



Review

# From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells <sup>☆</sup>

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## Abstract

This paper deals with a review and critical analysis on the mathematical kinetic theory of active particles applied to the modelling of the very early stage of cancer phenomena, specifically mutations, onset, progression of cancer cells, and their competition with the immune system. The mathematical theory describes the dynamics of large systems of interacting entities whose microscopic state includes not only geometrical and mechanical variables, but also specific biological functions. Applications are focused on the modelling of complex biological systems where two scales at the level of genes and cells interact generating the heterogeneous onset of cancer phenomena. The analysis also refers to the derivation of tissue level models from the underlying description at the lower scales. The review is constantly linked to a critical analysis focused on various open problems including the ambitious objective of developing a mathematical theory for complex biological systems.

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## 1. Motivations and plan of the review

This paper deals with a review of research papers devoted to developments of the mathematical kinetic theory for active particles to multiscale modelling of the early stage of cancer phenomena, namely mutations, onset and progression of cancer cells in competition with the immune system [114].

This mathematical theory was introduced in [10], while the book [13] reports about recent developments and applications. The modelling refers to the evolution of large systems of interacting individuals or entities, called *active particles*, characterized by the ability to express specific functions, called *activities*, that are typical of the living matter, for instance, competition, selection, evolution, reproduction. Interactions at the microscopic scale are modelled by stochastic games among active particles, which modify their microscopic state according to complex rules which attempt to describe some behaviors of the living matter, and specifically the ability of developing strategies based also on the analysis of the behaviors of the surrounding individuals. This theory has been applied in different fields of applied and life sciences as documented in the already cited book [13], for instance, complex psychological interactions [18,40], traffic flow [53], social dynamics [34].

This paper specifically refers to the above outlined complex biological system, namely the early stage of cancer onset and developments. The contents are strongly motivated by the fact that the scientific community is becoming increasingly aware that the great revolution of this century is going to be the mathematical formalization of phenomena in the life sciences, as well as the revolution of the past two centuries was the development of the mathematical approach in the physical sciences. It is a great challenge that will require the intellectual energy of scientists working in the field of mathematics and physics collaborating closely with biologists. The final target consists in joining the heuristic experimental approach, which is the traditional investigative method in the biological sciences, with the rigor induced by methods of mathematical and physical sciences.

The analysis of complex biological systems by a mathematical approach is motivated by top level biologists, and is documented in several recent papers appearing in journals dedicated to the life sciences. Among others, Antia et al. [9] analyze the role of mathematical models in biology, while May [87] analyzes relatively more general aspects of the use of mathematics in the biological sciences. This interesting paper looks for an equilibrium between a naive enthusiastic attitude and unreasonable scepticism. The beginning of the above cited paper captures the main conceptual ideas:

In the physical sciences, mathematical theory and experimental investigation have always marched together. Mathematics has been less intrusive in the life sciences, possibly because they have been until recently descriptive, lacking the invariance principles and fundamental natural constants of physics.

Remarkably similar concepts are proposed by Reed [102] according to the viewpoint of applied mathematicians. Once more, the author comments on the crucial difference between dealing with living matter and inert matter: essentially the lack of background models to support the derivation of mathematical equations. The brief note by Herrero [72] provides additional hints to develop a mathematical theory of complex biological systems.

Several hints to interdisciplinary approaches are offered by the paper by Hartwell et al. [71], which deeply analyze the conceptual differences between the difficulties in dealing with inert and living matter. Living systems are characterized by specific features absent in classical mechanics, as, for example, reproduction, competition, cell cycle, and the ability to communicate with other entities. Suggestions are not limited to general speculations, but provide a theory of functional modules defined as a discrete entity whose function is separable from those of other modules. As we shall see, this theory is mathematically developed through the approach of functional subsystems.

Focusing on cancer phenomena, it is important stressing that even at the very early stages the biological system under consideration appears with multiscale features: genes, cells and the early stage of tissues, corresponding to the molecular, cellular and tissue scale. The importance of examining the genetic mutations in cancer development is emphasized in Hanahan and Weinberg's landmark paper [70], where the authors identify the critical changes in cell physiology that characterize malignant cancer growth. These changes—self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, evading immune

system attack, and tissue invasion and metastasis—incorporate some aspect of genetic mutation, gene expression, and evolutionary selection [105], leading to malignant progression. Although preliminary work on cancer modelling has included one or more of these hallmarks, few theoretical papers have addressed the mutations and selection which lead to the outward expression of these characteristics. Indeed, it is well accepted that the onset of cancer occurs through a sequence of genetic mutations and evolutionary selection leading to malignancy, a concept not yet well addressed through mathematical modelling.

Various papers and books, among others [13,52,64,67,69,88,90,92,97], suggest the development of a new game theory, e.g., evolutionary games, as a fundamental paradigm to deal with interactions between genes, cells and the outer environment including, of course, therapeutical actions and vaccines. This topic may act as a fundamental paradigm towards the development of a bio-mathematical theory of cancer, that is the very final aim of the interaction between the biological and mathematical sciences in the research field under consideration.

Some of the relevant key aspects of the mathematical modelling process are listed below:

- Selecting, out of the multiscale aspects of the biological phenomena under consideration, the reference representation and modelling scale.
- Development of a strategy to select the correct mathematical framework to deal with modelling at each scale.
- Development of methods to link models at the scale selected with those at the corresponding lower and higher scales.
- Looking for paradigms for the development of a biological mathematical theory related to the complex system we are dealing with.

Considering that the existing mathematical approaches have not yet reached the identification of a uniquely defined approach, it is worth understanding how far scientists are from the development of a biological mathematical theory analogous to physical mathematical theories developed in the past century. This paper aims to provide not only a review of the existing literature, but also a critical analysis focused on new theoretical research perspectives. Indeed, the complexity of the system we are dealing with requires new ideas and, possibly, the invention of new mathematical methods.

The reader is guided to the specific literature by citations attempting to cover the various issues dealt with in the paper that are focused, as already mentioned, to the early stage of the tumor growth. Additional literature can be extracted from the review papers [27] and [89], or special issues of mathematical journals [28–30], and collection of surveys devoted to cancer modelling [2,19,101]. The contents of this paper, which is organized into six further sections, are as follows:

- Section 2 deals with a description of the relevant phenomena that appear in the early stage of cancer. Namely, mutations, heterogeneous progression, and competition with the immune system. This section also analyzes the observation and representation scales and the identification of the variables suited to identify the biological state of the system at each scale. These variables are related to the concept of functional subsystems, that allows to reduce the complexity of the overall system into suitable subsystems, where active particle express the same biological function.
- Section 3 reports, with reference to the existing literature, about mathematical tools of the kinetic theory and stochastic games that can be used to model the various phenomena described in the preceding section. These tools include a method to link the two lower scales, namely the molecular to the cellular scale, i.e. from genotypic to phenotypic distributions.
- Section 4 shows how specific models can be derived referring to the above mathematical framework. Models are obtained by a detailed description of interactions at the cellular level based on the dynamics at the molecular level. A survey of various models known in the literature is given, while various hints to further developments are proposed.
- Section 5 deals with the modelling of space phenomena and, specifically, with the space-time scaling finalized to the derivation of tissue level models from the underlying cellular description. Different models, parabolic or hyperbolic, can be derived according to the influence of the dynamics at the molecular scale to cell dynamics and aggregation.

- Section 6 proposes a critical analysis of the contents of the preceding sections mainly focused on research perspectives. The most challenging target consists in developing a proper mathematical theory of complex biological systems.

The above index shows that this paper is organized in three parts. The first part reports about biological sciences and mathematical tools. The second part, namely Sections 4 and 5, provides a survey and critical analysis of the literature in the field, while the third part is focused on open problems and hints to research perspectives. The third part is motivated by the fact that, despite several interesting contributions, the amount of open problems is definitely greater than those which may be considered closed.

## 2. Mutations, heterogeneity, progression of cancer cells

As mentioned in Section 1, modelling the complex biological system under consideration needs a multiscale mathematical approach. However, this is not the only problem considering that it is necessary, to reduce complexity, to decompose the whole system [90] into suitable subsystems, namely modules according to the theory by Hartwell [71]. While, according to [24,25], a specific biological function and a suitable representation scale have to be linked to each module, or functional subsystem. Interactions occur both within each module, due to heterogeneity, and among modules generally driven by networks.

This paper deals with modelling aspects and attempts to extract some interpretation of reality to set the essential background to mathematical description by equations. The reader, interested in a deeper understanding of the biology of cancer, will find the book by Weinberg [114] a highly valuable reference. Being well understood that modelling needs a deep understanding of the different functions expressed at the different scales: from genes to biological tissues.

The review, and critical analysis, refers to the early stage of cancer phenomena. Therefore, the first event to be considered is the generation of a neoplastic cell through phenotypic alterations resulting from genetic mutations occurring through genetic instability and environmental interactions. After the onset of neoplasia, various complex phenomena occur which are related to different scales.

The three following subsections are focused on the scaling problem, on the assessment of the definition of modules, or functional subsystems, and on a phenomenological interpretation of the role that the immune system plays in the early stage competition.

It is worth stressing that, although the description proposed in this section is not complete, may be even not satisfactory from the view point of biological sciences, it already shows that most of the complex phenomena characterizing the system under consideration have not yet been put within a well settled mathematical framework.

