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MATHEMATICAL TOPICS ON THE MODELLING COMPLEX MULTICELLULAR SYSTEMS AND TUMOR IMMUNE CELLS COMPETITION

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This paper deals with a critical analysis and some developments related to the mathematical literature on multiscale modelling of multicellular systems involving tumor immune cells competition at the cellular level. The analysis is focused on the development of mathematical methods of the classical kinetic theory to model the above physical system and to recover macroscopic equation from the microscopic description. Various hints are given toward research perspectives, with special attention on the modelling of the interplay of microscopic (at the cellular level) biological and mechanical variables on the overall evolution of the system. Indeed the final aim of this paper consists of organizing the various contributions available in the literature into a mathematical framework suitable to generate a mathematical theory for complex biological systems.

Keywords: Cell populations; biological complexity; immune competition; kinetic theory; nonlinear systems.

1. Introduction

The scientific community is aware that the great revolution of this century is going to be the mathematical formalization of phenomena belonging to the living matter, while the revolution of the past two centuries was the same approach applied to inert matter. Hints to develop a mathematical theory of biological systems can be recovered in various papers authored by scientists operating in the field of molecular and cellular biology. Some sentences are quoted from a paper by Hartwell *et al.*[50] that analyzes in-depth the conceptual differences between the difficulties to deal with inert and living matter:

Although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiate biology from other natural sciences.

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.

More important, what really distinguish biology from physics are survival and reproduction, and the concomitant notion of function.

A further hint which is recovered in Ref. 50, specifically also in the above sentences, is that a system 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 the cooperative and organized behaviors which may not, or are not, singularly observed.

A backward excursus to the approach of nonequilibrium statistical mechanics and kinetic theory to multiparticle systems is immediate. Indeed the mathematical kinetic theory developed by Ludwig Boltzmann,[30,73] is based on the essential idea that although particles cannot be individually observed, an analysis of their statistical behavior may lead to the description of macroscopic variables also in conditions far from equilibrium.

Is it possible to deal with multicellular systems by suitable development of the methods of nonequilibrium statistical mechanics? Applied mathematicians are already engaged by the above fascinating idea and are already tackling the main difficulty of this approach: the description in mathematical terms of the organized behavior of the several cells of a biological system.

While it is interesting to acknowledge that Ref. 50 already contains some speculations and motivations toward the development of the approach of the mathematical kinetic theory to the analysis of biological systems, it may be too ambitious to deal with this topic in full generality. Possibly the approach may be related to some specific phenomena.

An interesting and challenging field of investigation looks at the onset and development of cancer cells in the environment of vertebrates as well as at several related phenomena such as the competition with the immune system, aggregation of cells in solid forms, interactions with the outer environment with generation of angiogenesis phenomena, and so on.

Referring to the above topic, one may find again various hints in the scientific literature. For instance some sentences can be quoted by the paper by Gatenby and Maini.[46] The first one refers to the so-called Vogelgram theory:

These models might, for example, adapt methods of game theory and population biology to frame the Vogelgram mathematically as a sequence of competing populations that are subject to random mutations while seeking optimal proliferative strategies

in a changing adaptative landscape. The phenotypic expression of each mutation interacts with specific environmental selection factors that confer a proliferative advantage or disadvantage. Such models generate far less predictable (*and more biologically realistic*) *system behavior, including multiple possible genetic pathways and timeliness in the somatic evolution of invasive cancer.*

Going into the contents of this interesting paper, one may recover again various motivations and suggestions to develop an immuno-mathematical theory for multicellular systems.

Existing mathematical models may not be entirely correct. But they represent the necessary next step beyond simple verbal reasoning and linear intuition. As in physics, understanding the complex, nonlinear systems in cancer biology will require ongoing interdisciplinary, interactive research in which mathematical models, informed by existent data and continuously revised by new information, guide experimental design and interpretation.

It is plain that cells do not follow the rules of Newtonian mechanics. Indeed, cells organize their dynamics and play a collective game which may end up either with the blow up of cells or with their destruction due to the action of the immune defense.

The paper by Greller, Tobin and Poste,[49] although relatively more technical with respect to Ref. 46 and referring to some specific phenomena, also provides some significant hints addressed to the description of multicellular systems by equations of statistical mechanics.

Tumor cellular populations are characterized by progression distributions, progression velocities and progression dependent growth rates. Major genetic changes after the tumor dynamics as each subpopulation moves further away from genetic normality.

Indeed, the analysis developed in the sections which follow uses the above concepts to characterize the microscopic state of tumor cells. As we shall see, the analysis need a deep insight into cellular interactions, as mentioned again in Ref. 49:

The modelling paradigm provides conceptual foundation not only for modelling progression and heterogeneity phenomena, but acts as a language for describing their complex phenomena.

It is interesting to report the viewpoint on modelling from scientists, again Ref. 49, operating in the field of immunology:

To the degree that a model is an adequate representation of biological reality, it can be used to perform "experiments" that are impossible or impractical in the laboratory. The danger of discovering phenomena that are artifacts of the model must always be scrutinized, but the properties of a model may also foretell genuine biological situations that are yet to be observed.

It is a substantial progress with respect to the pessimistic attitude toward the interaction of mathematics with biological sciences which is encountered in Wigner's[81] paper.

Motivations are undoubtedly strong. Indeed, cancer is still one of the greatest killers in the world, and while all scientists are aware that mathematics cannot solve problems of immunology and medicine, it seems that a useful support to experiments and quantitative analysis of external actions to control the neoplastic growth can be developed by applied mathematics. Specifically, models and simulations of particular behaviors of the immune competition can reduce the amount of experiments which are necessary for therapy developments. As a final target, an immuno-mathematical theory can be developed in order to provide a detailed description of the evolution of the system, hopefully focusing phenomena which may be difficult to observe experimentally. As we shall see, pursuing this objective may generate new mathematical theories and, consequently, highly challenging problems which may engage relevant intellectual energy of applied mathematicians.

This paper deals with the development of a mathematical theory based on a suitable generalization of the equations and methods of the kinetic theory of gases applied to the modelling of the dynamics of large systems of interacting populations in a vertebrate. These models describe the evolution of the statistical distribution, for each cell population, of the microscopic state of the cells.

Applied mathematicians have already been involved in the development of the above mathematical theory as it is documented in the pioneering paper by Bellomo and Forni,[12] further developed by various authors, e.g. Refs. 13, 14, 43, 5, 36, 37, 7, 76, 57 and 58, as it also documented in the review paper.[17] Developments of methods of mathematical kinetic theory to model large complex systems in applied sciences, including biological sciences, is documented in the collection of surveys[15,16] as well as in the book.[27]

Let us indicate the essential features of the mathematical approach:

- The system is constituted by a large number of cells belonging to more than one-cell population.
- The microscopic state of cells is identified by both biological and mechanical variables. Interactions modify the above microscopic state.
- Both variables play a role in microscopic interaction. In other words, the biological state affects the mechanical dynamics and vice versa.
- The overall state of the system is described by a probability distribution function over the microscopic state, while the evolution of the system is described by a suitable evolution equation for the afore-mentioned distribution.

Although the above outlined approach has already given various interesting results and models, critically analyzed in Refs. 14 and 17, it is not possible to define them as a theory; in fact, several purely phenomenological assumptions are still necessary to deduce mathematical models. On the other hand, it seems worth providing

a unified presentation of the various results developed after Ref. 12. The present paper, together with a critical analysis of some open problems, may hopefully generate a mathematical theory of the complex biological system we are dealing with.

The content of this paper, which follows this introduction, is developed through seven sections:

Section 2 provides a phenomenological description of the physical systems which is mathematically dealt with in the paper. The description is proposed having in mind a multiscale mathematical description of a system constituted by a large number of interacting cells with special attention to the onset and growth of tumor cells possibly contrasted by immune cells and therapeutical actions. This section also indicates, starting from the phenomenological description, the logic lines to be followed toward the design of specific models and the above-mentioned immuno-mathematical theory.

Section 3 deals with the mathematical representation of the above system. This means dealing with the selection of the variables which, in the mathematical model, have to represent the overall state of the complex system under consideration. It is a delicate problem considering that one has to reduce a large number of variables into a limited number of them with the target of providing an effective representation without generating computational problems which may not be practically handled. The representation is addressed to all scales characterizing the system, while the mesoscopic description, based on the methods of the kinetic theory, is selected as the reference scale.

Section 4 deals with the modelling of microscopic interactions between cells of the various interacting populations. The main difficulty is related to the fact that the microscopic state of cells includes both mechanical and biological variables in a way that the dynamics of cells may be ruled by their biological state, while mechanical interactions modify the biological state.

Sections 5 and 6 deal with the modelling, qualitative analysis and simulations related to the mathematical description of the competition between tumor, and immune cells when biological interactions are predominant over the space dynamics. In more details Sec. 5 deals with models based on short range interactions, and Sec. 6 with models based on long range interactions. The contents of Sec. 5 are presented with a great deal of details, while those of Sec. 6 simply consists in a survey, with a critical analysis, of the existing literature. The reader interested in additional information on models with long range interactions is referred to Ref. 25, where the topic of Sec. 6 is exhaustively reviewed.

