \overline{\eta}_{41} d_{41} \beta_4 n_1 u f_4(t,u) + \overline{\eta}_{31} d_{31} \varepsilon_{31} n_1 A_3 \delta(u-u^{(0)})] u^2 du \\ &- \int_{D_u} f_4(t,u) (\overline{\eta}_{48} d_{48} \gamma_8 A_8) u^2 du \end{aligned} \tag{4.60}$$

For $i = 6$ we get:

$$\begin{aligned}\frac{dn_6}{dt} &= \int_{D_u} [\overline{\eta}_{62} d_{62} \alpha_6 n_2 (1-u) \left[f_6(t, u-a_6) - (1-(u+a_6)) f_6(t,u) \right] \\ &+ \overline{\eta}_{62} d_{62} \beta_6 n_2 f_6(t,u) + \overline{\eta}_{52} d_{52} \varepsilon_{52} n_2 A_5 \delta(u-u^{(0)})] du \\ &- \int_{D_u} \lambda_6 [f_6(t,u) - f_6(t_0,u_0)] du \end{aligned} \tag{4.61}$$

$$\begin{aligned}\frac{dA_6}{dt} &= \int_{D_u} [\overline{\eta}_{62} d_{62} \alpha_6 n_2 (1-u) \left[f_6(t, u-a_6) - (1-(u+a_6)) f_6(t,u) \right] \\ &+ \overline{\eta}_{62} d_{62} \beta_6 n_2 f_6(t,u) + \overline{\eta}_{52} d_{52} \varepsilon_{52} n_2 A_5 \delta(u-u^{(0)})] u du \\ &- \int_{D_u} \lambda_6 [f_6(t,u) - f_6(t_0,u_0)] u du \end{aligned} \tag{4.62}$$

$$\begin{aligned}\frac{dE_6}{dt} &= \int_{D_u} [\overline{\eta}_{62} d_{62} \alpha_6 n_2 (1-u) \left[f_6(t, u-a_6) - (1-(u+a_6)) f_6(t,u) \right] \\ &+ \overline{\eta}_{62} d_{62} \beta_6 n_2 f_6(t,u) + \overline{\eta}_{52} d_{52} \varepsilon_{52} n_2 A_5 \delta(u-u^{(0)})] u^2 du \\ &- \int_{D_u} \lambda_6 [f_6(t,u) - f_6(t_0,u_0)] u^2 du \end{aligned} \tag{4.63}$$

For $i = 7$ we get:

$$\begin{aligned}\frac{dn_7}{dt} &= \int_{D_u} [\overline{\eta}_{73} d_{73} \alpha_7 n_3 (1-u) \left[f_7(t, u-a_7) - (1-(u+a_7)) f_7(t,u) \right] \\ &+ (\overline{\eta}_{72} d_{72} n_2 + \overline{\eta}_{73} d_{73} n_3) \beta_7 n_2 f_7(t,u) + \overline{\eta}_{63} d_{63} \varepsilon_{63} n_3 A_6 \delta(u-u^{(0)})] du \\ &- \int_{D_u} \lambda_7 [f_7(t,u) - f_7(t_0,u_0)] du \end{aligned} \tag{4.64}$$

$$\begin{aligned}\frac{dA_7}{dt} &= \int_{D_u} [\overline{\eta}_{73} d_{73} \alpha_7 n_3 (1-u) \left[f_7(t, u-a_7) - (1-(u+a_7)) f_7(t,u) \right] \\ &+ (\overline{\eta}_{72} d_{72} n_2 + \overline{\eta}_{73} d_{73} n_3) \beta_7 f_7(t,u) + \overline{\eta}_{63} d_{63} \varepsilon_{63} n_3 A_6 \delta(u-u^{(0)})] u du \\ &- \int_{D_u} \lambda_7 [f_7(t,u) - f_7(t_0,u_0)] u du \end{aligned} \tag{4.65}$$

$$\begin{aligned}\frac{dE_7}{dt} &= \int_{D_u} [\overline{\eta}_{73} d_{73} \alpha_7 n_3 (1-u) \left[f_7(t, u-a_7) - (1-(u+a_7)) f_7(t,u) \right] \\ &+ (\overline{\eta}_{72} d_{72} n_2 + \overline{\eta}_{73} d_{73} n_3) \beta_7 f_7(t,u) + \overline{\eta}_{63} d_{63} \varepsilon_{63} n_3 A_6 \delta(u-u^{(0)})] u^2 du \\ &- \int_{D_u} \lambda_7 [f_7(t,u) - f_7(t_0,u_0)] u^2 du \end{aligned} \tag{4.66}$$