The first step of the analysis of the system under consideration in view of its modelling consists in the assessment of the *scaling problems and representations*. Specifically, let us consider a multicellular system constituted by a large variety of cell populations. The evolution of cells is regulated by the genes contained in its nucleus. Receptors on the cell surface can receive signals which are then transmitted to the cell nucleus, where the aforementioned genes can be activated or suppressed. The dynamics occurs at the *molecular scale* [111]. In extreme situations, particular signals can induce uncontrolled cell proliferation, or can induce the cell to neglect the signal the natural cell death, the so-called apoptosis or programmed cell death [5,36]. Unregulated proliferation may activate interactions between tumor cells and host cells, which occur at the cellular level but are mediated by sub-cellular processes, such as through signal cascades and receptor expression. These interactions can result in temporary, or even permanent alterations in gene expression [76–78,80,98].

Alteration in gene expression generates the onset of cancer phenomena, and can influence the immune defense, such as by activation or inactivation of immune cells. Cancer is then a multi-step genetic disease and the degeneration of neoplastic cells is called *progression* [90,93].

The *cellular scale* refers to cell–cell interactions, that are key elements at all stages of tumor formation, whether they are among tumor cells and host cells, or among tumor cells themselves. For example, early in tumor development, if the immune system is active and able to recognize tumor cells, it may be able to develop a destruction mechanism and induce cancer cell death; otherwise, the tumor may evade apoptosis or co-opt the host cells, allowing progressive growth. During invasion and metastasis, alterations in cell–cell adhesion between individual tumor cells are key to driving the process.

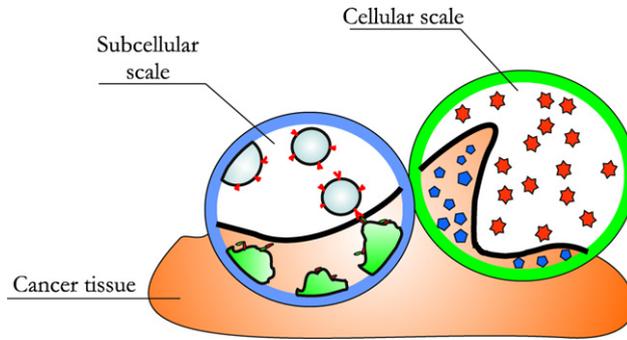


Fig. 1. Sketch of the coupling between molecular and cellular scale with interaction with the outer environment.

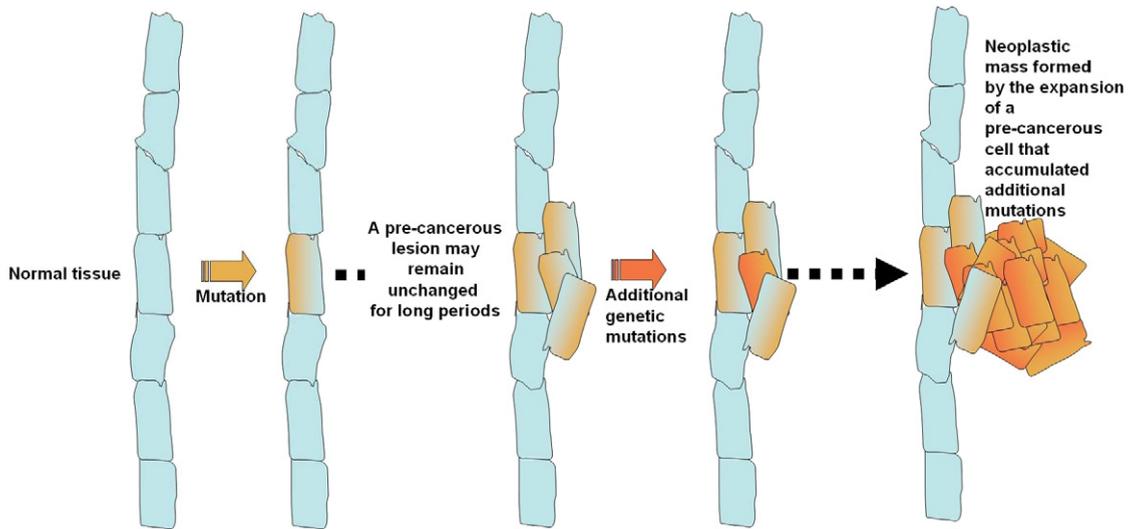


Fig. 2. Mutations.

These and other cellular interactions are regulated by signals emitted and received by cells through complex transduction processes. Therefore, the connection to the aforementioned sub-cellular scale is evident. On the other hand, the growth of tumor cells, if not cleared by the immune system, forms a mass so that macroscopic features become important. However, even after formation of a tumor structure, interactions between individual cells (signalling, migration or proliferation) are crucial to driving macroscopic processes (such as blood vessel formation or invasion), underscoring the need to link these multiple scales.

Fig. 1 visualizes some of the multiscale aspects of the phenomena under consideration. It is worth stressing that all events at the cellular and tissue scales are governed by the dynamics at the genetic scale. Therefore, the modelling at the higher scales needs to be constantly referred to the lowest scale. Fig. 2 visualizes the progressive mutations of cells from the differentiated to the progressing state.

Multiscale aspects of biological systems indicate, in general and specifically in cancer phenomena, the need of reducing complexity. Several authors suggest the approach of system biology as an essential tool to achieve this objective. For instance, Woese [116] indicates in system biology the key guideline to deal with the interpretation and modelling of complex biological systems. This objective can be achieved by a suitable development of the theory of *modules and functional subsystems*.

The idea of decomposing a biological system into several interacting subsystems can be arguably assigned to Hartwell who proposed the so-called *theory of modules*, that is clearly described in [71], where it is stated that modules can be regarded as subsystems that have the ability to express well defined biological functions and activities. Modules interact in networks.

The mathematical formalization of the above concepts can be organized precisely only if referred to well defined biological systems. A contribution to this matter is given in paper [25], that deals with the modelling of the immune competition in multicellular systems. This paper suggests to consider each population as a module suitable to express collectively a well defined biological function. For instance, this specific application indicates *progression* for cancer cells and *defense ability* for immune cells. Further analysis and generalizations are proposed in [27] focused on cancer modelling.

It is worth stressing that the decomposition into modules depends, according to [27], on the specific biological function expressed by each module, rather than by its particular components. In other words, a module can express the collective behavior of different components. Indeed, this is the case of the immune system when compacted into a unique module.

The above reasoning suggests to use the term *functional subsystem* as an alternative, proposed in the field of behavioral economy [4], to the term *module*. The analogy with economical sciences is not surprising as both sciences belong to the greater field of life sciences.

Bearing all above in mind, the following statements can be given:

- 2.1. A functional subsystem is a collection of active particles that have the ability to express a well defined biological function, called *activity*.
- 2.2. The activity within each functional subsystem is heterogeneously distributed.
- 2.3. If the number of active particles in a functional subsystem is sufficiently large and the heterogeneity is a continuous variable, the state of the system can be described by a continuous probability distribution.

Various examples of interactions of functional subsystems at different scales have been proposed in the literature. For instance, papers [7,8,108] deal with models where the properties and dynamics at the cellular scale play an essential role on models at the tissue scale. Moreover, papers [39,86,110] show how interactions between cellular and tissues scales need to be properly considered within the same model. Of course, the most important aspect is, as we shall see, the interaction between the molecular and cellular scales.

Bearing all above in mind, it is worth analyzing the role of the immune system. The human body rises several lines of defense to contrast the tumor onset and progression: some of them are specific of the cell life-cycle, as the monitoring of DNA duplication, other defenses are specific of the organization of tissues, as the protection of stem cells and their genome (their original DNA). Besides those defenses, human body is protected against infectious agents by the immune system. The phenomenological description that follows takes advantage of paper [85], where this topic is accurately presented.

The *immune system* is a complex of different cells and molecules which provides a strong and effective defense against pathogenic agents. The cells of the immune system, globally called *leukocytes* or white blood cells, communicate via cell-to-cell contact or via chemical signals through specific secreted substances, and cooperate in continuously monitoring the environment, detecting and attacking foreign infectious agents.

Moreover, the immune cells are able to perform complex tasks such as *learning*, acquiring the capability of distinguishing between host entities (*self*) and foreign or infected entities (*non-self*), and *evolving* in time to achieve more and more better results, retaining memory of previous encounters with foreign agents for a quicker response in case of re-infection, and constantly updating their reactive potential.

The response of the immune system to an infectious agent is subdivided in:

- *innate immunity response*, mediated by specialized cells as macrophages, granulocytes, “natural killer (NK)” cells;
- *adaptive immune response*, mediated by the *lymphocytes*.

Innate immunity is characterized by the ability of an efficient discrimination between *self* and *non-self*, and, in consequence, by the ability of recognizing a broad spectrum of pathogenic agents. The innate immunity acts immediately after an infection, but cannot learn anymore. Long-remembering the encounter with an infectious agent, once that it has been destroyed, is a task of the cells of the adaptive immune response. It is to point out, however, that the cells involved in innate response participate actively in adaptive response too, and that the actions used to destroy the foreign host are quite similar.

Lymphocytes are subdivided in two major classes.

- B-cells, which rise and mature in the bone marrow, and, after activation, differentiate in
  - plasma cells, which secrete free-floating *antibodies*;
- T-cells, which rise in the bone marrow and mature in the thymus, and, after activation, differentiate in:
  - cytotoxic T cells, which kill virus-infected cells and some tumor cells,
  - T-helper cells, which stimulate the growth and differentiation of B-cells,
  - T regulatory and T suppressor cells, which modulate the immune response and stop it when the infection has been defeat.

B-cells act on extracellular agents, while T-cells act on cells detected as *foreign*. Both of them have receptor molecules on their surface which can recognize molecules typical of the infectious agents, called *antigens*, which are presented to them by specialized cells of the immune system, the *antigen presenting cells*. The recognition is based on the complementary in the molecular shape (a sort of *lock-and-key* mechanism) between the receptor binding site of the lymphocyte and a portion of the antigenic complex, the *epitope*. Each lymphocyte has more than  $10^4$  receptors on its surface, all with the same molecular shape: therefore, each lymphocyte can detect only its specific antigen.