Section 7 shows how the class of models proposed in Secs. 5 and 6 can be generalized to the case of phenomena where the space dynamics plays a relevant role. This mathematical representation is then used to develop an asymptotic theory to derive macroscopic equations toward the representation of the system in its condensed phase which is reached when tumor cells aggregate into a solid form. This section also develops a critical analysis of the approaches existing in the literature indicating

how the phenomenological derivation, based on reaction diffusion equations, may be properly replaced by asymptotic methods suitable to provide macroscopic evolution equations based on the microscopic description.

Section 8 is devoted to research perspectives to be developed having in the background the contents of the above sections. Perspectives will not be simply outlined. Indeed, technical details will be given in order to define the methodological approach to their development. Special attention will be given to the development of a new statistical mechanics theory for large systems with internal structure, and to the multiscale representation of the complex system we are dealing with.

Referring to the contents of this paper, it is necessary to stress that although it essentially deals with mesoscopic modelling, multiscale methods have to be developed as the overall observation and description of the system needs both microscopic and macroscopic scales.

Referring to general bibliography, the interested reader is addressed to the books edited by Adam and Bellomo,[2] and by Preziosi,[75] which report about the various mathematical approaches developed in recent years. The reader can immediately identify that the passage from the contents of Ref. 2 to the one of Ref. 75 clearly shows the fast evolution of mathematical methods applied to cancer modelling related to the immune competition and therapeutical actions. Specifically, biological aspects of the immune competition are reviewed in the paper by Delves and Roitt,[42] while mathematical aspects are reviewed in Refs. 19 and 72. Additional references are reported in the sections which follow.

2. Phenomenological Description and Scaling

We want to stress that the mathematical description has to be based on multiscale methods. Therefore, it is worth describing precisely the scales which are consistent both with the phenomenological observation and with the mathematical representation. Moreover, a brief description of some relevant phenomena at each scale can be given. Providing a detailed description of the whole variety of phenomena related to the physical system dealt under consideration is certainly beyond our aims. The last part of this section will be devoted to describing the conceptual line to be followed toward the derivation of the bio-immuno-mathematical theory which is the final target of the research project. Indeed, this paper aims at showing how some objectives have been, at least partially, reached.

The evolution of a cell, as described by various authors, e.g. Forni *et al.*,[45] is regulated by the genes contained in its nucleus. These genes can either be activated or suppressed, when signals stimulate receptors on the cell surface and are transmitted to the nucleus of the cell. The reception of a particular signal can modify the usual behavior of a cell. In extreme situations, a particular signal can induce a cell to reproduce itself in the form of identical descendants giving rise to the so-called clone expansion or mitosis, or to die giving rise to the so-called apoptosis or programmed death.

Some theories state that genetic changes, distortion in the cell cycle and loss of apoptosis are related to DNA corruption, which may even be determined by external actions. Thus an interaction and competition at the cellular level is developed, including activation but also inhibition of the immune system. Later, if the number of degenerated cells increases significantly, various phenomena such as condensation of tumor cells into solid forms, macroscopic diffusion and formation of capillary sprouts from blood vessels to the tumor mass, can be observed, followed by detachment of metastases and invasion.

When cells loose their differentiation, a competition with the immune system begins. The immune competition is a complex phenomenon which involves cells or particles of the aggressive hosts and cells of the various populations of the immune system. In order to avoid ambiguities related to a frequent use of the word *complexity*, it is worth mentioning that here this term is applied to state that interactions are developed at different scales: the cellular dynamics is ruled by subcellular interactions. Moreover, different mechanisms operate on the same subject: mechanical for the dynamics and biological for the immune competition. The proliferation ability of the host and the defense ability of the immune system are common features of the competition. In addition, the ability to inhibit the recognition process by the immune cells plays a significant role in the competition against tumor cells, which is contrasted by immune cells operating with different specialized activities.

Referring to the cellular scale, cellular models are proposed to simulate the effects of the failure of programmed cell death, and of the loss of cell differentiation. Whether a tumor cell is recognized by immune cells, a competition starts and may end up either with the destruction of tumor cells or with the inhibition and depression of the immune system. Cellular interactions are regulated by signals emitted and received by cells through a complex biological dialogue. Therefore, the connection with the sub-cellular scale (already described above) is evident.

On the other hand, the development of tumor cells, if not suppressed by the immune system, tends towards condensation into a solid form so that macroscopic features become important. In particular, from the cellular scale one has to recover macroscopic properties which are observable when cells aggregate into solid forms.

At the *macroscopic scale* tumor cells, after a suitable maturation time, may start to condense and aggregate into an entity with eventually "quasi-fractal surface" interacting with the outer environment (for example normal host cells and the immune system). These interactions usually occur on the surface and within a layer where angiogenesis (the process of formation of new blood vessels, induced by factors secreted by the tumor and vital for tumor growth) takes place. Here, one has the overlap of phenomena at the cellular level with typical macroscopic behavior such as diffusion or, more generally, phenomena that can be related to the conservation and evolution of macroscopic variables such as the tumor size.

The description at the cellular scale can be obtained by studying the evolution of the probability distribution over the microscopic state of cells rather than identifying the dynamics of all cells. The above *mesoscopic modelling* can be developed

by methods of the mathematical kinetic theory. This type of modelling reduces the complexity induced by the need of dealing with a large number of cells, but it does not solve yet the problem of modelling the coupled dynamics of mechanical and biological variables.

Nevertheless, suppose that a mesoscopic model is obtained: then the development of a suitable asymptotic theory, analogous to the classical one known for multiparticle systems, see Chap. 3 of Ref. 9, can be applied to derive evolution equations for macroscopic quantities. The pioneering paper[18] gives some useful results on the analysis of the above mathematical problem.

The solution of mathematical problems for macroscopic equations, generally initial-boundary value problems, yields the evolution of macroscopic quantities to be related to those obtained from the mesoscopic description.

The conceptual lines to be followed toward the development of a mathematical theory for biological systems is reported in Figs. 1 and 2. Specifically, Fig. 1 refers to the path from the phenomenological observation of the system to the modelling by kinetic equations; while Fig. 2 refers to the line to be followed to recover, through an asymptotic theory from mesoscopic (kinetic) models, the macroscopic equations and to develop the analysis of related mathematical problems.

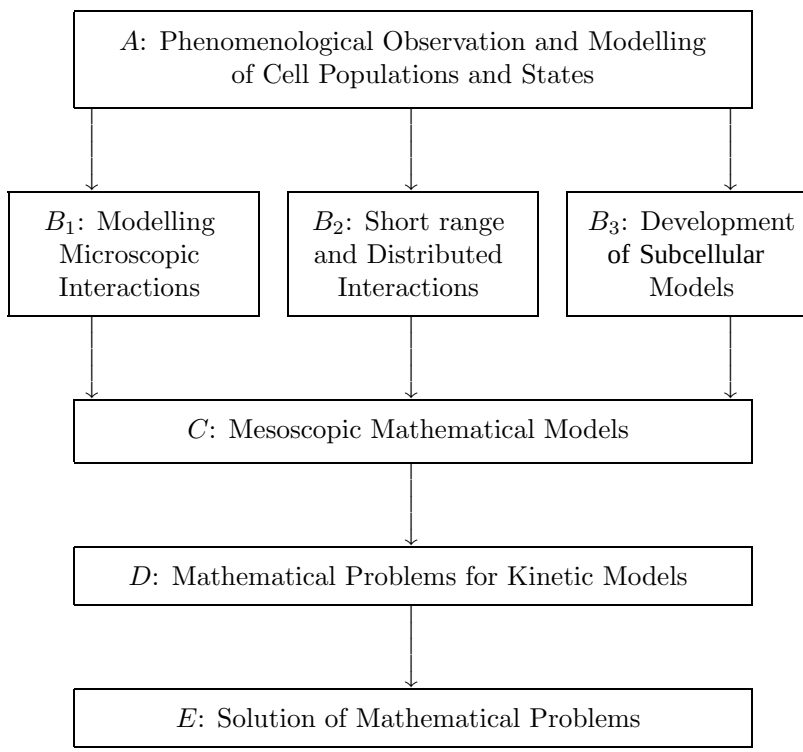

Fig. 1. Flow chart from phenomenologly to kinetic modelling.

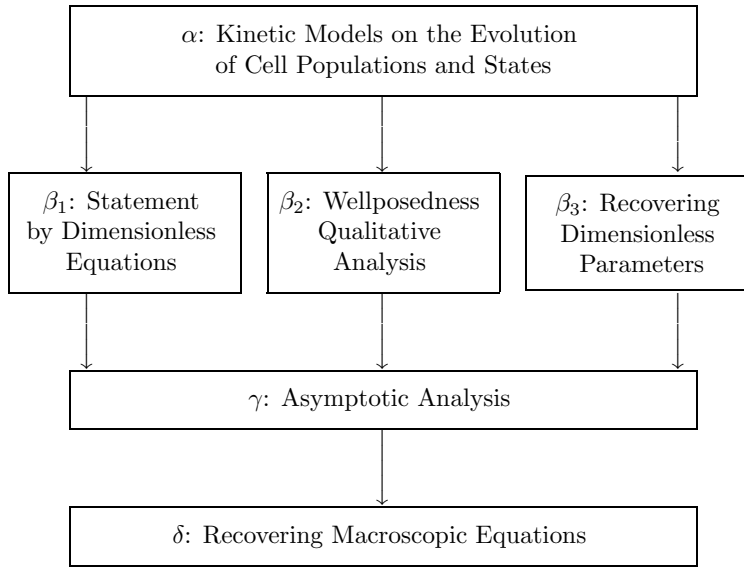

Fig. 2. Flow chart from kinetic to macroscopic models.