For $i = 8$ we get:

$$\begin{aligned}\frac{dn_8}{dt} &= \int_{D_u} [\overline{\eta}_{84} d_{84} \alpha_8 n_4 (1-u) \left[f_8(t, u-a_8) - (1-(u+a_8)) f_8(t,u) \right] \\ &+ (\overline{\eta}_{82} d_{82} n_2 + \overline{\eta}_{83} d_{83} n_3 + \overline{\eta}_{84} d_{84} n_4) \beta_8 f_8(t,u) + \overline{\eta}_{74} d_{74} \varepsilon_{74} n_4 A_7 \delta(u-u^{(0)})] du \\ &- \int_{D_u} \lambda_8 [f_8(t,u) - f_8(t_0,u_0)] du \end{aligned} \tag{4.67}$$

$$\begin{aligned}\frac{dA_8}{dt} &= \int_{D_u} [\overline{\eta}_{84} d_{84} \alpha_8 n_4 (1-u) \left[f_8(t, u-a_8) - (1-(u+a_8)) f_8(t,u) \right] \\ &+ (\overline{\eta}_{82} d_{82} n_2 + \overline{\eta}_{83} d_{83} n_3 + \overline{\eta}_{84} d_{84} n_4) \beta_8 f_8(t,u) + \overline{\eta}_{74} d_{74} \varepsilon_{74} n_4 A_7 \delta(u-u^{(0)})] u du \\ &- \int_{D_u} \lambda_8 [f_8(t,u) - f_8(t_0,u_0)] u du \end{aligned} \tag{4.68}$$

$$\begin{aligned}\frac{dE_8}{dt} &= \int_{D_u} [\overline{\eta}_{84} d_{84} \alpha_8 n_4 (1-u)\,[f_8(t,u-a_8) - (1-(u+a_8))f_8(t,u)] \\ &+ (\overline{\eta}_{82} d_{82} n_2 + \overline{\eta}_{83} d_{83} n_3 + \overline{\eta}_{84} d_{84} n_4)\beta_8 f_8(t,u) + \overline{\eta}_{74} d_{74} \varepsilon_{74} n_4 A_7 \delta(u-u^{(0)})]u^2 du \\ &- \int_{D_u} \lambda_8 [f_8(t,u) - f_8(t_0,u_0)]u^2 du \end{aligned} \tag{4.69}$$

In equations (4.52)–(4.69) the encounter rate depends on the distance $d_{hk}[\mathbf{f}]$ between the h-th and the k-th functional subsystems.

Different choices are possible. Following Bellouquid et al.(2013) [7], we assume that the distance d_{hk} is a functional of the distributions that characterize the two interacting functional subsystems:

$$d_{hk}[\mathbf{f}] = \begin{cases} \exp\left(-\tau \dfrac{\|f_h - f_k\|}{\|f_h\| + \|f_k\|}\right) & \|f_h\|, \|f_k\| \neq 0, \\ 0 & \|f_h\| = \|f_k\| = 0, \end{cases} \tag{4.70}$$

where $\tau > 0$ and the norm L^1 is used. In this way the increasing values of the distance d_{hk} between the h-th and the k-th functional subsystems correspond to decreasing values of the encounter rate η_{hk} [15]. Another more simple choice for the encounter rate will be made in Section 4.2.2.