The specificity of the mechanism *receptor-antigen* is quite efficient, and allows a strong defense against a very large spectrum of possible infectious agents.

The receptors of the lymphocytes are created through genetic rearranging of their specific genes in a pretty random fashion: the number of possible receptors, the *potential repertoire* of the immune system, is roughly  $10^{11}$  different elements for the B-cells, and  $10^{16}$  different elements for the T-cells. Because there are about  $10^{12}$  immune cells in a healthy human body, it is not possible to maintain the whole repertoire: the number of different receptors which are present at any time—and thus the capability to detect an infectious agent—is called the *expressed repertoire*.

As their first job, lymphocytes must learn to distinguish between *self* and *non-self* antigens to avoid an autoimmune response which may destroy healthy cells which are not recognized as belonging to the body's tissues, namely T-cells mature into the thymus, where the cells which fail to recognize self-antigens, or are not activated by non-self antigens, are selected for apoptosis. Matured *naive* lymphocytes migrate then to the peripheral lymphoid organs, where they normally resides in absence of infections. There, the expressed repertoire is continuously updated by signals specific to the receptors of each lymphocyte: only those which receive the *survival signal* by their environment will survive, while the others are selected for apoptosis, and are replaced by new lymphocytes, with different receptors.

Finally, in the case of an infection, those lymphocytes which are activated by their specific antigens quickly proliferate and differentiate into effector cells (plasma cells, cytotoxic and helper T-cells), according to the so-called *clonal selection*. By this way, the number of lymphocytes which are able to destroy the agent which carries the specific antigen is greatly increased during the infection, and a considerable number of them will survive after the defeat of infectious agent, thus allowing a quicker response in case of re-infection.

The question whether the immune system, which is specialized to detect and eliminate foreign agents, may recognize as *foreign* also tumor cells, which are native to the body and substantially indistinguishable from normal cells, has been matter of discussions between biologists. Today, evidence is rapidly accumulating that the immune system contributes to the body multilayered defenses against tumors.

The immune competition may, in some cases, not be able to contrast the onset and development of tumor cells. Therefore, the biological events include *tumorigenesis and tumor progression*.

Almost every tumor is generated by *mutagenic* agents which corrupt the genome of a cell. The corruption of a genetic locus (a specific site along the length of a specific chromosome) may occur because of physical or chemical exogenous agents, or, more usually, because of some mistake during DNA replication, in the process of the mitosis of the cell. Remembering that approximately  $10^{16}$  mitoses occur during a normal human life span, it seems likely that every day everyone has to suffer some kind of genome alteration, despite the protection of stem cells and the efficient processes of *check and repair* of the duplicated DNA, which are typical of the mammalian organisms.

Luckily, not every genetic corruption leads to the arising of a tumor: many of them are indifferent to the normal cell life, many others make the genome of the mutated cell so unstable that the cell dies after a short time. It is supposed that more than four successive genetic mistakes are necessary to a cell to become malignant. Moreover, the vast majority of mutated cells remain in a dormant, pre-malignant state for an entire lifetime.

It is worth stressing that the number of genetic mutations which are required in order to justify tumorigenesis is very high, far beyond the number of genetic mutations which occur during normal human life. However, sometimes a random DNA mutation may provide a normal cell with a sort of *genomic instability*: even if it does not seem to provide an immediate benefit in terms of proliferation and survival, genomic instability greatly increases the speed of further genetic mutations and makes easier the acquisition of other characteristics. Even if not easily quantified, the acquired genomic instability should be considered as the first hallmark in tumorigenesis.

Therefore a cell may incur into a specific alteration in one of its genes, which gives to it a significant advantage with regard to survival and proliferation, and allows to it and its descendant to quickly advance along the tumor progression. Only a small portion of hundreds of the alterations present in many neoplastic cell's genome actually play causal roles in the process of tumorigenesis: mutation of a small number of critical control genes seems to be the way to acquire neoplastic cell phenotype. Generally, a tumor develops *progressively*, demonstrating different gradations of abnormality along the way from being benign to metastatic. Besides, a tumor generally arises from the genetic mutation of a single cell (the so-called *monoclonal cancer*, but there are, at the same time, descendant cells with different types of genetic mutations, i.e. different progression; thus the tumor tissue presents *genetic heterogeneity* of cells. Between two extremes of fully normal tissues and highly malignant tissues lies a broad spectrum of intermediate appearance, which we will read as a statistical distribution heterogeneity of cells progression. The different gradations of abnormality may well reflect cell populations that are evolving progressively away from normal and toward greater degrees of aggressive and invasive behavior.

Human cancer cells share a set of common characteristics (the so-called *hallmarks of cancer*), acquired on the way to full malignant state [70]:

- (i) autocrine signalling, namely capability of providing their own growth signals;
- (ii) resistance to growth-inhibitory signals;
- (iii) capability to proliferate indefinitely;
- (iv) capability of angiogenesis;
- (v) capability of escaping apoptosis;
- (vi) metastatic capability;
- (vii) capability of avoiding the immune system attack.

Each characteristic, which is reached through multi-step evolution, may represent a distinct step. They are acquired in different ways and times from tumor to tumor (though hallmarks (1) and (2) are generally reached firstly), and even a single genetic mutation may help in reaching more than one characteristic simultaneously. Completion of each step in tumor progression can be viewed as the successful reaching of one of the above attributes. In other words, normal cells are meticulously programmed to construct and maintain the diverse tissues that make possible the survival of the whole organism, tumor cells proliferate indefinitely, having the objective of making always more copies of themselves.

### 3. Mathematical tools

The preceding section has shown how the biological system under consideration needs different scales to represent the complex phenomena that occur during tumor onset and progression. Therefore, multiscale methods should be developed to model the overall system viewed as a network of several interconnected subsystems. This section reports the mathematical tools of the kinetic theory for active particles that can be used to develop a modelling strategy focused on the molecular and cellular scales, but also in view of deriving equations modelling biological tissues at the macroscopic scale. The approach specifically deals with heterogeneous phenomena, namely the non-uniform distribution of the microscopic states (biological functions) at each scale. For instance, the variables that characterize the heterogeneous competition between at the cellular level are the *progression* [68] and the *immune activity* [93]. Specifically, the present section reports about various mathematical frameworks that can be properly specialized into specific models. A review of applications is offered in the following sections technically referred to a decomposition into functional subsystems related to the afore-mentioned biological functions.

Let us consider a biological system viewed as a complex network of various interacting subsystems, each of them expressing a well defined function. The state of each subsystem is described at a specific scale, molecular, cellular

or tissue, and is constituted by entities called *active particles*, while the variable describing their specific biological expression is called *activity*. Activities differ in each subsystem, that can be regarded as a population.

This section refers to spatial homogeneity, while space dependent problems are reported later in Section 5. The overall representation within each subsystem, labelled by the subscript  $i$ , is statistically described by the distribution functions:

$$f_i = f_i(t, u) : [0, T] \times D_u \rightarrow \mathbb{R}_+, \quad i = 1, \dots, n, \quad (1)$$

over the microscopic state  $u \in D_u$  of the active particles. By definition,  $dn_i = f_i(t, u) du$  denotes the number density of active particles, which, at time  $t$ , are in the element  $[u, u + du]$  of the space of the microscopic state. Mathematical models should then describe the evolution in time of the distribution functions  $f_i$ .

Gross averaged quantities can be computed, when these functions are obtained by solution of the resultant equations. For instance, the local *number density* is calculated, under suitable integrability assumptions on  $f_i$ , as follows:

$$v_i(t) = \int_{D_u} f_i(t, u) du, \quad (2)$$

while the following quantities:

$$a_i = a[f_i](t) = \int_{D_u} u f_i(t, u) du, \quad (3)$$

and

$$A_i = A[f_i](t) = \frac{a[f_i](t)}{v_i(t)} \quad (4)$$

have been called [25], respectively, *activation* and the *activation density*. These quantities represent, respectively, the overall activity of the cells per unit volume and their mean activity. Analogous calculations can be developed for higher order moments.

Moreover, it is worth discussing the concept of *populations* with reference to the idea of *modules* proposed by Hartwell et al. [71]. After having observed that biological systems may be characterized by an enormous number of copies, while only a few copies generally characterize the inert matter, it is proposed to reduce complexity by grouping different entities by looking at their collective expression of biological functions related to the specific biological events under observation.

It is worth mentioning that the representation (1) is proposed to model heterogeneity phenomena over the activity variable. On the other hand, a simplified description of biological reality is obtained when biological functions are assumed to be the same within the active particles of each population. In this case, the mathematical approach is that of population dynamics. The book by Perthame [100] provides, in Chapter 1, a survey of population models in biology, related to a vast bibliography documented in several books, e.g., Edelstein-Keshet [60], Thieme [106]. Various authors have used the approach of population dynamics to model open systems subject to different therapies, e.g., De Pillis et al. [54], d'Onofrio [58], Kirschner and Panetta [75], Moore and Li [91], see also [74]. The approach of population models is based on the assumption that the activity variable is the same within each population for all particles. Consequently, mathematical models are stated in terms of ordinary differential equations. However, this assumption appears to be quite restrictive. Therefore, various developments have been proposed. For instance, Tomlinson and Bodmer [107], d'Onofrio and Tomlinson [59], Johnston et al. [73] deal with an additional insight into cell dynamics modelling failure of programmed cell death and differentiation as causes of tumor growth. Smieja and Swierniak [103] develop models of chemotherapy based on gene amplification analysis. A detailed report on the application of population dynamics models in immunology is given in the review paper by Perelson and Weisbuch [99].