The various sections which follow deal with the contents of each box, respectively A–F, and $\alpha - \delta$, as well as with the mathematical analysis of the various links connecting each box to the others.

Before approaching the various specific problems reported in this figure, it is useful stressing the following conceptual aspects related to macroscopic modelling. In particular, macroscopic models can also be obtained by a purely phenomenological approach based on suitable mass and momentum conservation equations properly closed by models of the material behavior. The closure deals with a matter constituted by a mixture of different biological materials. Although rather sophisticated models are available in the literature, e.g. Ref. 35, which also describe the growth property of the matter, often the derivation needs heuristic assumptions which are difficult to be fully justified in rigorous terms.

This means that the development of an asymptotic theory suitable to describe the passage from the microscopic to the macroscopic description may possibly design a new modelling scenario. Indeed, the analysis proposed in Ref. 18 has already shown that different models can be obtained from different scaling related to mechanical and biological interactions. Dealing with the above topics is one of the aims of this paper.

3. On the Concept of Generalized Distribution Function

The first step in the modelling large complex systems consists in selecting a variable suitable to describe their physical state. Then suitable differential equations can be derived to describe the evolution of the above variable.[8] This paper deals with

the modelling and analysis of a system constituted by n interacting cell populations labelled by the indexes $i = 1, \ldots, n$. Each population is characterized by a different way of organizing their peculiar activities as well as the interactions with the other populations.

The physical variable used to describe the state of each cell is called *microscopic state*, and is denoted by the variable $\mathbf{w}$:

$$\mathbf{w} = \{\mathbf{q}, \mathbf{u}\} \in D_{\mathbf{w}} = D_{\mathbf{q}} \times D_{\mathbf{u}}\,, \tag{3.1}$$

where $\mathbf{q} \in D_{\mathbf{q}}$ is the *mechanical microscopic state* and $\mathbf{u} \in D_{\mathbf{u}}$ is the *biological microscopic state*.

The mechanical microscopic state $\mathbf{q}$ includes, at least, position $\mathbf{x}$ and velocity $\mathbf{v}$, $\mathbf{q} = \{\mathbf{x}, \mathbf{v}\}$; however it may also include angular and rotational variables. The biological microscopic state $\mathbf{u}$ refers to the specific activity of the cell population.

In principle the evolution can be described by a system of ordinary differential equations of the type

$$\frac{d\mathbf{w}_h}{dt} = f_h(\mathbf{w}_1, \ldots, \mathbf{w}_H)\,, \tag{3.2}$$

for a system of H cells, where f_h depends on the state of all cells, and $h = 1, \ldots, H$.

In some cases the action between pair of cells is not affected by the presence of other cells. In this case the evolution equation writes:

$$\frac{d\mathbf{w}_h}{dt} = \sum_{k=1}^{H} \varphi_{hk}(\mathbf{w}_h, \mathbf{w}_k)\,, \tag{3.3}$$

for $h, k = 1, \ldots, H$, and where φ_{hk} is the action applied to the hth cell by the kth cell. However, in both cases, the complexity of the mathematical model does not allow to overcome the computational complexity related to Systems (3.2) or (3.3).

Therefore it is reasonable considering a statistical collective description of the system by methods of the mathematical kinetic theory, namely by suitable statistical distributions rather than following the evolution of each single cell, that in the whole ensemble cannot anyway be identified.

Let us consider, for each population, the number distribution function

$$N_i = N_i(t, \mathbf{w}) = N_i(t, \mathbf{q}, \mathbf{u}) : [0, T] \times D_{\mathbf{q}} \times D_{\mathbf{u}} \to \mathbb{R}_+\,, \tag{3.4}$$

for $i = 1, \ldots, n$, and such that $dn_i = N_i(t, \mathbf{w})\, d\mathbf{w}$ denotes the number of cells whose state, at time t, is in the interval $[\mathbf{w}, \mathbf{w} + d\mathbf{w}]$. It follows that the number of cells of the ith population is given by

$$\nu_i(t) = \int_{D_{\mathbf{w}}} N_i(t, \mathbf{q}, \mathbf{u})\, d\mathbf{q}\, d\mathbf{u}\,, \tag{3.5}$$

which may depend on time due to proliferation and/or destruction phenomena, as well as to the flux of cells through the walls of the volume. The initial number is denoted by ν_{i0}, and ν_0 denotes the number of all cells at $t = 0$:

$$\nu_0 = \sum_{i=1}^{n} \nu_{i0}\,. \tag{3.6}$$

Supposing that the microscopic state $\mathbf{q}$ is simply defined by position $\mathbf{x}$ and velocity $\mathbf{v}$, then the description of the state of the system can be given by the normalized density distribution function

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) = \frac{1}{\nu_0} N_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \,, \tag{3.7}$$

where ν_0 is a positive constant.

If f_i, called *generalized distribution function*, is known, then macroscopic variables can be computed, under suitable integrability properties, by weighted moments of the above distribution function. Calculations, technically developed in what follows, refer to systems such that the mechanical variable simply include position and velocity. However, their generalization is simply a matter of additional notations and technical calculations.

Marginal densities over the mechanical state or biological state are given, under suitable integrability conditions, as follows: *generalized distribution over the mechanical state*

$$f_i^m(t, \mathbf{x}, \mathbf{v}) = \int_{D_\mathbf{u}} f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \, d\mathbf{u} \,, \tag{3.8}$$

or the *generalized distribution* over the biological state:

$$f_i^b(t, \mathbf{u}) = \int_{D_\mathbf{x} \times D_\mathbf{v}} f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \, d\mathbf{x} \, d\mathbf{v} \,. \tag{3.9}$$

In the first case the marginal density corresponds to a homogeneous distribution of the biological state, while in the second case it deals with a space homogeneous distribution of cells.

Actually, we are interested in physical phenomena such that the distribution over the biological state plays a significant role. Thus, with respect to the aims of this paper, the marginal density (3.9) is of a relatively greater interest.

First-order moments provide *first-order mechanical macroscopic* quantities. Referring again to the above interest on biological aspects, the following moments can be defined:

$$\mathbf{F}^m[f_i](t, \mathbf{x}, \mathbf{v}) = \int_{D_\mathbf{u}} \mathbf{u} f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \, d\mathbf{u} \,, \tag{3.10}$$

which assume a different meaning corresponding to the different cell populations. Specifically, referring to a system of tumor, immune and environmental cells, the above moment assumes, referring to the distribution function f^b, respectively the meaning of *progression*, *activation*, and *feeding ability*:

$$\mathbf{F}^b[f_i](t) = \int_{D_\mathbf{u}} \mathbf{u} f_i^b(t, \mathbf{u}) \, d\mathbf{u} \,. \tag{3.11}$$

The above reasoning can be developed for higher order moments. Detailed calculations are developed in the sections which follow with reference to specific models and problems.

The above generalized distribution function is based on the assumption that the biological state $\mathbf{u}$ is a continuous variable over $D_{\mathbf{u}}$. On the other hand, the assessment of some biological systems may require a discrete valued variable to describe microscopic biological functions. Indeed, some models have been proposed according to discrete values assumption, see Refs. 63, 7 and 10. Starting from the above motivations a mathematical framework for discrete models was proposed in Ref. 26, where both biological and velocity variables where properly discretized into suitable sets. Discrete models have been developed, not only to reduce the computational complexity but also according to those biological theories which suggest that the microscopic biological state is discrete rather than continuous.

4. Modelling Microscopic Interactions

This section deals with the design of the mathematical modelling of the interactions between the various cells which play the game. Specific models can be developed within the above framework on the basis of phenomenological and theoretical interpretations. Only pair interactions are dealt with: namely it is assumed that interactions between pair of cells is not modified by the presence of a third cell. In other words, the modelling is consistent with the approximation of Eq. (3.3). Referring to the flow chart of Fig. 1, this section deals with boxes B_1, B_2 and B_3.

Consider binary interactions between two cells which may belong to the same or different populations. In order to fix a proper terminology similar to the one of the mathematical kinetic theory, consider binary interactions between the *test* and the *field* cells, where the distribution function corresponds to test cells.