Then, for $i = 2$ we get:

$$\begin{aligned}\frac{dn_2}{dt} &= \overline{\eta}_{21} d_{21} a_2 \alpha_2 n_1 n_2 + \overline{\eta}_{21} d_{21} \beta_2 n_1 A_2 + \overline{\eta}_{11} d_{11} \varepsilon_{11} n_1 A_1 \\ &- n_2(\overline{\eta}_{26} d_{26} \gamma_6 A_6 + \overline{\eta}_{27} d_{27} \gamma_7 A_7 + \overline{\eta}_{28} d_{28} \gamma_8 A_8) \end{aligned} \tag{4.71}$$

$$\begin{aligned}\frac{dA_2}{dt} &= \overline{\eta}_{21} d_{21} a_2 \alpha_2 n_1 A_2 + \overline{\eta}_{21} d_{21} \beta_2 n_1 E_2 + \overline{\eta}_{11} d_{11} \varepsilon_{11} n_1 A_1 u^{(0)} \\ &- A_2(\overline{\eta}_{26} d_{26} \gamma_6 A_6 + \overline{\eta}_{27} d_{27} \gamma_7 A_7 + \overline{\eta}_{28} d_{28} \gamma_8 A_8) \end{aligned} \tag{4.72}$$

$$\begin{aligned}\frac{dE_2}{dt} &= \overline{\eta}_{21} d_{21} a_2 \alpha_2 n_1 E_2 + \overline{\eta}_{21} d_{21} \beta_2 n_1 Q_2 + \overline{\eta}_{11} d_{11} \varepsilon_{11} n_1 A_1 [u^{(0)}]^2 \\ &- E_2(\overline{\eta}_{26} d_{26} \gamma_6 A_6 + \overline{\eta}_{27} d_{27} \gamma_7 A_7 + \overline{\eta}_{28} d_{28} \gamma_8 A_8) \end{aligned} \tag{4.73}$$

For $i = 3$ we get:

$$\begin{aligned}\frac{dn_3}{dt} &= \overline{\eta}_{31} d_{31} a_3 \alpha_3 n_1 n_3 + \overline{\eta}_{31} d_{31} \beta_3 n_1 A_3 + \overline{\eta}_{21} d_{21} \varepsilon_{21} n_1 A_2 \\ &- n_3(\overline{\eta}_{37} d_{37} \gamma_7 A_7 + \overline{\eta}_{38} d_{38} \gamma_8 A_8) \end{aligned} \tag{4.74}$$

$$\begin{aligned}\frac{dA_3}{dt} &= \overline{\eta}_{31} d_{31} a_3 \alpha_3 n_1 A_3 + \overline{\eta}_{31} d_{31} \beta_3 n_1 E_3 + \overline{\eta}_{21} d_{21} \varepsilon_{21} n_1 A_2 u^{(0)} \\ &- A_3(\overline{\eta}_{37} d_{37} \gamma_7 A_7 + \overline{\eta}_{38} d_{38} \gamma_8 A_8) \end{aligned} \tag{4.75}$$

$$\begin{aligned}\frac{dE_3}{dt} &= \overline{\eta}_{31}d_{31}a_3\alpha_3n_1E_3 + \overline{\eta}_{31}d_{31}\beta_3n_1Q_3 + \overline{\eta}_{21}d_{21}\varepsilon_{21}n_1A_2[u^{(0)}]^2 \\ &- E_3(\overline{\eta}_{37}d_{37}\gamma_7A_7 + \overline{\eta}_{38}d_{38}\gamma_8A_8) \end{aligned} \tag{4.76}$$

For $i = 4$ we get:

$$\begin{aligned}\frac{dn_4}{dt} &= \overline{\eta}_{41}d_{41}a_4\alpha_4n_1n_4 + \overline{\eta}_{41}d_{41}\beta_4n_1A_4 + \overline{\eta}_{31}d_{31}\varepsilon_{31}n_1A_3 \\ &- \overline{\eta}_{48}d_{48}n_4\gamma_8A_8 \end{aligned} \tag{4.77}$$

$$\begin{aligned}\frac{dA_4}{dt} &= \overline{\eta}_{41}d_{41}a_4\alpha_4n_1A_4 + \overline{\eta}_{41}d_{41}\beta_4n_1E_4 + \overline{\eta}_{31}d_{31}\varepsilon_{31}n_1A_3u^{(0)} \\ &- \overline{\eta}_{48}d_{48}A_4\gamma_8A_8 \end{aligned} \tag{4.78}$$

$$\begin{aligned}\frac{dE_4}{dt} &= \overline{\eta}_{41}d_{41}a_4\alpha_4n_1E_4 + \overline{\eta}_{41}d_{41}\beta_4n_1Q_4 + \overline{\eta}_{31}d_{31}\varepsilon_{31}n_1A_3(u^{(0)})^2 \\ &- \overline{\eta}_{48}d_{48}E_4\gamma_8A_8 \end{aligned} \tag{4.79}$$