Further developments are obtained by including an internal variable related to biological functions. For instance, the internal variable can be the age of the cells as determined by the cell cycle, which has crucial influence on various biological phenomena such as apoptosis, cell division, mutation. A systematic introduction to cell population dynamics with internal structure has been given by Webb [113], followed by several interesting books, Dieckmann and Heesterbeek [56], Thieme [106]. The bibliography cited in these monographs cover the existing literature in the field.

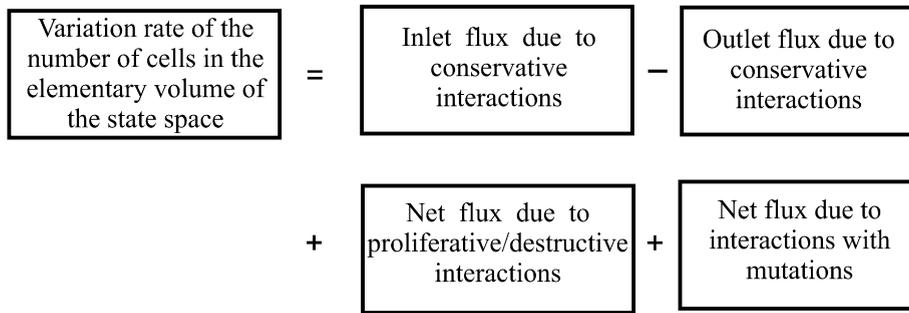


Fig. 3. Flow chart.

Bearing all above in mind, let us consider the derivation of suitable mathematical structures that can be used for the modelling of large systems of active particles (whose activity is heterogeneously distributed) interacting within each functional-subsystem and with the particles of the other subsystems. These structures represent the mathematical background if the models reviewed in the next section. The overall evolution of the system is caused by interactions. Specifically, the following phenomena (interactions), focused on cancer modelling, are considered:

- Stochastic modification of the microscopic state of genes or cells due to binary interactions with other cells of the same or of different populations. These interactions are called *conservative* as they do not modify the number density of the interacting populations.
- Genetic alteration of cells which may either increase the progression of tumor cells or even generate, by clonal selection, new cells in a new population of cancer cells with higher level of malignancy.
- Proliferation or destruction of cells due to binary interactions with other cells of the same or of different populations.
- External actions, either therapeutical actions or other external agents, which modify the distribution function.

Of course, additional interactions can be considered, as it will be critically analyzed in the last section. However the analysis of this section is restricted to the above description, while the formal structure, which describes the evolution of  $f_i$ , is obtained by the balance of particles in the elementary volume of the microscopic state. The balance is represented in the flow chart of Fig. 3.

Consequently one has:

$$\partial_t f_i(t, u) + F_i(t)\partial_u f_i(t, u) = J_i[f](t, u) = C_i[f](t, u) + D_i[f](t, u) + P_i[f](t, u), \tag{5}$$

where the right-hand side models the flow, at time  $t$ , into the elementary volume  $[u, u + du]$  of the state space of the  $i$ th population, for  $i = 1, \dots, n$ , due to transport and interactions. In detail:

- $F_i(t)$  models the external action over the  $i$ th population.
- $C_i[f](t, u)$  models the flow, at time  $t$ , into the elementary volume of the state space of the  $i$ th population due to conservative interactions:

$$C_i[f](t, u) = \sum_{j=1}^n \int_{D_u} \int_{D_u} \eta_{ij}(u_*, u^*) \mathcal{B}_{ij}(u_*, u^*; u) f_i(t, u_*) f_j(t, u^*) du_* du^* - f_i(t, u) \sum_{j=1}^n \int_{D_u} \eta_{ij}(u, u^*) f_j(t, u^*) du^*, \tag{6}$$

where  $\eta_{ij}$  is the encounter rate, namely, the encounters of a *candidate particle*, with state  $u_*$  in the  $i$ th population, with a *field particle*, with state  $u^*$  in the  $j$ th population. The probability that, as a result of this interaction, the particular acquires the state  $u$  is given by the probability density function  $\mathcal{B}_{ij}(u_*, u^*; u)$ .

- $D_i[f](t, u)$  models the net flow, at time  $t$ , into the elementary volume of the state space of the  $i$ th population due to proliferative and destructive interactions without transition of population:

$$D_i[f](t, u) = \sum_{j=1}^n f_j(t, u) \int_{D_u} \eta_{ij}(u, u^*) \mu_{ij}(u, u^*) f_j(t, u^*) du^*, \tag{7}$$

where  $\mu_{ij}(u, u^*)$  models net flux within the same population due to interactions, which occur with rate  $\eta_{ij}$ , of the test particle, with state  $u$ , of the  $i$ th population and the field particle, with state  $u^*$ , of the  $j$ th population.

- $P_i[f](t, u)$  models the flow, at time  $t$ , into the elementary volume of the state space of the  $i$ th population due to proliferation:

$$P_i[f](t, u) = \sum_{h=1}^n \sum_{k=1}^n \int_{D_u} \int_{D_u} \eta_{ijk}(u_*, u^*) \mu_{hk}(i \neq h)(u_*, u^*; u) f_h(t, u_*) f_k(t, u^*) du_* du^*, \tag{8}$$

where  $\mu_{hk}(i \neq h)(u_*, u^*; u)$  models the net proliferation into the  $i$ th population, due to interactions, which occur with rate  $\eta_{ijk}$ , of the *candidate particle*, with state  $u_*$ , of the  $h$ th population and the *3 field particle*, with state  $u^*$ , of the  $k$ th population.

Substituting the above expression into (5) yields:

$$\partial_t f_i(t, u) + F_i(t) \partial_u f_i(t, u) = J_i[\mathbf{f}](t, u) \tag{9}$$

where

$$\begin{aligned} J_i[\mathbf{f}](t, u) = & \sum_{j=1}^n \int_{D_u} \int_{D_u} \eta_{ij}(u_*, u^*) \mathcal{B}_{ij}(u_*, u^*; u) f_i(t, u_*) f_j(t, u^*) du_* du^* \\ & - f_i(t, u) \sum_{j=1}^n \int_{D_u} \eta_{ij}(u, u^*) f_j(t, u^*) du^* \\ & + f_i(t, u) \sum_{j=1}^n \int_{D_u} \eta_{ij}(u, u^*) \mu_{ij}(u, u^*) f_j(t, u^*) du^* \\ & + \sum_{h=1}^n \sum_{k=1}^n \int_{D_u} \int_{D_u} \eta_{ijk}(u_*, u^*) \mu_{hk}(i \neq h)(u_*, u^*; u) f_h(t, u_*) f_k(t, u^*) du_* du^*. \end{aligned} \tag{10}$$

The mathematical framework (9), (10) is based on the assumption that the action over the active particles is the same for all of them. On the other hand, specific therapeutical actions can be applied directly at the cellular scale by actions of the type

$$g_i = g_i(t, v) : [0, T] \times D_v \rightarrow \mathbb{R}_+, \quad i = 1, \dots, n, \tag{11}$$

acting on each population by a given distribution function over microscopic state  $v \in D_v$ .

The derivation of a mathematical framework for an open system subject to the actions (11) follows precisely the same guidelines of the preceding subsection. The result is as follows:

$$\partial_t f_i(t, u) = J_i[\mathbf{f}](t, u) + Q_i[\mathbf{f}, \mathbf{g}](t, u), \tag{12}$$

where  $J_i[\mathbf{f}]$  is given by Eq. (10), while  $Q_i$  is as follows:

$$Q_i[\mathbf{f}, \mathbf{g}](t, u) = \sum_{j=1}^n \int_{D_u \times D_v} \eta_{ij}^e(u_*, v^*) C_{ij}(u_*, v^*; u) f_i(t, u_*) g_j(t, v^*) du_* dv^*$$

$$\begin{aligned}
& - f_i(t, u) \sum_{j=1}^n \int_{D_v} \eta^*(u, v^*) g_j(t, v^*) dv^* \\
& + f_i(t, u) \sum_{j=1}^n \int_{D_v} \eta_{ij}^e(u, v^*) \mu_{ij}^e(u, v^*) g_j(t, v^*) dv^* \\
& + \sum_{h=1}^n \sum_{k=1}^n \int_{D_u} \int_{D_u} \eta_{hk}(u_*, v^*) \mu_{hk}^e(i)(u_*, v^*; u) f_h(t, u_*) g_k(t, v^*) du_* dv^*, \tag{13}
\end{aligned}$$

where:

$\eta_{ij}^e(u_*, v^*)$  models the encounter rates between the  $j$ th external action with state  $v^*$  and the  $i$ th candidate particle with state  $u_*$ . Analogous is the definition of  $\eta_{ij}^e(u, v^*)$  and  $\eta_{hk}^e(u_*, v^*)$ .

$C_{ij}(u_*, v^*; u)$  denotes the probability density that the candidate particle the  $i$ th population with state  $u_*$ ,  $h$  falls into the state  $u$  of the same population due to interactions with the  $j$ th action with state  $v^*$ .

$\mu_{ij}(u, v^*)$  denotes the proliferative/destructive rate of the *test* particle, with state  $u$ , of the  $i$ th population due to the interaction with the  $j$ th *field* external action with state  $v^*$ .

$\mu_{hk}(i \neq h)(u_*, v^*; u)$  models the net proliferation into the  $i$ th population, due to interactions, which occur with rate  $\eta_{hk}$ , of the *candidate* particle of the population  $h$ th with state  $u_*$  with the  $k$ th action with state  $v^*$ .