The modelling of microscopic interactions can be developed according to two types of interaction schemes:

- *Short range pair interactions*, which occur when two cells are sufficiently closed to each other. Their distance is lower than a certain critical value and the surrounding cells do not influence the above interaction. Only pair interactions, instantaneous in time, are significant. Moreover, if external actions are not applied to each cell, the state of the interacting pair is not modified between two successive interactions.
- *Mean field pair interactions*, which occur between all pairs of cells which are in a certain action domain. A cell in a certain position $\mathbf{x}$ feels the action of all cells localized into a certain volume Ω around $\mathbf{x}$, the so-called *action domain.*

The phenomenology of the encounters is visualized in Fig. 3 which shows a picture of the conceivable encounters according to the above scheme. Moreover, for both the above schemes one may distinguish the following two types of interactions:

- *conservative interactions*, either short range or mean field, such that mass is preserved, while the microscopic state is modified;

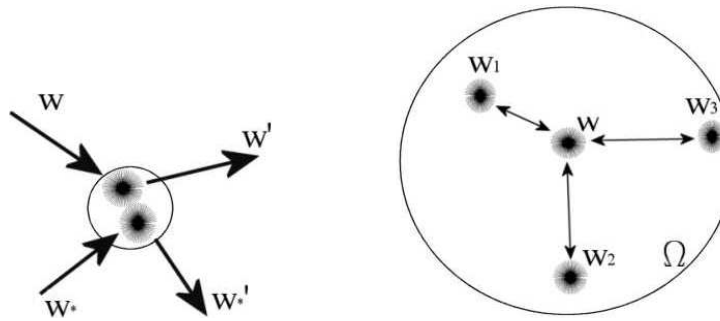

Fig. 3. Short range and mean field interactions.

- *proliferating and destructive interactions*, either short range or mean field, which generate death or birth of cells in the state of the test cell.

Although the modelling of cellular flow,[55] regarded as a multicellular system, has a relevant role in the understanding of the biological system under consideration, for instance in the description of the formation of capillary sprouts,[61,71] or of the mechanics of growing material,[6,54] only a preliminary approach is available in the literature within the framework of the mathematical kinetic theory. Therefore, the contents proposed in what follows will first deal with interactions such that the evolution of mechanical variables is not relevant. This means that cells are homogeneously distributed in space with constant distribution over the velocity variable, and that interactions modify only the distribution over the biological variable. The modelling of interactions depends also on the space and velocity variables are dealt with after the above-mentioned preliminary analysis.

The space variable is omitted in the notations which follow assuming that the various terms analyzed in what follows have been obtained after averaging over the space variable. A detailed analysis of the technical calculations to recover the specific case of models with predominant biological interactions from the general one is proposed in Ref. 20.

Bearing all above in mind, it can be shown how pair interactions can be modelled by different types of microscopic models:

- Consider *short range interactions* between the *test* cell with state $\mathbf{u}_1$ belonging to the ith population, and the *field* cell with state $\mathbf{u}_2$ belonging to the jth population. Interactions occur with an *encounter rate*

$$\eta_{ij}(\mathbf{u}_1, \mathbf{u}_2) : D^2_{\mathbf{u}} \to \mathbb{R}_+ \,, \tag{4.1}$$

  depending both on the states and on the type of populations of the interacting pairs.

Conservative interactions modify the microscopic state $\mathbf{u}$ according to the *transition probability density*

$$\varphi_{ij}(\mathbf{u}_1, \mathbf{u}_2; \mathbf{u}) : D_{\mathbf{u}}^2 \to D_{\mathbf{u}}\,, \tag{4.2}$$

which is such that $\varphi_{ij}(\mathbf{u}_1, \mathbf{u}_2; \mathbf{u})\, d\mathbf{u}$ defines the probability density that a test cell with state $\mathbf{u}_1$ belonging to the ith population falls into the state $\mathbf{u}$ after an interaction with a field cell, belonging to the jth population, with state $\mathbf{u}_2$. φ_{ij} satisfies the following property:

$$\forall\, i, j\,, \quad \forall\, \mathbf{u}_1, \mathbf{u}_2 : \int_{D_{\mathbf{u}}} \varphi_{ij}(\mathbf{u}_1, \mathbf{u}_2; \mathbf{u})\, d\mathbf{u} = 1\,. \tag{4.3}$$

Proliferating and destructive interactions occur, with rate η_{ij}, in the microscopic state $\mathbf{u}$ of the test cell with rate defined by the microscopic states of the pair of the interacting cells. The modelling of the interaction is described by the following quantities:

$$\psi_{ij}(\mathbf{u}_1, \mathbf{u}_2; \mathbf{u}) = p_{ij}(\mathbf{u}_1, \mathbf{u}_2)\delta(\mathbf{u}_1 - \mathbf{u}) - d_{ij}(\mathbf{u}_1, \mathbf{u}_2)\delta(\mathbf{u}_1 - \mathbf{u})\,, \tag{4.4}$$

where d_{ij} and p_{ij} are positive quantities.

Occasionally it may be useful, generally for mathematical proofs, summing the above contributions:

$$A_{ij} = \varphi_{ij}(\mathbf{u}_1, \mathbf{u}_2; \mathbf{u}) + \psi_{ij}(\mathbf{u}_1, \mathbf{u}_2; \mathbf{u})\,, \tag{4.5}$$

where A_{ij} does not satisfy condition (4.3).

- Consider *mean field interactions* between the test cell with state $\mathbf{u}_1$ belonging to the ith population, and field cell with state $\mathbf{u}_2$ belonging to the jth population. The microscopic modelling of pair interactions provides the action $\mathcal{P}_{ij} = \mathcal{P}_{ij}(\mathbf{u}, \mathbf{u}_*)$ on the *test* cell with microscopic state $\mathbf{u}$ due to the *field* cell with state $\mathbf{u}_*$. The resultant action is

$$\mathcal{F}_{ij}[f^b](t, \mathbf{u}) = \int_{D_{\mathbf{u}}} \mathcal{P}_{ij}(\mathbf{u}, \mathbf{u}_*) f_j^b(t, \mathbf{u}_*)\, d\mathbf{u}_*\,, \tag{4.6}$$

  where $\mathcal{F}_{ij}[f]$ is an m-dimensional vector.

Mean field nonconservative interactions refer to interactions between the *test* cell with microscopic state $\mathbf{u}_*$ with the cell with state $\mathbf{u}_{**}$ which generate a proliferation and/or destruction phenomenon in the state $\mathbf{u}$ described as follows:

$$\mathcal{S}_{ij}[f^b](t, \mathbf{u}) = \int_{D_{\mathbf{u}}{}^2} \sigma_{ij}(\mathbf{u}_*, \mathbf{u}_{**}; \mathbf{u}) f_i^b(t, \mathbf{u}_*) f_j^b(t, \mathbf{u}_{**})\, d\mathbf{u}_*\, d\mathbf{u}_{**}\,, \tag{4.7}$$

where σ is a suitable *proliferation–destruction function.* As in the case of short range interactions σ can be split as follows:

$$\sigma_{ij}(\mathbf{u}_*, \mathbf{u}_{**}; \mathbf{u}) = p_{ij}(\mathbf{u}_*, \mathbf{u}_{**})\delta(\mathbf{u}_* - \mathbf{u}) - d_{ij}(\mathbf{u}_*, \mathbf{u}_{**})\delta(\mathbf{u}_* - \mathbf{u})\,. \tag{4.8}$$

In this case, the source term can be rewritten as follows:

$$\mathcal{S}_{ij}[f^b](t,\mathbf{u}) = f_i^b(t,\mathbf{u}) \int_{D_\mathbf{u}} [p_{ij}(\mathbf{u},\mathbf{u}_{**}) - d_{ij}(\mathbf{u},\mathbf{u}_{**})] f_j^b(t,\mathbf{u}_{**})\, d\mathbf{u}_{**}\,. \tag{4.7b}$$

The technical difficulty to deal with interactions depending both on mechanical and biological variables is not yet satisfactory solved in the literature. Formally, one may define the above physical quantities η, φ, ψ, φ, $\mathcal{P}$ and σ as depending on the whole variable $\mathbf{w}$ (instead of on $\mathbf{u}$ only). However, transferring formal expression into specific models related to experiments is not yet supported by a consistent theory despite several interesting results documented in the literature, specifically in the book[4] as well as in various research papers, e.g. among others.[40]

Dealing with space and velocity depending interactions requires a distribution functions of the type $f_i = f_i(t,\mathbf{x},\mathbf{v},\mathbf{u})$. This means, referring to models with short range interactions, that the biological terms η, φ and ψ should depend on the full microscopic variables, say $\eta_{ij}(\mathbf{w}_1,\mathbf{w}_2)$ and $\varphi_{ij}(\mathbf{w}_1,\mathbf{w}_2;\mathbf{w})$, while the proliferation destruction terms are modelled similarly to Eq. (4.4), that is

$$\psi_{ij}(\mathbf{w}_1,\mathbf{w}_2;\mathbf{w}) = p_{ij}(\mathbf{w}_1,\mathbf{w}_2)\delta(\mathbf{w}_1-\mathbf{w}) - d_{ij}(\mathbf{w}_1,\mathbf{w}_2)\delta(\mathbf{w}_1-\mathbf{w})\,. \tag{4.9}$$

However, following Ref. 20, a detailed analysis of phenomenology of the microscopic interactions leads to a relatively more particularized specifications of the above terms. In particular, the encounter rate can be related, through the constants c_{ij}, to the relative velocity of the interacting pair:

$$\eta_{ij} = c_{ij}|\mathbf{v}_1 - \mathbf{v}_2|\,, \tag{4.10}$$

while the conservative interaction term is localized for the test and field particles in the point $\mathbf{x} = \mathbf{x}_1 = \mathbf{x}_2$, and is given by the product of the mechanical and biological interactions, say:

$$\varphi_{ij} = \delta(\mathbf{x}_1-\mathbf{x})\delta(\mathbf{x}_2-\mathbf{x})\varphi_{ij}^b(\mathbf{u}_1,\mathbf{u}_2;\mathbf{u})\varphi_{ij}^m(\mathbf{v}_1,\mathbf{v}_2;\mathbf{v}|\mathbf{u}_1,\mathbf{u}_2)\,, \tag{4.11}$$

where φ^b corresponds to biological interactions, and φ^m to mechanical interactions which are conditioned by the biological state. Finally the terms corresponding to proliferating and destructive interactions may be assumed to be determined only by the biological state, hence given again by Eq. (4.4).