For $i = 6$ we get:

$$\frac{dn_6}{dt} = \overline{\eta}_{62}d_{62}a_6\alpha_6n_2n_6 + \overline{\eta}_{62}d_{62}\beta_6n_2n_6 + \overline{\eta}_{52}d_{52}\varepsilon_{52}n_2A_5 - \lambda_6n_6 \tag{4.80}$$

$$\begin{aligned}\frac{dA_6}{dt} &= \overline{\eta}_{62}d_{62}a_6\alpha_6n_2A_6 + \overline{\eta}_{62}d_{62}\beta_6n_2A_6 + \overline{\eta}_{52}d_{52}\varepsilon_{52}n_2A_5u^{(0)} \\ &- \lambda_6A_6 \end{aligned} \tag{4.81}$$

$$\begin{aligned}\frac{dE_6}{dt} &= \overline{\eta}_{62}d_{62}a_6\alpha_6n_2E_6 + \overline{\eta}_{62}d_{62}\beta_6n_2E_6 + \overline{\eta}_{52}d_{52}\varepsilon_{52}n_2A_5(u^{(0)})^2 \\ &- \lambda_6E_6 \end{aligned} \tag{4.82}$$

For $i = 7$ we get:

$$\begin{aligned}\frac{dn_7}{dt} &= \overline{\eta}_{73}d_{73}a_7\alpha_7n_3n_7 + (\overline{\eta}_{72}d_{72}n_2 + \overline{\eta}_{73}d_{73}n_3)\beta_7n_7 + \overline{\eta}_{63}d_{63}\varepsilon_{63}n_3A_6 \\ &- \lambda_7n_7 \end{aligned} \tag{4.83}$$

$$\begin{aligned}\frac{dA_7}{dt} &= \overline{\eta}_{73}d_{73}a_7\alpha_7n_3A_7 + (\overline{\eta}_{72}d_{72}n_2 + \overline{\eta}_{73}d_{73}n_3)\beta_7A_7 + \overline{\eta}_{63}d_{63}\varepsilon_{63}n_3A_6u^{(0)} \\ &- \lambda_7A_7 \end{aligned} \tag{4.84}$$

$$\begin{aligned}\frac{dE_7}{dt} &= \overline{\eta}_{73}d_{73}a_7\alpha_7 n_3 E_7 + (\overline{\eta}_{72}d_{72}n_2 + \overline{\eta}_{73}d_{73}n_3)\beta_7 E_7 + \overline{\eta}_{63}d_{63}\varepsilon_{63}n_3 A_6(u^{(0)})^2 \\ &- \lambda_7 E_7 \end{aligned} \tag{4.85}$$

For $i = 8$ we get:

$$\begin{aligned}\frac{dn_8}{dt} &= \overline{\eta}_{84}d_{84}a_8\alpha_8 n_4 n_8 + (\overline{\eta}_{82}d_{82}n_2 + \overline{\eta}_{83}d_{83}n_3 + \overline{\eta}_{84}d_{84}n_4)\beta_8 n_8 + \overline{\eta}_{74}d_{74}\varepsilon_{74}n_4 A_7 \\ &- \lambda_8 n_8 \end{aligned} \tag{4.86}$$

$$\begin{aligned}\frac{dA_8}{dt} &= \overline{\eta}_{84}d_{84}a_8\alpha_8 n_4 A_8 + (\overline{\eta}_{82}d_{82}n_2 + \overline{\eta}_{83}d_{83}n_3 + \overline{\eta}_{84}d_{84}n_4)\beta_8 A_8 \\ &+ \overline{\eta}_{74}d_{74}\varepsilon_{74}n_4 A_7 u^{(0)} - \lambda_8 A_8 \end{aligned} \tag{4.87}$$

$$\begin{aligned}\frac{dE_8}{dt} &= \overline{\eta}_{84}d_{84}a_8\alpha_8 n_4 E_8 + (\overline{\eta}_{82}d_{82}n_2 + \overline{\eta}_{83}d_{83}n_3 + \overline{\eta}_{84}d_{84}n_4)\beta_8 E_8 \\ &+ \overline{\eta}_{74}d_{74}\varepsilon_{74}n_4 A_7 (u^{(0)})^2 - \lambda_8 E_8 \end{aligned} \tag{4.88}$$

Remark 4.2.1. *Note that, we have assumed null initial conditions in the equations* (4.80)–(4.88)*, that is:* $f_i(t_0, u_0) = 0$ *for* $i = 6, 7, 8$.