The above frameworks (9)–(10) and (12)–(13) can be used to derive specific models when a detailed analysis of the phenomenology of the system under consideration allows to model the various interaction terms that have been defined in this section. Actually, various models known in the literature have been derived following the above guidelines. A survey is given in the next section. On the other hand, it is well understood [25] that these terms should be delivered by the dynamics at the lower molecular scale [64]. This delicate matter is discussed in Section 4 and again in the last section.

#### 4. A survey of models

This section provides a review of models derived using the mathematical tools reported in Section 3. The modelling is focused on the early stage of tumor onset and competition with the immune system. The variable that characterize the heterogeneous competition between the two functional subsystems are the *progression* [68] and the *immune activity* [93]. Models should have the ability to describe progression of cancer cells and their competition with immune cells which, on the other side, express their antagonistic ability, unless inhibited, to limit cancer cell density growth.

Particular pathological states may be thought of as an emergent property of the output of various genetic mutations which generate new cells with increasing degree of malignancy. After various genetic mutations, cells may acquire the ability to succeed in escaping from the immune system despite the sentinel guards which, should, in principle, limit cell growth. See, for example, [3,12,35,85,97,111].

Actually, the mathematical frameworks of Section 3 offer a variety of tools greater than those effectively used in the models known in the literature. Therefore, this section is also focused on research perspectives based on a full use of the afore mentioned tools.

Let us first consider modelling at the cellular scale. The literature in the field developed after the pioneer paper Bellomo and Forni [23], where a model concerning the early stage of cancer onset and competition with the immune system was proposed. Simulations developed in [22] and [26] have shown the ability of the model to describe, according to a proper selection of the parameters, two different asymptotic behaviors in time:

- (i) growth of the number of tumor cells due also to their increasing progression and subsequent inhibition of immune cells;
- (ii) progressive reduction of the number of tumor cells due to the action of immune cells that remain active.

Before reviewing the various developments generated by the model proposed in [23], it is useful showing how the derivation of models can be developed. Therefore, let us consider, as an application, the modelling of the competition among two cellular populations,  $n = 2$ . The first population is constituted by endothelial cells, whose activity denotes how far cells are from the biological normality. The activity of the environmental cells is called *progression*, and is defined by the scalar variable  $u \in \mathbb{R}$ , where  $u \leq 0$  identifies the state of the normal cells, and  $u > 0$  the state of abnormal cells. The level of malignancy increases with increasing progression: growth-autonomous, tissue-invasive, metastatically competent. The second population is constituted by cells of the immune system, whose activity denotes how immune cells contrast cells of the first population. The activity of the immune cells is called *activation*, and it is defined by the scalar variable  $u \in \mathbb{R}$ , where  $u \leq 0$  identifies the state of the inhibited immune cells, and  $u > 0$  the state of the active immune cells. The degree of ability to contrast abnormal cells increases with increasing activation.

As already mentioned, the derivation of models needs a detailed description of interactions at the cellular level. Consider first the early stage of tumor onset corresponding to a competition where no proliferation or destruction yet occur, while interactions only modify the biological functions of the cells of the two populations. This model can be used to analyze latent immune competitions, when cells degenerate before the onset of relevant proliferation phenomena which give evidence of the presence of a pathological state. The modelling of cell interactions can be based on the following phenomenological assumptions:

- 4.1C:** The most probable output of conservative interactions between cells of the first population is:  $m_{11} = u_* + \alpha_{11}$ , for  $u_*, u^* \in \mathbb{R}$ .
- 4.2C:** The progression of an abnormal cell decreases due to encounters with an active immune cell, and the most probable output of the microscopic state after the interaction is given as follows:  $m_{12} = u_* - \alpha_{12}$  for  $u_*, u^* \geq 0$ .
- 4.3C:** The most probable output of the microscopic state of the immune cell after the interaction with progressing cells, with state  $u^*$ , is given as follows:  $m_{21} = u_* - \alpha_{21}$  for  $u_*, u^* \geq 0$ .

All the other interactions generate a trivial output, namely do not lead to a modification of the microscopic state of the candidate cell. Moreover, assuming that  $B_{ij}$  is a delta function over the most probable output  $m_{ij}(u_*, u^*)$ , which depends on the microscopic states  $u_*$  and  $u^*$  of the interacting pairs.

$$B_{ij}(u_*, u^*; u) = \delta(u - m_{ij}(u_*, u^*)), \tag{14}$$

and inserting all above assumptions into the framework (10) yields:

$$\left\{ \begin{aligned} \partial_t f_1(t, u) &= [f_1(t, u - \alpha_{11}) - f_1(t, u)] \int_{-\infty}^{\infty} f_1(t, u) du \\ &\quad + [f_1(t, u + \alpha_{12})U_{[0, \infty)}(u + \alpha_{12}) - f_1(t, u)U_{[0, \infty)}(u)] \int_0^{\infty} f_2(t, u) du, \\ \partial_t f_2(t, u) &= [f_2(t, u + \alpha_{21})U_{[0, \infty)}(u + \alpha_{21}) - f_2(t, u)U_{[0, \infty)}(u)] \int_0^{\infty} f_1(t, u) du. \end{aligned} \right. \tag{15}$$

This model is characterized by three phenomenological parameters related to mass conservative encounters  $\alpha_{11}$ ,  $\alpha_{12}$ , and  $\alpha_{21}$ , that have been defined in the above assumptions. The qualitative analysis of the initial value problem for model (15) can be found in [33] and [42].

The second example, see [31], refers to the stage where the distribution over the biological functions reaches a slowly varying value, while the proliferative or destructive events become predominant. This model can be used to analyze the last stage of the competition, when both cell populations have reached a fixed stage of the biological functions, and only proliferative or destructive phenomena are relevant. The model is derived according to the assuming that:

**4.1P:** The proliferation rate of cells of the first populations with  $u_* \geq 0$ , stimulated (*uncontrolled mitosis*) by encounters with non-progressing cells  $u_* < 0$ , is modelled as follows:

$$\mu_{11}(u_*, u^*) = \beta_{11} U_{[0, \infty)}(u_*) U_{(-\infty, 0)}(u^*).$$

**4.2P:** Progressing cells, with activity  $u_* \geq 0$ , are partially destroyed (*immune defense*) due to encounters with active immune cells. The modelling is:

$$\mu_{12}(u_*, u^*) = -\beta_{12} U_{[0, \infty)}(u_*) U_{[0, \infty)}(u^*).$$

**4.3P:** Active immune cells, with  $u^* \geq 0$ , proliferate (*activation towards defense*) due to encounters with progressing cells:

$$\mu_{21}(u_*, u^*) = \beta_{21} U_{[0, \infty)}(u_*) U_{[0, \infty)}(u^*).$$

All the other interactions give a trivial output, i.e. do not lead to a modification of the microscopic state of the interacting cells. The model, using again (10) and (14), is as follow:

$$\begin{cases} \partial_t f_1(t, u) = f_1(t, u) \left[ \beta_{11} \int_{-\infty}^0 f_1(t, u) du - \beta_{12} \int_0^{\infty} f_2(t, u) du \right] U_{[0, \infty)}(u), \\ \partial_t f_2(t, u) = \beta_{21} f_2(t, u) \int_0^{\infty} f_1(t, u) du U_{[0, \infty)}(u). \end{cases} \tag{16}$$

This model is characterized by three phenomenological parameters related to proliferative and destructive encounters  $\beta_{11}, \beta_{21}, \beta_{21}$ . Also in this case parameters are positive quantities (eventually equal to zero) small with respect to unity. The qualitative analysis of the initial value problem for model (16) can be found in [32].

The above mathematical models, although stated by a relatively simple structure, can possibly describe two important stages of the immune competition, where during the first stage, cells of the two interacting populations simply modify their respective biological functions, while later the onset of proliferative or destructive phenomena may end up with the growth or the destruction of the cells of the progressing population. The output of the competition mostly depends on the ability of immune cells to identify and destroy the abnormal cells.

The dynamics, in the case of model (15), is visualized in Figs. 4 and 5. Specifically Fig. 4 shows how cancer cells increase their progression and immune cells decrease their activation, while the number of cells remains constant in time. The opposite behavior is observed in Fig. 5 corresponding to lower values of the parameter modelling the inhibition ability of tumor cells.

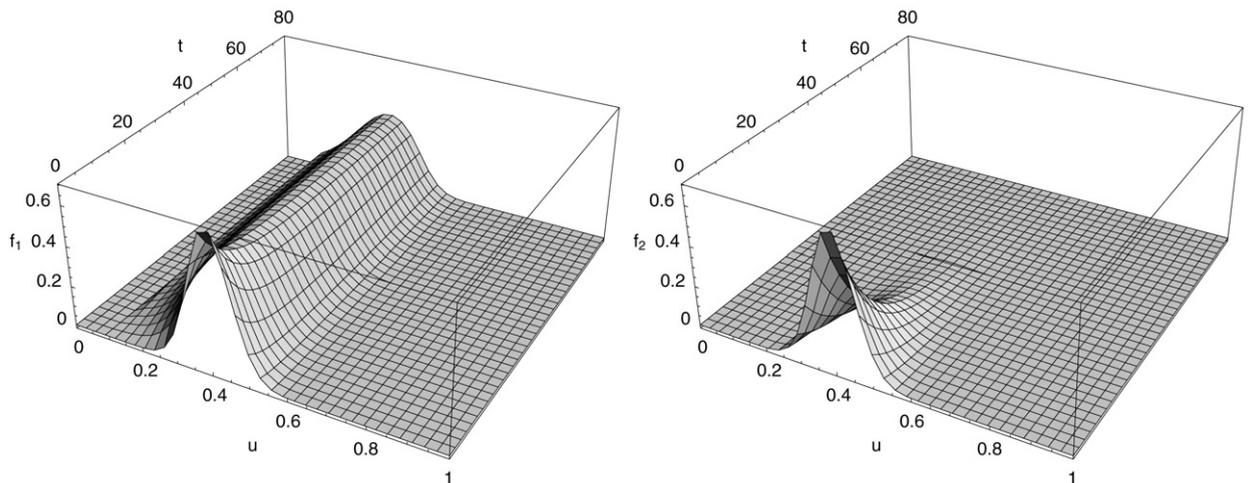


Fig. 4. Evolution of abnormal cells (on the left) and immune inhibition (on the right).