Due to the technical difficulties generated by the above microscopic modelling, some simplified descriptions can be recovered in the literature. A particular case is the model proposed in Ref. 18, which simplifies the description of the phenomena by the assumption that interactions generate a velocity jump process independent on the biological interactions. The process, following some ideas of Refs. 51 and 52, can be written as follows:

$$\nu \sum_{j=1}^{p} \left[\int_{D_\mathbf{v}} (T(\mathbf{v},\mathbf{v}^*) f_i(t,\mathbf{x},\mathbf{v}^*,\mathbf{u}) - T(\mathbf{v}^*,\mathbf{v}) f_j(t,\mathbf{x},\mathbf{v},\mathbf{u}))\, d\mathbf{v}^* \right]. \tag{4.12}$$

Of course the above model can be technically replaced by different ways of describing the stochastic evolution of the velocity variable. Useful ideas can be recovered in Ref. 77.

Unfortunately, the above description leaves totally open the problem of describing the mechanics of the interactions which are effectively related both to biological and mechanical variables. For instance, tumor cells show a trend to condense into solid forms, while endothelial cells are attracted by tumor cells. In other words, the biological state is able to organize the dynamics of cells.

The mean field description may possibly be able to consider phenomena of the type just mentioned above. A useful reference, to the developments of models in biology, may be the mathematical literature on classical or quantum interactions, see among others Refs. 48 and 59. As we have seen, the main problem consists again in describing, by mathematical equations, the interplay between biological and mechanical variables.

Microscopic interactions have to be related to the full microscopic variable $\mathbf{w}$. However, also in this case, the interaction terms may be further specialized assuming that only some of the microscopic variables have a role. For instance, $\mathcal{P}_{ij}$ may be assumed to depend on the whole variable: $\mathcal{P}_{ij} = \mathcal{P}_{ij}(\mathbf{x}, \mathbf{u}, \mathbf{v}, \mathbf{x}_*, \mathbf{u}_*, \mathbf{v}_*)$, while σ_{ij} only depends on the biological variables: $\sigma_{ij} = \sigma_{ij}(\mathbf{u}, \mathbf{u}_*)$. In this case models developed in the spatially homogeneous case can be properly generalized to describe proliferating and destructive interactions also when space and velocity variables cannot be neglected. In particular, the technical expression of the action over the test cell is as follows:

$$\mathcal{F}_{ij}[\mathbf{f}](t, \mathbf{x}, \mathbf{u}) = \int_{\mathcal{D}} \mathcal{P}_{ij}(\mathbf{x}, \mathbf{u}, \mathbf{v}, \mathbf{x}_*, \mathbf{u}_*, \mathbf{v}_*) f_j(t, \mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)\, d\mathbf{x}_*\, d\mathbf{v}_*\, d\mathbf{u}_*\,, \qquad (4.13)$$

where $\mathcal{D} = \Omega \times D_{\mathbf{v}} \times D_{\mathbf{u}}$, with Ω interaction domain of the test cell: $\mathbf{x}_* \notin \Omega \Rightarrow \mathcal{F} = 0$.

5. Short Range Models — Biological Predominant Interactions

The above described microscopic interactions, corresponding to two different types of modelling, generate two types of evolution equations which can be used to design specific models related to biological phenomena for multicellular systems. This section deals with the above topic for a system of cells homogeneously distributed in space, where only biological interactions are relevant.

Specifically, the case of short range interactions is dealt with. This means that only the framework offered by Eqs. (4.1)–(4.5) will be used. As a matter of fact, the literature in the field produced only models in the spatially homogeneous case, while only recently the difficult (however challenging) problem of modelling the complex interplay between biological and mechanical variables has given some preliminary results.[20] This paper also shows how models with biologically predominant interactions can be obtained as a particular case of the general case when both mechanical and biological interactions are present.

Referring to short range interaction models the first result available in the literature was proposed by Ref. 12. Afterwards various authors have proposed technical

developments related to a relatively more precise identification of cell populations[13] or to development of computational schemes[22,43] related to bifurcation analysis. Generalizations to the analysis of progression models and qualitative analysis of the solutions can be recovered in Ref. 10. The substantial difference of the models proposed in Refs. 10 and 11 with respect to the preceding ones is the ability to describe the evolution of differentiated cells to the state of progressing cells.

Considering that this paper deals with methodological aspects, the subsection which follows aims to show how the modelling of microscopic interactions developed in Sec. 4 generates a class of evolution equations where the various models available in the literature can be related to. Specifically, the analysis which follows is developed through three steps, and each is dealt with in the subsections which follow. The first one is devoted to the formal derivation of the evolution equations, and the second one to the description of a model related to short range interactions. The third one deals with the qualitative analysis of the initial value problem, the fourth subsection develops some sample simulations to show the ability of the model to describe various biological phenomena. The above subsections essentially refer to boxes C, D and E of Fig. 1.

All technical details are given so that the interested reader will be aware of the methodological aspects necessary to refer the framework proposed in Sec. 5.1 to other types of models obtained using the same reasoning.

The selection of models, dealt with in the subsections which follow, is essentially based on the contents of papers Refs. 10 and 11. In fact the models proposed in the above papers have given reliable results in the comparison between experiments and theoretical prediction. Moreover, the generalization proposed in Ref. 11 shows how the model can be generalized to describe several types of immune competition related to phenomena somehow different from those dealt with in this paper.

The framework dealt with in what follows refers to the continuous distribution function. Analogous calculations can be developed for the discrete function following the scheme proposed in Ref. 26. The evolution equations reported in this section refer to the distribution function f^b, however the superscript is eliminated to avoid heavy notations.

5.1. *General framework*

Let us consider a large system on n cell populations. The evolution equation is derived equating the time derivative of the distribution function, at time t in the state $\mathbf{u}$, to the positive and negative flow of cells into the volume $[\mathbf{u}, \mathbf{u} + d\mathbf{u}]$ due to interactions. If the interactions are described by Eqs. (4.1)–(4.5), the evolution equation is:

$$\frac{\partial f_i}{\partial t}(t,u) = \sum_{j=1}^{n} \left(\int_{D^2_{\mathbf{u}}} \eta_{ij}(\mathbf{u}_1,\mathbf{u}_2) A_{ij}(\mathbf{u}_1,\mathbf{u}_2;\mathbf{u}) f_i(t,\mathbf{u}_1) f_j(t,\mathbf{u}_2)\, d\mathbf{u}_1\, d\mathbf{u}_2 \right.$$

$$\left. - f_i(t,\mathbf{u}) \int_{D_{\mathbf{u}}} \eta_{ij}(\mathbf{u},\mathbf{u}_2) f_j(t,\mathbf{u}_2)\, d\mathbf{u}_2 \right). \tag{5.1}$$

Taking into account property (4.3) of φ_{ij}, the model describes proliferation and destruction phenomena according to the sign of ψ_{ij}.

The above equation defines a framework suitable to be specialized into models able to describe various phenomena related to the immune competition between tumor and immune cells. Of course, the simplification related to the above models does not allow the description of important processes, such as pattern formations, which can be obtained only if space and velocity variables are inserted into the microscopic variable. This topic is analyzed in the sections which follow, while the above equations have to be regarded as a way, based on methods of mathematical kinetic theory, to reduce the complexity of the description of a multicellular system.

A specific model is described with reference to the phenomenological description given in Ref. 49 for a system of endothelial cells homogeneously distributed in space. Some of these cells may have lost their differentiation and may start progressing towards replicant and metastatic state. The state of these cells is identified by a scalar variable $u \in \mathbb{R}$, such that negative states denote normal state, while positive values denote a progressing state. The above cell population interacts in competition with immune cells which proliferate when the aggressive host is recognized, while are partially inhibited by the host.

The general properties of the above system can be described, referring to Eq. (5.1), by the following phenomenological assumptions:

Assumption G.5.1. The *cell populations of the system* is constituted by two interacting populations: the first one, labelled by the subscript $i, j = 1$, refers to endothelial cells, while the second one, labelled by the subscript $i, j = 2$, refers to immune cells. The *biological state* of the endothelial cells is identified by a scalar variable u such that negative values correspond to *normal* cells, while positive values correspond to *progressing* cells. The biological state of the immune cells is identified by a scalar variable u such that negative values correspond to *inhibited* cells, while positive values correspond to *active* cells.

Assumption G.5.2. *Interactions* can be subdivided into conservative encounters, which modify the state of the cells but not their number, and proliferating-destructive encounters related to proliferation or destruction of cells in a certain fixed state. *Conservative encounters* modify the progression of endothelial cells and the activation of immune cells. *Proliferating* and *destructive* encounters modify the number of cells.

The above assumptions simply characterize the number of populations $n = 2$ which play the game, while u is a scalar variable with values $u \in (-\infty, \infty)$.