4.2.2 Closure of the evolution equations

The macroscopic equations obtained are a nonlinear system of ordinary differential equations. Particularly, they are useful for giving some information about the healthy state of given individuals.

To close them, one can use the traditional methods of continuum mechanics, choosing appropriate constitutive expressions for the encounter rate η_{hk} and for the cubic activities Q_2, Q_3 and Q_4 and the other unknown quantities.

We will make, therefore, the following assumptions:

- *Encounter rate.* We will assume that η_{hk} depends only on h and k and not on the functional expression of f_h and f_k. Specifically we will choose the encounter between tumor ($h = 2, 3, 4$) and epithelial cells ($h = 1$) proportional to h ($\eta_{h1} = h$), and the encounter rate between immune and cancer cells is chosen constant ($\eta_{hk} = \sigma$, for each pair $(h, k) = (5, 2)$, $(6, 2)$, $(6, 3)$, $(7, 2)$, (7.3), $(7, 4)$, $(8, 2)$, (8.3), $(8, 4)$).

- *Transition Probability Density.* We assume in the expressions (4.17) and (4.19) of the transition probability density $\alpha_i = \alpha$ and $a_i = a = u^{(0)}$.

- *Proliferation rate.* We assume that the proliferation rate of the cancer cells (subsystems $h = 2, 3, 4$), owing to their interactions with epithelial cells $k = 1$ is $\beta_h = h\beta$, and the proliferation rate of the cells of the immune system (subsystems $h = 5, 6, 7, 8$), owing to their interactions with cancer cells $k = 2, 3, 4$ is $\beta_h = \beta'$.

- *Mutation rate.* We assume that the mutation rate of the cancer cells (subsystems $i = 2, 3, 4$) related with the encounters of cells of the functional subsystems $h = 1, 2, 3$ respectively with epithelial cells of first functional (subsystem $k = 1$) is $\varepsilon_{(i-1)1} = \varepsilon$.
  We assume also that the mutation rate in immune subsystems $i = 6, 7, 8$ related with the encounters of particles of the functional subsystems $h = 5, 6, 7$ respectively with cancer cells (functional subsystems $k = 2, 3, 4$) is $\varepsilon_{(i-1)k} = \varepsilon'$.

- *Destruction rate.* We assume that the destruction rate of cancer cells (due to the encounter with immune cells of the corresponding hallmark is $\gamma_i = \gamma$ for $i = 2, 3, 4$.

- *Relaxation and apoptosis rate.* We assume that the coefficient characterizing the relaxation of immune systems is given by $\lambda_i = \lambda$ for $i = 6, 7, 8$.

- *Number density and activity of epithelial cells.* We assume that epithelial cells do not modify their primitive state, therefore n_1 and A_1 are assumed constant quantities.

- *Number density and activity of innate immune system cells.* We assume that the innate immune system does not modify its primitive state, therefore n_5 and A_5 are assumed constant quantities.

- *Cubic activation of cancer cells.* We assume that the cubic activations of the cancer cells Q_2, Q_3 and Q_4 are constant in time.

This model is sufficiently appealing for a qualitative understanding of some biological features influencing the immune-cancer competition.

Under the above assumption, the evolution equations for the number densities, activation densities and quadratic activation densities of each cellular population

are:

$$\frac{dn_2}{dt} = 2a\alpha n_1 n_2 + 4\beta n_1 A_2 + \varepsilon n_1 A_1 - n_2\sigma\gamma(A_6 + A_7 + A_8) \quad (4.89)$$

$$\frac{dn_3}{dt} = 3a\alpha n_1 n_3 + 9\beta n_1 A_3 + 2\varepsilon n_1 A_2 - n_3\sigma\gamma(A_7 + A_8) \quad (4.90)$$