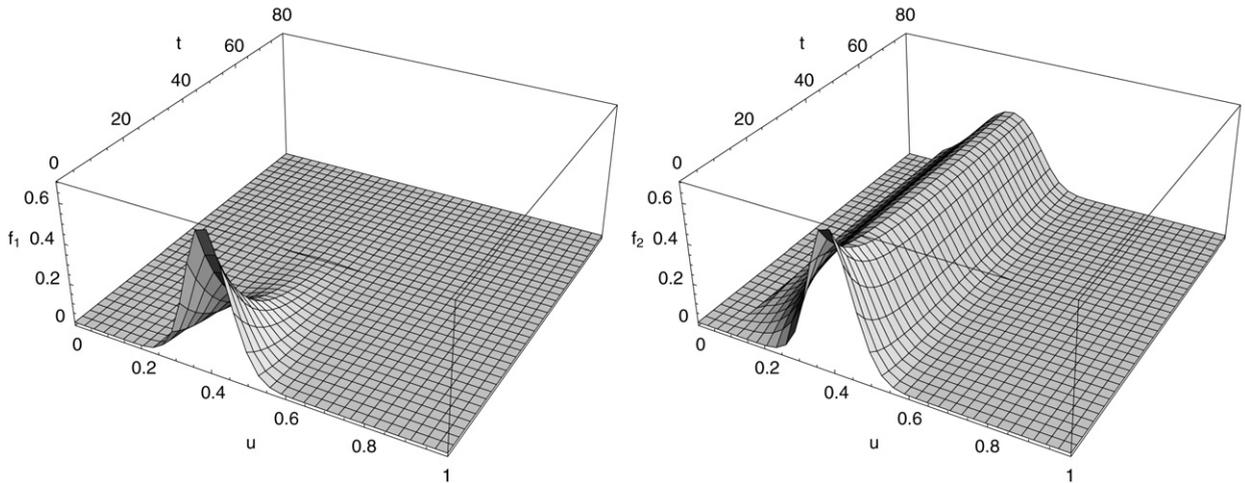


Fig. 5. Reduction of abnormal cells (on the left) and immune survival (on the right).

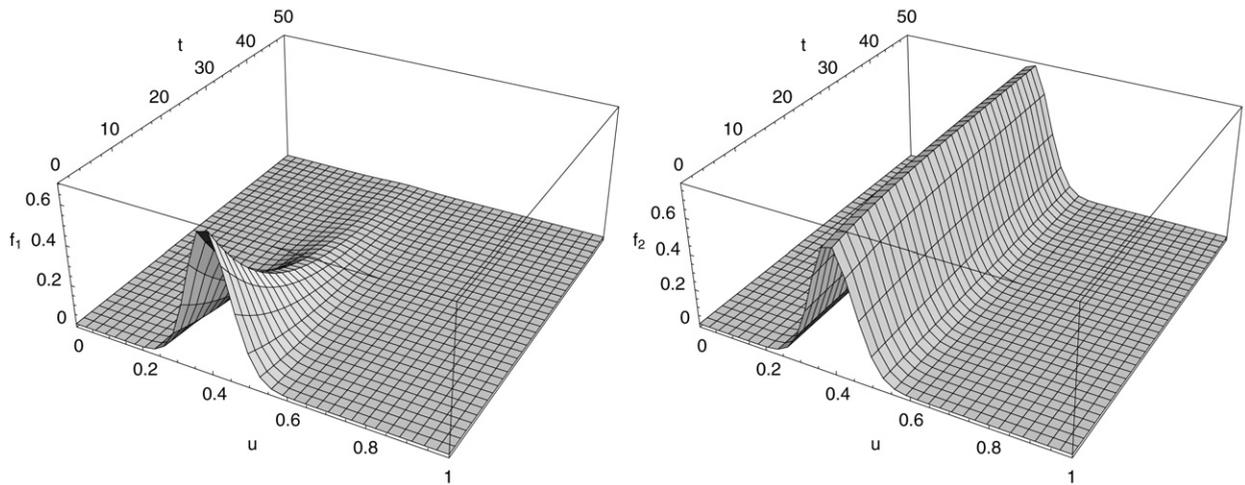


Fig. 6. Depletion of abnormal cells (on the left) and immune cells proliferation (on the right).

The qualitative analysis reported in Chapter 4 of [33] provides a detailed analysis on the influence of the parameters of the model and of the initial conditions on the output of the competition focused on the number density of cells. Simulations show the evolution of the distribution function, namely of the heterogeneity over the biological states.

Fig. 6, referring now to model (16), shows, corresponding to a choice of parameters  $\beta$ , that the number of cancer cells increases in time, while the number of immune cells decreases in time. The opposite behavior with an initial increase of cancer cells is observed in Fig. 7 corresponding to a different choice of parameters. The two different behaviors depend both on the size of the initial conditions and on the size of proliferative destructive parameters [32].

Developments of the above modelling approach have been proposed by various authors, generally followed by qualitative analysis and simulations. In details:

- De Angelis and Mesin [48] introduced long distance interactions that take into account the ability of cells to communicate, by signals, before their contact. The qualitative analysis of the asymptotic behavior of the solutions has been developed by De Angelis and Jabin [49], while simulations [51] confirm the bifurcation discussed with reference to above reported Figs. 4–7.

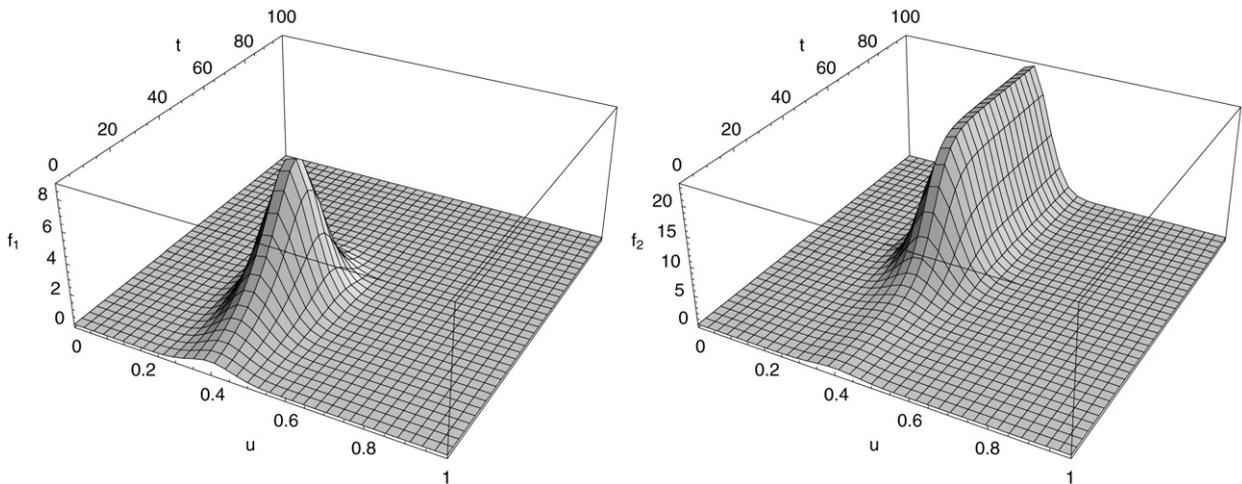


Fig. 7. Initial increase and final depletion of abnormal cells (on the left) and immune proliferation (on the right).

- Derbel [55] introduces the modelling of the sentinel level of immune cells and their trend to such a state when cancer cells have been progressively eliminated. A technically different model was proposed by De Angelis and Lods [47], again postulating the trend to equilibrium.
- Kolev et al. [81–83] consider various aspects of the immune competition corresponding to different activation or inhibition of the immune system also related to the application of specific therapeutical actions.
- Specialization of the different populations of the immune system are considered by Arlotti et al. [11].
- Brazzoli and Chauviere [38] studied different types of models with discrete activity states corresponding to progressive genetic mutations rather than a continuous variation.
- Bellouquid and Delitala [32] introduced interaction potentials for the forces (attractive and/or repulsive) mutually exchanged by cells corresponding to their specific activities. This topic is connected to the modelling of space structures.

The various models that have been reviewed above refer to the mathematical structure (9), (10), corresponding to closed system. The generalizations (12), (13) allow to model therapeutical actions simply by adding new populations corresponding to particles acting on cells. In particular, the time evolution of the actions  $g_i$  can be supposed known within a certain time interval. In general, interactions with cells produce a subsequent degradation.

A modelling approach, followed by a detailed qualitative analysis of the initial value problem, has been developed by De Angelis and Jabin [50], who 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. Coupling different scales is needed in some specific cases, for instance in the modelling of radiotherapy [63].

It is worth mentioning that the above models generated several studies related to the qualitative analysis of the initial value problem for models such as those referring to Eqs. (9), (10), and (12), (13). The specific objective consists in analyzing the role of the parameters of the model, say  $\alpha$  and  $\beta$  and those corresponding to the external action, to predict the evolution of the system and the qualitative behavior of the solutions.