5.2. *A short range interaction model*

Let us derive a specific model based on short range interactions assumptions, exploiting the framework designed in Sec. 5.1. Referring to Ref. 10, we assume for all types of interactions the following:

Assumption 5.1. The *encounter rate* is assumed constant for all interacting pairs

$$\eta_{ij} = \eta = 1\,, \quad \forall\, i,j = 1,2\,. \tag{5.2}$$

Assumption 5.2. The *transition probability density* related to *conservative interactions* is assumed to be a Gaussian with the most probable output defined by the mean value $m_{ij}(v,w)$, which may depend on the microscopic state of the interacting pair and with a finite variance s_{ij}:

$$\varphi_{ij}(v,w;u) = \frac{1}{\sqrt{2\pi s_{ij}}} \exp\left\{-\frac{(u - m_{ij}(v,w))^2}{2s_{ij}}\right\}, \tag{5.3}$$

where the following notations have been used: $v = u_1$ and $w = u_2$.

Assumption 5.3. *Proliferating and destructive interactions* occur, with rate η_{ij}, in the microscopic state u of the *test* cell with rate defined by the microscopic states of the pair of the interacting cells.

Equation (5.1) can be further specialized as follows:

$$\frac{\partial f_i}{\partial t} = \sum_{j=1}^{2} \int_{\mathbb{R}^2} \varphi_{ij}(v,w;u) f_i(t,v) f_j(t,w)\, dv\, dw$$

$$+ f_i(t,u) \sum_{j=1}^{2} \int_{\mathbb{R}} [p_{ij} - d_{ij}](u,w) f_j(t,w)\, dw - f_i(t,u) \sum_{j=1}^{2} n_j(t)\,, \tag{5.4}$$

where

$$n_j(t) = \int_{\mathbb{R}} f_j(t,u)\, du\,. \tag{5.5}$$

Moreover, some technical calculations exploit the stepwise function $U(z)$ defined as follows:

$$U_{[a,b]}(z) : U_{[a,b]}(z) = \begin{cases} 1 & \text{if } z \in [a,b]\,, \\ 0 & \text{if } z \notin [a,b]\,. \end{cases} \tag{5.6}$$

Based on the above general rules, a specific modelling of microscopic interactions can be developed according to the following (see Ref. 11) assumptions:

• Interactions between cells of the first population:

Conservative microscopic interactions are modelled assuming that the transition probability density is a Gaussian, as in Eq. (5.3), with the most probable output given as follows:

$$v, w \in \mathbb{R} : m_{11} = v(1 + \alpha_{11})\,, \tag{5.7}$$

where α_{11} is a parameter related to the inner tendency of both a normal and progressing endothelial cell to degenerate and progress.

The *proliferation rate* of normal endothelial cells $v < 0$ due to encounters with other endothelial cells, is equal to zero. On the other hand, when $v \geq 0$, cells undergo

uncontrolled mitosis stimulated by encounters with nonprogressing cells, which have a feeding ability. Encounters between tumor cells do not lead any proliferation or destruction:

$$p_{11}(v,w) = \beta_{11} U_{[0,\infty)}(v) U_{(-\infty,0)}(w)\,, \quad d_{11} = 0\,, \tag{5.8}$$

where β_{11} is a parameter which characterizes the proliferating ability of tumor cells.

• Interactions between cells of the first with second population:

Conservative microscopic interactions are modelled assuming that if a cell of the first population is not progressing, then its state does not change due to interactions with immune cells. Moreover, if $v \geq 0$, then the state of the cell does not change if the immune cell is not active:

$$v < 0,\ w \in \mathbb{R}\,, \quad v \geq 0,\ w < 0 : \varphi_{12} = \delta(u - v)\,. \tag{5.9}$$

On the other hand, for positive values of v, if $w \geq 0$, the transition probability density is a Gaussian, as in Eq. (5.3), with the most probable output given as follows:

$$v, w \geq 0 : m_{12} = v(1 - \alpha_{12})\,, \tag{5.10}$$

where α_{12} is a parameter which indicates the ability of the immune system to reduce the progression of a tumor cell.

The *proliferation rate* of nonprogressing cells, $v < 0$, due to encounters with immune cells, is equal to zero. On the other hand, when $v \geq 0$ cells are partially destroyed due to encounters with active immune cells:

$$d_{12}(v,w) = \beta_{12} U_{[0,\infty)}(v) U_{[0,\infty)}(w)\,, \quad p_{12} = 0\,, \tag{5.11}$$

where β_{12} is a parameter which characterizes the destructive ability of active immune cells.

• Interactions between cells of the second with the first population:

Conservative microscopic interactions are modelled assuming that immune cells do not change state due to interactions with non-progressing endothelial cells, $w < 0$. Moreover, if the cell is inhibited, its state does not change interacting with progressing endothelial cells:

$$v \in \mathbb{R},\ w < 0\,, \quad v < 0,\ w \geq 0 : \varphi_{21} = \delta(u - v)\,. \tag{5.12}$$

On the other hand, for positive values of w, the transition probability density is a Gaussian, as in Eq. (5.3), with the most probable output given as follows:

$$v \geq 0,\ w \geq 0 : m_{21} = v - \alpha_{21}\,, \tag{5.13}$$

where α_{21} is a parameter which indicates the ability of tumor cells to inhibit immune cells.

The *proliferation rate* of inhibited immune cells $v < 0$ due to encounters with cells of the first population, is equal to zero. On the other hand, when $v \geq 0$, cells proliferate due to encounters with progressing cells:

$$p_{21}(v,w) = \beta_{21} U_{[0,\infty)}(v) U_{[0,\infty)}(w)\,, \quad d_{21} = 0\,, \tag{5.14}$$

where β_{21} is a parameter which characterizes the proliferating ability of tumor cells.

• Interactions between cells of the second population:

Interactions between immune cells always have a trivial output:

$$v, w \in \mathbb{R} : \varphi_{22} = \delta(u-v)\,, \quad d_{22} = p_{22} = 0\,. \tag{5.15}$$

Based on the above modelling of cell interactions, we are able to derive, after some technical calculations, the following *evolution equation*:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{n_1(t)}{\sqrt{2\pi s_{11}}} \displaystyle\int_{-\infty}^{\infty} \exp\left\{-\frac{(u - v(1+\alpha_{11}))^2}{2s_{11}}\right\} f_1(t,v)\,dv \\ \qquad\qquad + \dfrac{n_2^A(t)}{\sqrt{2\pi s_{12}}} \displaystyle\int_{0}^{\infty} \exp\left\{-\frac{(u - v(1-\alpha_{12}))^2}{2s_{12}}\right\} f_1(t,v)\,dv \\ \qquad\qquad - f_1(t,u) n_1(t) + f_1(t,u)[\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t)] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = \dfrac{n_1^T(t)}{\sqrt{2\pi s_{21}}} \displaystyle\int_{0}^{\infty} \exp\left\{-\frac{(u - (v-\alpha_{21}))^2}{2s_{21}}\right\} f_2(t,v)\,dv \\ \qquad\qquad + (\beta_{21} - 1) U_{[0,\infty)}(u) f_2(t,u) n_1^T(t)\,, \end{cases} \tag{5.16}$$

where

$$n_1(t) = \int_{-\infty}^{\infty} f_1(t,u)\,du\,, \quad n_2(t) = \int_{-\infty}^{\infty} f_2(t,u)\,du\,,$$

$$n_1^E(t) = \int_{-\infty}^{0} f_1(t,u)\,du\,, \quad n_1^T(t) = \int_{0}^{\infty} f_1(t,u)\,du\,,$$

$$n_2^I(t) = \int_{-\infty}^{0} f_2(t,u)\,du\,, \quad n_2^A(t) = \int_{0}^{\infty} f_2(t,u)\,du\,.$$

The above model is characterized by nine phenomenological parameters:

α_{11} is referred the variation of the progression due to encounters between endothelial cells. It describes the tendency of a normal cell to degenerate and to increase its progression.

α_{12} is the parameter corresponding to the ability of the active immune cells to reduce the progression of tumor cells. The parameter takes values in $[0,1)$.

α_{21} is the parameter corresponding to the ability of tumor cells to inhibit the active immune cells. The parameter takes values in $[0,1)$.

s_{11} is the variance of the function describing the natural trend to degenerate of endothelial cells.

s_{12} is the variance of the function describing the deactivation of tumor cells by the interaction of immune cells.

s_{21} is the variance of the function describing the deactivation of immune cells by the interaction of tumor cells.

β_{11} is the proliferation rate of tumor cells due to their encounters with normal endothelial cells.

β_{12} is the ability of immune cells to destroy tumor cells.

β_{21} is the parameter corresponding to the proliferation rate of immune cells due to their interaction with progressed cells.

It is worth mentioning that if the variance goes to zero, a deterministic output in the conservative interaction functions is described:

$$s_{ij} \to 0 \Longrightarrow \varphi_{ij}(v, w; u) = \delta(u - m_{ij}(v, w)) .$$

In this case Eq. (5.16) writes:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{1}{1+\alpha_{11}} n_1(t) f_1\left(t, \dfrac{u}{1+\alpha_{11}}\right) - f_1(t,u) n_1(t) \\ \qquad\qquad + \dfrac{1}{1-\alpha_{12}} n_2^A(t) f_1\left(t, \dfrac{u}{1-\alpha_{12}}\right) U_{[0,\infty)}(u) \\ \qquad\qquad + f_1(t,u)[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)] U_{[0,\infty)}(u) , \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t)[f_2(t, u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) \\ \qquad\qquad + (\beta_{21} - 1) f_2(t,u) U_{[0,\infty)}(u)] . \end{cases} \tag{5.17}$$

This relatively simpler model is characterized by six parameters only: α-type parameters related to mass conservative encounters, and β-type parameters related to proliferating/destructive encounters.