$$\frac{dn_4}{dt} = 4a\alpha n_1 n_4 + 16\beta n_1 A_4 + 3\varepsilon n_1 A_3 - \sigma\gamma n_4 A_8 \quad (4.91)$$

$$\frac{dn_6}{dt} = \sigma a\alpha n_2 n_6 + \sigma\beta^{'} n_2 n_6 + \sigma\varepsilon^{'} n_2 A_5 - \lambda n_6 \quad (4.92)$$

$$\frac{dn_7}{dt} = \sigma a\alpha n_3 n_7 + \sigma\beta^{'} n_7(n_2 + n_3) + \sigma\varepsilon^{'} n_3 A_6 - \lambda n_7 \quad (4.93)$$

$$\frac{dn_8}{dt} = \sigma a\alpha n_4 n_8 + \sigma\beta^{'} n_8(n_2 + n_3 + n_4) + \sigma\varepsilon^{'} n_4 A_7 - \lambda n_8 \quad (4.94)$$

$$\frac{dA_2}{dt} = 2a\alpha n_1 A_2 + 4\beta n_1 E_2 + \varepsilon n_1 A_1 u^{(0)} - A_2\sigma\gamma(A_6 + A_7 + A_8) \quad (4.95)$$

$$\frac{dA_3}{dt} = 3a\alpha n_1 A_3 + 9\beta n_1 E_3 + 2\varepsilon n_1 A_2 u^{(0)} - A_3\sigma\gamma(A_7 + A_8)) \quad (4.96)$$

$$\frac{dA_4}{dt} = 4a\alpha n_1 A_4 + 16\beta n_1 E_4 + 3\varepsilon n_1 A_3 u^{(0)} - \sigma\gamma A_4 A_8 \quad (4.97)$$

$$\frac{dA_6}{dt} = \sigma a\alpha n_2 A_6 + \sigma\beta^{'} n_2 A_6 + \sigma\varepsilon^{'} n_2 A_5 u^{(0)} - \lambda A_6 \quad (4.98)$$

$$\frac{dA_7}{dt} = \sigma a\alpha n_3 A_7 + \sigma\beta^{'} A_7(n_2 + n_3) + \sigma\varepsilon^{'} n_3 A_6 u^{(0)} - \lambda A_7 \quad (4.99)$$

$$\frac{dA_8}{dt} = \sigma a\alpha n_4 A_8 + \sigma\beta^{'} A_8(n_2 + n_3 + n_4) + \sigma\varepsilon^{'} n_4 A_7 u^{(0)} - \lambda A_8 \quad (4.100)$$

$$\frac{dE_2}{dt} = 2a\alpha n_1 E_2 + 4\beta n_1 Q_2 + \varepsilon n_1 A_1[u^{(0)}]^2 - E_2\sigma\gamma(A_6 + A_7 + A_8) \quad (4.101)$$

$$\frac{dE_3}{dt} = 3a\alpha n_1 E_3 + 9\beta n_1 Q_3 + 2\varepsilon n_1 A_2[u^{(0)}]^2 - E_3\sigma\gamma(A_7 + A_8) \quad (4.102)$$

$$\frac{dE_4}{dt} = 4a\alpha n_1 E_4 + 16\beta n_1 Q_4 + 3\varepsilon n_1 A_3[u^{(0)}]^2 - \sigma\gamma E_4 A_8 \quad (4.103)$$

$$\frac{dE_6}{dt} = \sigma a\alpha n_2 E_6 + \sigma\beta^{'} n_2 E_6 + \sigma\varepsilon^{'} n_2 A_5[u^{(0)}]^2 - \lambda E_6 \quad (4.104)$$

$$\frac{dE_7}{dt} = \sigma a\alpha n_3 E_7 + \sigma\beta^{'} E_7(n_2 + n_3) + \sigma\varepsilon^{'} n_3 A_6[u^{(0)}]^2 - \lambda E_7 \quad (4.105)$$

$$\frac{dE_8}{dt} = \sigma a\alpha n_4 E_8 + \sigma\beta^{'} E_8(n_2 + n_3 + n_4) + \sigma\varepsilon^{'} n_4 A_7[u^{(0)}]^2 - \lambda E_8 \quad (4.106)$$