Various issues are offered by the papers [11,31,32,41,47,49,50,55]. Their common characteristics is that theorems provide a detailed analysis of how parameters and the initial conditions influence the asymptotic behaviors, see for instance Figs. 4–7. The qualitative analysis provides results for the time evolution of the densities, while simulations are needed to visualize the evolution of the distribution function and hence of the heterogeneity phenomena. The book [33] provides several simulations of this type focused on different specializations of the general model, which is obtained by considering both conservative and proliferating interactions.

The various mathematical models reviewed in the preceding subsection are characterized by phenomenological parameters that have a well defined physical meaning, that need to be derived by means of suitable experiments. Guidelines to develop experiments are proposed in the paper [20], where it is suggested to explore the late stage of

the evolution to identify the  $\beta$ -type parameters. Subsequently, experiments in the previous stage can be developed to identify the  $\alpha$ -type parameters.

On the other hand, it is well understood that cellular properties depend on the dynamics at the molecular (genetic) scale, as it is documented in various papers in the field of biological sciences, e.g., papers [66,90], and books [64] and [114].

Although the literature in the field is still at an early stage, some interesting results concerning the interpretation of cell dynamics and mutation as an adaptive evolutionary process are available. Relevant contributions have been given by Nowak et al., see [90,92] whose theory has been put into a mathematical framework by Komarova et al. [76–79], who classified the various loss and gain events of gene expression in the adaptive evolution assigning to each of them a suitable probability related to different stages of the evolution. Detailed analysis focused on referring the afore mentioned gain and loss events to shape compatibility have been proposed in [109] and [112], while models need to consider the adaptive and evolutionary aspects of gene expression [1,105].

However, it is recognized that the system evolves in time. Therefore, the modelling by dynamical systems is motivated [104], although determinism cannot be claimed. The modelling approach can take advantage of the reasoning proposed in [25], where it is observed that the cellular dynamics is related to the expression of genes, that is heterogeneously distributed. Therefore a perspective guideline is proposed to applied mathematicians for future research activity, summarizing the reasoning proposed in [21].

Bearing all above in mind, let us consider a system constituted by two interacting populations of active particles, genes and cells respectively, corresponding to two different scales, namely the molecular (genetic) scale and the cellular scale. The overall state of the system, at the higher and lower scales, respectively, is defined by the probability density distributions:

$$f = f(t, u) : [0, T] \times D_u \rightarrow \mathbb{R}_+, \quad i = 1, \dots, n, \tag{17}$$

and

$$\varphi = \varphi(t, v) : [0, T] \times D_v \rightarrow \mathbb{R}_+, \quad i = 1, \dots, n, \tag{18}$$

over the microscopic states  $u \in D_u$  and  $v \in D_v$  of the interacting entities regarded as active particles.

The interaction scheme from the lower to the higher scale can be represented as follows:

$$[\partial_t \varphi = N[\varphi, \varphi]] \rightarrow [\partial_t f = M_g[f, \varphi]], \tag{19}$$

that corresponds to the following dynamics:

- The evolution of the system at the lower scale is determined by the interaction between genes among themselves and with the outer environment that is supposed known.
- The evolution of the system at the higher scale is determined by the interaction between active particles, of the population, among themselves and with particles of the lower system that is obtained by solution of the evolution equation for such a system.

Methods of the mathematical kinetic theory of active particles reviewed in Section 3 can be used to put the above formal scheme into mathematical structure. Technical calculations yield:

$$\begin{cases} \partial_t \varphi(t, v) = K_1[\varphi, \psi](t, v) = J_1[\varphi, \varphi](t, v) + Q_1[\varphi, \psi](t, v), \\ \partial_t f(t, u) = K_2[f, \varphi](t, u) = J_2[f, f](t, u) + Q_2[f, \varphi](t, u), \end{cases} \tag{20}$$

where only one cell population has been considered for simplicity of notations. Generalizations to more than one population is simply matter of technical calculations.

The expressions of  $K_1$  and  $K_2$  are obtained with the same reasonings developed in Eqs. (10) and (13), related to the new interaction terms. Details are not reported here, and we refer the reader to paper [21]. Here we simply recall that  $J_1[\varphi, \varphi]$  takes into account the interaction within active particles at the lower scale and  $Q_1[\varphi, \psi]$  the interactions of the active particles at the lower scale with the outer environment. While  $J_2[f, f]$  takes into account the interaction within active particles at the higher scale and  $Q_2[f, \varphi]$  the coupling, i.e. the interactions of the active particles at the higher scale with the lower scale.

The above structure can be regarded as a candidate to model the dynamical gene expression and their influence over cellular dynamics. The analysis of mathematical properties of the above system and applications are scheduled to be studied in a forthcoming paper.

## 5. From cells to tissues

The mathematical methods and models reviewed in the preceding sections are focused on biological phenomena where space dynamics does not yet play a relevant role. On the other hand, when the number of cancer cells becomes relevant, various space phenomena, including invasion and pattern formation due to aggregation and chemotaxis [43, 44, 57, 61, 62], play a relevant role in the overall dynamics. An interesting problem is the derivation of tissue level equation from the microscopic description delivered by methods of the kinetic theory, that is an alternative to the classical approach of continuum mechanics, namely by using mass and momentum conservation equations properly closed by phenomenological models corresponding to the material behavior of the system. Section 4 of paper [27] reviews various models used in the field under consideration and shows how different models are obtained according to the different way chosen to close the conservation and equilibrium equations. On the other hand, the macroscopic behavior should be properly related to the dynamics at the cellular level. Namely, macroscopic models should be derived from the underlying cellular models by letting intercellular distances tend to those of the tissue level.

The above approach is widely studied in the case of classical particles by asymptotic methods developed in mathematical kinetic theory. In recent years, the analysis of the applicability of asymptotic methods has reached an important development in the so-called parabolic and hyperbolic limits or equivalently low and high field limits. The parabolic (low field) limit of kinetic equations leads to a drift–diffusion type system (or reaction–diffusion system) in which the diffusion processes dominate the behavior of the solutions, see Bonilla and Soler [37]. In principles, the same methodological approach can be developed starting from multicellular models obtained by methods of the kinetic theory for active particles, however various additional difficulties have to be considered. Specifically, microscopic interactions not only modify the microscopic state, but may also generate proliferative and/or destructive phenomena.

The review proposed in the following is in three steps: first the modelling of space structures, subsequently the analysis is focused on the derivation of macroscopic equations, finally a critical analysis is proposed referring to the role of the dynamics at the molecular scale.

A technically simple way to modelling space phenomena has been proposed by Othmer et al. [94, 95], by adding to the space homogeneous description stochastic velocity jump process. The approach refer for the case of a multicellular system modelling cell movement only. Subsequently various authors have developed the modelling method including additional biological phenomena such as proliferative/destructive interactions related to the dynamics at the cellular level, see [14] for a one component system and [15, 16] for binary mixtures.

The model writes for a one population system, in absence of external action, as follows:

$$(\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}}) f(t, \mathbf{x}, \mathbf{v}, u) = (L[f] + C[f] + D[f] + P[f])(t, \mathbf{x}, \mathbf{v}, u), \quad (21)$$

where the term

$$L[f] = \int_{D_{\mathbf{v}}} [T(\mathbf{v}, \mathbf{v}_*) f(t, \mathbf{x}, \mathbf{v}_*, u) - T(\mathbf{v}_*, \mathbf{v}) f(t, \mathbf{x}, \mathbf{v}, u)] d\mathbf{v}_*, \quad (22)$$

models a linear velocity-jump process, where  $\nu$  is the turning rate or turning frequency (hence  $\tau = 1/\nu$  is the mean run time) and  $T(\mathbf{v}, \mathbf{v}_*)$  is the probability kernel for the new velocity  $\mathbf{v} \in D_{\mathbf{v}}$  assuming that the previous velocity was  $\mathbf{v}_*$ . This corresponds to the assumption that cells choose any direction with bounded velocity. Specifically, the set of possible velocities is denoted by  $D_{\mathbf{v}}$ , where  $D_{\mathbf{v}} \subset \mathbb{R}^3$ , and it is assumed that  $D_{\mathbf{v}}$  is bounded and spherically symmetric (i.e.  $\mathbf{v} \in D_{\mathbf{v}} \Rightarrow -\mathbf{v} \in D_{\mathbf{v}}$ ).

The physical-biological meaning of the nonlinear terms  $C[f]$ ,  $D[f]$  and  $D[f]$  was given in Section 3, corresponding, respectively, to conservative and proliferative/destructive interactions, and to genetic mutations, into a population different from that of the interacting cells.

Asymptotic methods technically amount to expanding the distribution function in terms of a small dimensionless parameter related to the intermolecular distances (the space-scale dimensionless parameter) that is equivalent to the connections between the biological constants. The limit that we obtain is singular and the convergence properties

can be proved under suitable technical assumptions. In these papers biological systems are considered for which interactions do not follow classical mechanical rules, and biological activity may play a relevant role in determining the dynamics.

The review proposed in the sequel is focused on the hyperbolic scaling in absence of population transition, that corresponds to the following:

$$t \rightarrow \varepsilon t, \quad \mathbf{x} \rightarrow \varepsilon \mathbf{x} \quad \Rightarrow \quad t v = \frac{1}{\varepsilon}, \tag{23}$$

and to the parameters

$$v = \frac{1}{\varepsilon}, \quad \eta = \varepsilon^{q-1}, \quad \mu = \varepsilon^\delta, \quad q \geq 1, \delta \geq 0. \tag{24}$$

Therefore, the scaled non-dimensional model takes the form:

$$(\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}}) f_\varepsilon = \frac{1}{\varepsilon} (L(f_\varepsilon) + \varepsilon^q C(f_\varepsilon, f_\varepsilon) + \varepsilon^{q+\delta} D(f_\varepsilon, f_\varepsilon)). \tag{25}$$

The derivation of macroscopic models needs the following technical assumptions:

**Assumption 5.1 (Solvability conditions).** The turning operator  $L$  satisfies the following solvability conditions:

$$\int_{D_{\mathbf{v}}} L(f)(\mathbf{v}) d\mathbf{v} = 0, \quad \int_{D_{\mathbf{v}}} \mathbf{v} L(f)(\mathbf{v}) d\mathbf{v} = \mathbf{0}, \tag{26}$$

where  $L(f)$  is the linear operator, corresponding to the preceding equation acting on  $f$  (the arguments  $t$  and  $\mathbf{x}$  have been dropped to simplify notations).