Remark 4.2.2. *Note that the state vector of this model is:*

$$\Gamma = (n_2, n_3, n_4, n_6, n_7, n_8, A_2, A_3, A_4, A_6, A_7, A_8, E_2, E_3, E_4, E_6, E_7, E_8). \quad (4.107)$$

and is a vector with 18 components.
More simple systems of macroscopic equations can be obtained choosing as state vector, the vector with 12 components

$$\Gamma_1 = (n_2, n_3, n_4, n_6, n_7, n_8, A_2, A_3, A_4, A_6, A_7, A_8), \tag{4.108}$$

considering only the first 12 equations (4.89)–(4.100) *of previous system and giving for the energies* E_2, E_3, E_4 *suitable constitutive equations,*
or also the vector with 6 components

$$\Gamma_2 = (n_2, n_3, n_4, n_6, n_7, n_8), \tag{4.109}$$

considering only the first 6 equations (4.89)–(4.94) *of previous system and giving for the activities* A_2, A_3, A_4 *suitable constitutive equations.*

Chapter 5

Conclusions and Further Lines of Research

5.1 Conclusions

This chapter presents the conclusions of the research described in the thesis. The aim and objectives of the research, outlined in the Introduction of this thesis, are reviewed and their achievement described. Proposals for future work indicated by the research are suggested.

Throughout this thesis, we have presented some tools as powerful techniques to analyze the immune competition with Darwinian dynamics. The main point in this analysis is the modeling of complex biological systems using a mathematical approach which is related to mathematical kinetic theory. The application refers to the mathematical description of the immune-cancer competition. This is a very active and recent frontier in current medical research, as it has opened new promising perspectives complementary and more far reaching than those in classical radiotherapy and chemotherapy.

- Chapter 1 is devoted to define the framework of the mathematical kinetic theory of active particles, which has been used to describe the general evolution equations of the biological system. According to KTAP, the system is divided into interacting functional subsystems, each subsystem with a specific biological function.

  In the general framework of KTAP, the microscopic state includes geometrical mechanical and biological functions, while for the spatial homogeneous models considered in this thesis, the microscopic state includes only the biological scalar function u.

A system in mathematical biology is called closed in the absence of any effect from outside the system on the internal system, and is called open when the effect occurs. In this thesis only closed systems are analyzed.

- In Chapter 2, an overview of the immune system and hallmarks of cancer is given. Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. The growth of normal cells is kept under control by growth-inhibitors or signals. Cancer cells generally have defects in the control mechanisms that govern how often they are able to be divided and are able to stimulate their own growth, due to the dominant character of oncogenes. The immune system responds to foreign pathogens and cancer cells by activating specific and nonspecific immune responses. The goal of immunotherapy is to enhance these responses to control the growth of cancer cells.

- In Chapter 3 the model by Bellouquid et al.(2013), that describes the competition between the immune system and cancer cells, is studied in details. In this model, the activity is characterized by discrete scalar values. A number of simulations were performed showing that the immune system is able to suppress cancer cells when we select specific values for the unknown parameters of the model.

  We have tested the effect of changing the values of the parameters previously obtained. The results are the following:

  1. Concerning the parameter β_2, that characterizes the proliferation rate of the immune cell populations, as found in the number 1 of the Section 3.2.3 and according with the Figure 3.10, this parameter cannot take values less than 10^{-1} because it will not give improved results.
  2. Concerning the parameter β_1, that characterizes the proliferation rate of cancer cells, as found in the number 2 of the Section 3.2.3 and according with the Figure 3.11, this parameter cannot take values greater than 10^{-4} because it will not give improved results.
  3. Concerning the parameter λ, that characterizes the relaxation rate, as found in the number 3 of the Section 3.2.3 and according with the Figure 3.12, this parameter cannot take the value 0.016 or any values greater than it.
  4. Concerning the parameter α, that characterizes the probability density in conservative interactions in the progression phenomena, as found in the number 4 of the Section 3.2.3 and according with the Figure 3.13, this parameter cannot take values greater than 10^{-3}.

5. Concerning the parameter σ, that characterizes the encounters between immune cells and cancer cells, as found in the number 5 of the Section 3.2.3 and according with the Figure 3.14, this parameter cannot take values lesser than 0.5 and the values must be in the interval $[0.5, 0.9]$.
6. Concerning the parameters ε_{26}, ε_{27} and ε_{28} that characterize the mutation rate in immune system, as found in the number 6 of the Section 3.2.3 and according with the Figure 3.15, we have seen that changes in one of these parameters from 10^{-1} to 10^{-4} do not produce significant modifications of the behaviour of the system and lead to equivalent results.
7. Concerning the parameter ε_1 that characterizes the mutation rate in cancer cells, as found in the number 7 of the Section 3.2.3 and according with the Figure 3.16, we have seen that, when this rate takes very small values, the immune system is incapable to suppress cancer cells. Our interpretation of this result is that 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 3.16. This could be due to the fact that in this situation the immune system relaxes too quickly to recognize malignant cancer cells.
8. Concerning the parameter γ that characterizes the destruction rate of cancer cells, as found in the number 8 of the Section 3.2.3 and according with the Figure 3.17, this parameter plays a fundamental role in the cancer-immune system competition, as an increase in this parameter corresponds to an increase of the immune systems ability to suppress cancer cells. From simulations, we showed that for $\gamma = 0.1$ the immune system is not able to resist cancer cells.

In Section 3.4, we have presented a proposal to modify the parameter α that models the probability density in conservative interactions in the progression phenomena, by differentiating it for cancer cells (coefficient α_1) and immune system cells (coefficient α_2). The analysis shows that the behavior of cancer cells, when they interact with epithelial cells, differs from that when they interact with immune cells.

- In Chapter 4, we have generalized the model proposed by Bellouquid et al.(2013), choosing for the activity variable continuous values $u \in (0, \infty)$. This allows us to derive a macroscopic model by suitable asymptotic methods from the microscopic description given by the kinetic theory approach.

The most important points we have considered in the our thesis are:

1. Cells in a multicellular system are characterized by biological functions and the ability to organize their dynamics and interactions with other cells.

2. The mathematical kinetic theory for multicellular systems is defined by a system of integro-differential equations describing the evolution in time and space of the distribution functions over the microscopic state of cells of each population.

3. In the modeling of biological systems it is important to consider a multiscale approach. In fact, we have shown how macroscopic equations can be derived from the microscopic descriptions.

   These features are introduced in our model through the specification of the internal state of each cell and of the interaction between different cells according to their respective internal states.

5.2 Further Lines of Research

Our thesis has been a detailed exploration of a model of immune-cancer competition with Darwinian dynamics, by using the kinetic theory of active particles and following, in its general lines, the model formulated by Bellouquid et al..

The results of this thesis are interesting and non-trivial, but exclude the possibility to study how cells move away from their site of origin and travel to distant sites, and how the system would responds to medical therapies. In fact, the problem of immune-cancer competition is much wider and complex than the situations we have been able to deal with. From this point of view, the main drawbacks of our thesis are: (1) to consider only the activity in the microscopic state of each cell, (2) to consider only the behavior of closed systems, without considering interactions with the outside.

Future works that could be done as an extension of this thesis are :

- Generalization of the model, considering more complete biological hypothesis, as for example to better describe the growth of tumor cells, that in this model has been considered exponential, without differentiating different types of cancer.

- Incorporate in the model the possibility of metastasis, assuming for the microscopic state of each active particle $\mathbf{w} = (\mathbf{x}, \mathbf{v}, u)$. In this case, the system must be considered as inhomogeneous and the transport of cancer cells to different organs must be taken into account, as well as the different kinds of evolution according to the organ where they have arrived and

settled. This will depend not only on the internal state of the cancer cells but also on their interaction with the surrounding cells of the particular organ.

- Consider biological open systems, with the aim to incorporate into the model the possibility of introducing medical therapies. This will allow us to incorporate the combination of chemotherapy techniques and immunotherapy technique. For instance, external chemical factors may modify the internal state of the cells of the immune system enhancing their effects on cancer cells. This is in contrast with usual chemotherapy, which directly acts on the cancer cells. Furthermore, the open system approach will allow, in principle, progress and perspectives in chemotherapy and immunotherapy of cancer. In this way, the interaction with the outer environment(i.e. the therapeutical action) is not limited to fix the cell internal parameters (as in the closed system approach), but is able to continue in the time, so modifying the dynamics of the biological system.

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