**Assumption 5.2 (Kernel of  $L$ ).** There exists a unique function  $M_{\rho,U} \in L^1(D_{\mathbf{v}}, (1 + |\mathbf{v}|) d\mathbf{v})$ , for all  $\rho \in [0, +\infty)$  and  $U \in \mathbb{R}^n$ , such that

$$L(M_{\rho,U}) = 0, \quad \int_{D_{\mathbf{v}}} M_{\rho,U}(\mathbf{v}) d\mathbf{v} = \rho, \quad \int_{D_{\mathbf{v}}} \mathbf{v} M_{\rho,U}(\mathbf{v}) d\mathbf{v} = \rho U, \tag{27}$$

where  $\rho$  is the density and  $U$  is the mass velocity.

Let us now consider the equilibrium distribution given in the form  $f_0 = M_{\rho,U}$  and look for the solution  $f_\varepsilon$  as a perturbation of this equilibrium in the following way:

$$f_\varepsilon(t, x, v, u) = M_{\rho,U} + \varepsilon g(t, \mathbf{x}, \mathbf{v}, u). \tag{28}$$

The result of the paper [17] shows that hyperbolic equations with different source term are obtained as follows:

- **Negligible biological (both conservative and proliferative/destructive) activity**  $\delta \geq 0$ , and  $q > 1$ : First order moments with respect to  $\varepsilon$  generate the hyperbolic system without source term:

$$\begin{cases} \partial_t \rho + \nabla_{\mathbf{x}}(\rho U) = 0, \\ \partial_t(\rho U) + \nabla_{\mathbf{x}}(\rho U \otimes U + p) = 0. \end{cases} \tag{29}$$

This corresponds to biological tissues characterized by negligible biological (both conservative and proliferative/destructive) activities concerning mutations and onset of cancer phenomena.

- **Variation biological activity, but negligible proliferative/destructive activities**  $\delta > 0$ , and  $q = 1$ : In this case, in first order with respect to  $\varepsilon$ , the following hyperbolic system with a source term related to conservative interactions is obtained:

$$\begin{cases} \partial_t \rho + \nabla_{\mathbf{x}}(\rho U) = \int_{D_{\mathbf{v}}} G(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}, \\ \partial_t(\rho U) + \nabla_{\mathbf{x}}(\rho U \otimes U + p) = \int_{D_{\mathbf{v}}} \mathbf{v} G(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}. \end{cases} \tag{30}$$

This corresponds to biological tissues corresponding to the early stage of cancer onset when cells have initiated mutations, but only conservative biological activities are relevant.

- **Both conservative and proliferative/destructive play a role**  $\delta = 0$ , and  $q = 1$ . In this case, in first order with respect to  $\varepsilon$ , the following hyperbolic system with a source term related to both conservative and proliferative interactions is obtained:

$$\left\{ \begin{aligned} \partial_t \rho + \nabla_{\mathbf{x}}(\rho U) &= \int_{D_{\mathbf{v}}} G(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}, u) d\mathbf{v} + \int_{D_{\mathbf{v}}} I(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}, u) d\mathbf{v}, \\ \partial_t(\rho U) + \nabla_{\mathbf{x}}(\rho U \otimes U + p) &= \int_{D_{\mathbf{v}}} \mathbf{v} G(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}) d\mathbf{v} \\ &+ \int_{D_{\mathbf{v}}} \mathbf{v} I(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}. \end{aligned} \right. \tag{31}$$

This corresponds to biological tissues corresponding to advanced stage of cancer phenomena, when cells have initiated clonal proliferation.

- **Negligible biological mutations and relevant proliferative/destructive activities** The asymptotic analysis can also be developed in the case of the late stage of tumor growth when conservative interactions are not any longer significant. In this case, in first order with respect to  $\varepsilon$ , the following hyperbolic system with a source term related to conservative interactions is obtained:

$$\left\{ \begin{aligned} \partial_t \rho + \nabla_{\mathbf{x}}(\rho U) &= \int_{D_{\mathbf{v}}} I(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}, u) d\mathbf{v}, \\ \partial_t(\rho U) + \nabla_{\mathbf{x}}(\rho U \otimes U + p) &= \int_{D_{\mathbf{v}}} \mathbf{v} I(M_{\rho,U}, M_{\rho,U})(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}. \end{aligned} \right. \tag{32}$$

This corresponds to biological tissues where cells have stabilized their biological functions, while proliferative and destructive events play a dominant role.

A different scaling leads to **diffusive models**. In this case the scaling is as follows:

$$\eta = \varepsilon^q, \quad \mu = \varepsilon^\delta, \quad q, \delta \geq 0, \quad \text{and} \quad \nu = \frac{1}{\varepsilon^p}, \quad p > 0, \tag{33}$$

where the slow time scale  $\tau = \varepsilon t$  is used so that the following scaled equation is obtained:

$$\varepsilon \partial_t f_\varepsilon + \mathbf{v} \cdot \nabla_{\mathbf{x}} f_\varepsilon = \frac{1}{\varepsilon^p} L f_\varepsilon + \varepsilon^q g(f_\varepsilon, f_\varepsilon) + \varepsilon^{q+\delta} I(f_\varepsilon, f_\varepsilon). \tag{34}$$

The analysis is technically different as documented in [14] and [15], while, besides the parabolic structure, the macroscopic equations have some analogy concerning the onset of source terms corresponding to the predominance of one of the three aspects of the biological dynamics, i.e. encounter rate between cells, mutations and proliferative/destructive events, with respect to the other two.

Finally, let us remark that an interesting topic, not yet considered in the literature, is that the biological system under consideration modifies its structure in time due to genetic mutations. Therefore, the mathematical structure of tissue models may change and should, at least in principle, be coupled with an evolution equation for genetic mutations. This key feature technically refers also if the approach to model space phenomena is technically different, for instance by stochastic differential equations, e.g., [6] and [46], or by means of models with non-local interactions [84]. An essential reference is given by [45] focused on cell movement and specifically traffic-like phenomena in complex biology systems, where the specific and heterogeneous behavior of cells plays an essential role in the overall dynamics.

### 6. Research perspectives

The review presented in the preceding sections has been focused on modelling aspects of the early stage of cancer onset and competition with the immune system. As we have seen, all scales, molecular, cellular and tissue, characterize

the biological system under consideration. The survey has been preliminarily referred to the cellular scale, while modelling aspects of the interaction with the lower and higher scale have been treated. The following key issues have been specifically considered:

- (i) The notion of function or purpose differentiates living systems in biology from those of inert matter. Biological functions have the ability to modify the conservation laws of classical mechanics and, in addition, can generate destructive and/or proliferative processes;
- (ii) Modular approaches can be applied to decompose complex biological systems into several modules, called functional subsystems, that may, at least in some cases, be constituted by several elements which cooperatively express the above-mentioned biological functions;
- (iii) Mathematical models may be derived at different scale in each subsystem. Therefore, connection among subsystems needs developing methods to match variables at different scales;
- (iv) Systems in biology cannot be simply observed and interpreted at a macroscopic level. A system constituted by millions of cells shows at the macroscopic level only the output of cooperative and organized behaviors which may not, or are not, singularly observed. Moreover, when macroscopic phenomena become significant, the role of the dynamics at the lower scale is still affecting the dynamics at the higher scale. That is the multiscale essence of the system under consideration.

The paper by Hanahan and Weinberg [70], referring to the context of item (i), reports how the relevant biological functions are related to genetic mutations, where undesired corruptions are often transferred into the expression of function. Section 4 critically analyzed various mathematical approaches to model the dynamics at the molecular scale with the attempt to understand how it affects dynamics and evolution at the higher scales.

As we have seen, biological events at the higher scale of cells and tissues depend on the dynamics at the molecular scale. Transferring the information from genes to cells is key to complete the mathematical approach. The mathematical structures reported in Section 3 can generate specific models if the following parameters that, in general, depend on the microscopic states, are properly identified: the encounter rate  $\eta_{hk}$ , the transition probability density  $B_{hk}$ , the population transition terms  $\mu_{hk}^i$ , the proliferative/destructive terms  $\mu_{hk}$ . The approach proposed in Section 4 can be possibly developed to achieve this challenging target.

The above analysis can contribute to a deeper understanding of the behavior of tissues where the model may involve interactions at different scales [39,65,96,110,115], as well as a mathematical structure that evolves in time according to the derivation of tissue level equations reported in Section 5.

In general, various requirements can be addressed to mathematical models of complex biological systems. For instance, one may ask to a model to reproduce experiments that have given a well defined result, possibly well interpreted by biology. The advantage is that the model can reproduce similar experiments and reduce the time and costs of experiments. On the other hand, a more ambitious aim can be linked to models, namely the ability to show the emergence of biological events that are not precisely shown by experiments. When, this nice result is reached, the interaction between mathematical and biological sciences is really successful.

Finally, looking at research perspectives, the multiscale analysis from the onset of the first mutations to the generation of cancer tissues appear to be, at least according to the bias of the authors of this present paper, the most challenging research objective. Hopefully, some ideas reported in the previous sections can be addressed to the aforementioned objective.

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