Models corresponding to specific biological competition can be obtained when some of the conservative phenomena are not relevant. For instance when the speed of progression of tumor cells is negligible $\alpha_{11} = 0$, the model writes:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{1}{1-\alpha_{12}} n_2^A(t) f_1\left(t, \dfrac{u}{1-\alpha_{12}}\right) U_{[0,\infty)}(u) \\ \qquad\qquad + f_1(t,u)[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)] U_{[0,\infty)}(u) , \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t)[f_2(t, u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) \\ \qquad\qquad + (\beta_{21} - 1) f_2(t,u) U_{[0,\infty)}(u)] . \end{cases} \tag{5.18}$$

A particular model is obtained if $\alpha_{21} = 0$, which corresponds to absence of inhibition ability of tumor cells. In this particular case the evolution equation reduces

to:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{1}{1+\alpha_{11}} n_1(t) f_1\left(t, \dfrac{u}{1+\alpha_{11}}\right) - f_1(t,u) n_1(t) \\ \qquad\qquad + \dfrac{1}{1-\alpha_{12}} n_2^A(t) f_1\left(t, \dfrac{u}{1-\alpha_{12}}\right) U_{[0,\infty)}(u) \\ \qquad\qquad + f_1(t,u)[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t) \beta_{21} f_2(t,u) U_{[0,\infty)}(u)\,, \end{cases} \tag{5.19}$$

and when $\alpha_{11} = 0$

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{1}{1-\alpha_{12}} n_2^A(t) f_1\left(t, \dfrac{u}{1-\alpha_{12}}\right) U_{[0,\infty)}(u) \\ \qquad\qquad + f_1(t,u)[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t) \beta_{21} f_2(t,u) U_{[0,\infty)}(u)\,. \end{cases} \tag{5.20}$$

The above models, as analyzed in Ref. 11, can describe competitions somehow different from those dealt with in this paper. Indeed, immune cells can react to cells carrier of some pathology without being inhibited. The model may also describe the competition in the case of an immune system fully activated by suitable therapeutical actions.

A different situation is described by the above class of models in the case of a totally suppressed immune system. In this case tumor cells proliferate and progress without any contrast as described by a model such that $n_2^A = 0$. The evolution equation for f_1 is as follows:

$$\frac{\partial f_1}{\partial t}(t,u) = \frac{1}{1+\alpha_{11}} n_1(t) f_1\left(t, \frac{u}{1+\alpha_{11}}\right) - f_1(t,u) n_1(t) + f_1(t,u) \beta_{11} n_1^E(t)\,. \tag{5.21}$$

This model depends on the parameters β_{11} and α_{11} only. If the self progression can be neglected $\alpha_{11} = 0$, the model writes:

$$\frac{\partial f_1}{\partial t}(t,u) = f_1(t,u) \beta_{11} n_1^E(t)\,,$$

which shows the exponential-type growth of tumor cells with eigenvalue identified by the parameter β_{11}. The parameter identification proposed in Ref. 10 is based on the above analysis.

The above models correspond to evolution of a closed system: the number of endothelial cells may decrease due to absence of inlet from the outer environment. For an open system one may consider models with constant number of cells. In this

case: $n_1^E = n_{10}^E = \text{const.}$, and the evolution equation for $\alpha_{11} = 0$ writes:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{1}{1-\alpha_{12}} n_2^A(t) f_1\left(t, \dfrac{u}{1-\alpha_{12}}\right) U_{[0,\infty)}(u) \\ \qquad\qquad + f_1(t,u)[\beta_{11} n_{10}^E - \beta_{12} n_2^A(t)] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t)[f_2(t,u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) \\ \qquad\qquad + (\beta_{21}-1) f_2(t,u) U_{[0,\infty)}(u)]\,. \end{cases} \tag{5.22}$$

It is worth mentioning that a model based both on continuous and discrete distribution can be developed by the above one assuming that the state of the immune cells is simply concentrated on an active or inhibited state. Considering that the inhibited cells do not contribute to the evolution of the progressed cells, the model can refer to $f_1 = f_1(t,u)$ and $n_2 = n_2(t)$, representing, respectively, the distribution function of tumor cells and the number density of active immune cells. Due to this assumption, and with a slight modification or the phenomenological assumptions on the conservative and non-conservative terms, see Ref. 10, the following model is obtained:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = [f_1(t,u-\alpha_{11}) - f_1(t,u)] n_1(t) \\ \qquad\qquad + \dfrac{1}{1-\alpha_{12}} f_1\left(t, \dfrac{u}{1-\alpha_{12}}\right) n_2^A(t) U_{[0,\infty)}(u) \\ \qquad\qquad + [\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t)] f_1(t,u) U_{[0,\infty)}(u)\,, \\ \dfrac{dn_2^A}{dt}(t) = \gamma_{21} n_2^A(t) n_1^T(t)\,, \end{cases} \tag{5.23}$$

where $\gamma_{21} = \beta_{21} - \alpha_{21}$. The above model is further simplified with respect to the model proposed in (5.17); in fact it is characterized by five parameters rather than six. The same model, in absence of self progression, becomes:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{1}{1-\alpha_{12}} f_1\left(t, \dfrac{u}{1-\alpha_{12}}\right) n_2^A(t) U_{[0,\infty)}(u) \\ \qquad\qquad + [\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t)] f_1(t,u) U_{[0,\infty)}(u)\,, \\ \dfrac{dn_2^A}{dt}(t) = \gamma_{21} n_2^A(t) n_1^T(t)\,. \end{cases} \tag{5.24}$$

An additional technical modification, already suggested in Ref. 11, consists in introducing a natural decay, when the number of progressing cells tends to zero, of immune cells to a sentinel level identified by the initial distribution $f_2(t=0,u)$.

5.3. *Qualitative analysis of the initial value problem*

This subsection deals with the analysis of the well-posedness of the initial value problem related to model (5.16). The initial value problem can be written as follows:

$$\begin{cases} \dfrac{\partial f}{\partial t} = N(f)\,, \\ f(t=0,u) = f_0(u)\,, \end{cases} \tag{5.25}$$

where $f = (f_1, f_2)$, $f_0(u) = (f_{10}(u), f_{20}(u))$, while the operator N is given by

$$N(f)(t) = \{N_1(f)(t), N_2(f)(t)\}^T\,, \tag{5.26}$$

with

$$\begin{aligned} N_1(f)(t) = {} & \frac{n_1(t)}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{\infty} \exp\left\{-\frac{(u - v(1+\alpha_{11}))^2}{2s_{11}}\right\} f_1(t,v)\,dv \\ & + \frac{n_2^A(t)}{\sqrt{2\pi s_{12}}} \int_0^{\infty} \exp\left\{-\frac{(u - v(1-\alpha_{12}))^2}{2s_{12}}\right\} f_1(t,v)\,dv \\ & - f_1(t,u) n_1(t) + f_1(t,u) U_{[0,\infty)}[\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t)] \end{aligned}$$

and

$$\begin{aligned} N_2(f)(t) = {} & \frac{n_1^T(t)}{\sqrt{2\pi s_{21}}} \int_0^{\infty} \exp\left\{-\frac{(u - (v - \alpha_{21}))^2}{2s_{21}}\right\} f_2(t,v)\,dv \\ & + (\beta_{21} - 1) U_{[0,\infty)}(u) f_2(t,u) n_1^T(t)\,. \end{aligned}$$

The analysis of Problem (5.25) needs the definition of some suitable function spaces. Specifically:

- $L_1(\mathbb{R})$ is the Lebesgue space of measurable, real-valued functions which are integrable on $\mathbb{R}$. The norm is denoted by $\|\cdot\|_1$.
- $\mathcal{X} = L_1(\mathbb{R}) \times L_1(\mathbb{R}) = \{f = (f_1, f_2) : f_1 \in L_1(\mathbb{R}), f_2 \in L_1(\mathbb{R})\}$ is the Banach space equipped with the norm

$$\|f\| = \|f_1\|_1 + \|f_2\|_1\,.$$

- $\mathcal{X}_+ = \{f = (f_1, f_2) \in \mathcal{X} : f_1 \geq 0, f_2 \geq 0\}$ is the positive cone of $\mathcal{X}$.
- $\mathcal{Y} = C([0,T], \mathcal{X})$ and $\mathcal{Y}_+ = C([0,T], \mathcal{X}_+)$ is the space of the functions continuous on $[0,T]$ with values in a Banach spaces $\mathcal{X}$ and $\mathcal{X}_+$, respectively, equipped with the norm

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

Local existence and uniqueness of the solution to the initial value problem is stated by the following:

Theorem 5.1. *Let $f_0 \in \mathcal{X}_+$. Then there exist positive constants T and a_0, such that the initial value problem* (5.25) *has a unique solution $f \in C([0,T], \mathcal{X})$, that moreover satisfies*

$$f(t) \in \mathcal{X}_+\,, \quad t \in [0,T]\,, \tag{5.27}$$

and

$$\|f\| \leq a_0 \|f_0\|\,, \quad \forall\, t \in [0,T]\,. \tag{5.28}$$

Proof of Theorem 5.1. The proof can be obtained by application of classical fixed point methods. First, Eq. (5.25) is written in the form of an integral equation

$$f = M(f) = f_0(u) + \int_0^t N(f)(s)\, ds = f_0(u) + \Psi(f)(t)\,. \tag{5.29}$$

Theorem 5.1 is proved by showing that the map M is a contraction in a ball of $\mathcal{Y}$. This requires the following estimates of Ψ, which can be stated as follows:

(i) Ψ is a continuous map from $\mathcal{Y}$ into $\mathcal{Y}$ and $\exists\, C_1 > 0$ such that:

$$\|\Psi(f)\|_{\mathcal{Y}} \leq C_1 T \|f\|_{\mathcal{Y}}^2\,, \tag{5.30}$$

(ii) Ψ is Lipschitz continuous in $\mathcal{Y}$

$$\|\Psi(f) - \Psi(g)\|_{\mathcal{Y}} \leq C_1 T (\|f\|_{\mathcal{Y}} + \|g\|_{\mathcal{Y}}) \|f - g\|_{\mathcal{Y}}\,. \tag{5.31}$$

The technical proof of the above estimates is given in Ref. 11 and is not repeated here. Then exploiting the above estimates, it is possible to show that M is a contraction in a ball of $\mathcal{Y}$. In fact, at first we note that M maps $\mathcal{Y}$ into itself. Moreover,

$$\|M(f)\|_{\mathcal{Y}} \leq \|f_0\| + C_1 T \|f\|_{\mathcal{Y}}^2\,, \tag{5.32}$$

$$\|M(f) - M(g)\|_{\mathcal{Y}} \leq C_1 T (\|f\|_{\mathcal{Y}} + \|g\|_{\mathcal{Y}}) \|f - g\|_{\mathcal{Y}}\,. \tag{5.33}$$

This implies that there exist constants a_0, T determined only by C_1 and $\|f_0\|$ such that M is a contraction on a ball in $\mathcal{Y}$ of radius a_0. This proves that there exists a unique local solution $f(t)$ of Eq. (5.25) on $[0,T]$. In order to show the positivity of solutions let $K = t_{(K_1,K_2)}$ and $B = t_{(B_1,B_2)}$ be the operators defined as follows:

$$K_1(f)(t) = n_1(t) + (1+\beta_{12}) n_2^A(t) U_{[0,\infty)}(u)\,, \tag{5.34a}$$

$$K_2(f)(t) = n_1^T(t) U_{[0,\infty)}(u)\,, \tag{5.34b}$$

and

$$\begin{aligned} B_1(f)(t) = {} & \frac{n_1(t)}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{\infty} \exp\left\{ -\frac{(u - v(1+\alpha_{11}))^2}{2 s_{11}} \right\} f_1(t,v)\, dv \\ & + \frac{n_2^A(t)}{\sqrt{2\pi s_{12}}} \int_0^{\infty} \exp\left\{ -\frac{(u - v(1-\alpha_{12}))^2}{2 s_{12}} \right\} f_1(t,v)\, dv \\ & + \beta_{11} f_1(t,u) U_{[0,\infty)}(u) n_1^E\,, \end{aligned} \tag{5.35}$$

$$\begin{aligned} B_2(f)(t) = {} & \frac{n_1^T(t)}{\sqrt{2\pi s_{21}}} \int_0^{\infty} \exp\left\{ -\frac{(u - v + \alpha_{21}))^2}{2 s_{21}} \right\} f_2(t,v)\, dv \\ & + \beta_{21} f_2(t,u) U_{[0,\infty)}(u) n_1^T\,. \end{aligned} \tag{5.36}$$

It is easy to show that the map M can also be written as

$$M(f) = \exp\left(-\int_0^t K(f)(s)\,ds\right) f_0(u) + \int_0^t \exp\left(\int_t^\tau K(f)(s)\,ds\right) B(f)(\tau)\,d\tau\,. \tag{5.37}$$

Then due to the non-negativity of the operator B, it is clear that M map $\mathcal{X}_+$ into itself if the initial data is positive. One can apply again the fixed point theorem in $\mathcal{Y}_+$ by using inequalities (i) and (ii). This completes the proof. □

Global existence and, more in details, suitable information on the asymptotic behavior can be obtained analyzing the influence of the parameters of the model on the qualitative behavior of the solutions. The analysis should be addressed toward suitable biological interpretations. A systematic analysis of the asymptotic behavior of the solutions is developed in Ref. 11 with special attention to the role of the parameters α and β. As documented in Refs. 10 and 11 the asymptotic behavior depends not only on the above parameters but also on the size of the initial conditions. The qualitative analysis is addressed to investigate the role of the parameters on the identifications of two different asymptotic behaviors:

(i) Blow up of tumor cells and inhibitions of immune cells;
(ii) Asymptotic (in time) destruction of tumor cells due to immune cells which keep their specific functions.

As we shall see in the next subsection, the α-type parameters play a crucial role in this game, while the output also depends on the initial conditions and on the role of the β-type parameters. For instance, the second one of the above trends appears if the number at $t = 0$ of tumor cells is sufficiently small compared with the specific proliferation ability of tumor cells.

To obtain a relatively more detailed idea of the above remarks, the main theorem on the asymptotic behavior of the model (5.24), see Ref. 10, is reported.

Theorem 5.2. *Consider the initial value problem for the model* (5.24) *and let the constant* δ (*related to the initial condition*) *given by*

$$\delta = \beta_{11} n_E(0) - \beta_{12} n_2(0)\,. \tag{5.38}$$

Then:

(i) *If* $n_2^A = 0$, *then* n_1^T *increases and* $n_1^E = \text{const.}$
(ii) *If* $n_2^A = \text{const.}$ *and* $\gamma_{21} \neq 0$, *then* $n_1^T = 0$ *and* $n_1^E = \text{const.}$
(iii) *If* n_2^A *is nonvanishing, then four cases are possible*:

(a) *if* $\gamma_{21} < 0$, *and* $\frac{n_2^A(0)}{n_1^E(0)} < \frac{\beta_{11}}{\beta_{12}}$, *then* n_2^A *decreases and* n_1^T *increases*; *moreover* $\delta > 0$, *and the following lower bound holds*:

$$n_1^T(t) \geq n_1^T(0) \exp(\delta t)\,, \tag{5.39}$$

(b) *if* $\gamma_{21} < 0$, *and* $\frac{n_2^A(0)}{n_1^E(0)} \geq \frac{\beta_{11}}{\beta_{12}}$, *then* n_2^A *decreases, while* n_1^T *satisfies the estimate* (5.39), *where now* $\delta < 0$.

(c) *if* $\gamma_{21} > 0$, *and* $\frac{n_2^A(0)}{n_1^E(0)} < \frac{\beta_{11}}{\beta_{12}}$, *then* n_2^A *increases,* $\delta > 0$, *and the following upper bound holds*:

$$n_1^T(t) \leq n_1^T(0) \exp(\delta t)\,, \tag{5.40}$$

(d) *if* $\gamma_{21} > 0$, *and* $\frac{n_2^A(0)}{n_1^E(0)} \geq \frac{\beta_{11}}{\beta_{12}}$, *then* n_2^A *increases,* n_1^T *decreases*; *moreover the upper bound* (5.40) *holds where now* $\delta < 0$.

The above theorem provides a description of various phenomena interesting from the viewpoint of sciences of immunology and it shows that the asymptotic behavior depends, in a rather complex way, also on the size of the initial condition and on the β-type parameters related to the proliferation ability. A suitable analysis of the influence of the parameters in determining the asymptotic scenario, may suggest some interesting information toward the development of therapeutical actions.

5.4. *Simulations*

Theorem 5.1 provides the necessary support for the application of computational schemes to obtain quantitative description of the behavior of the solutions to complete those delivered by qualitative theorems.

A specific objective related to the class of equations dealt with in this paper is the analysis of the sensitivity of the solutions to parameter variations. The interest of biological sciences for the analysis appears when the modification of a certain parameter causes different asymptotic behaviors. This aspect can be related to the development of specific therapies. Various papers have studied this aspect with special attention to focusing the ability of tumor cells to inhibit immune cells. For instance, simulations have been developed in Ref. 38 with reference to the qualitative analysis proposed in Ref. 37. Specifically, it is shown that the parameter related to the above inhibition action is actually a bifurcation parameter: for values lower than a critical value the number of tumor cells asymptotically decays to zero, while immune cells remain sufficiently active. On the other hand, for values greater than the above critical value a blow up of tumor cells is observed with progressive inhibition of immune cells. Analogous results are obtained in Ref. 10 for a model with short range interactions.

Moreover, the analysis developed in Ref. 11 has shown that the qualitative and computational analysis need to be related to all parameters. In fact, even when the asymptotic behavior is the desired one, it is necessary to analyze it quantitatively to control if the number of tumor cells pass over a certain critical value which corresponds to the onset of condensation into a solid form or other dangerous events such as the onset of angiogenesis phenomena.

A specific example of this type of analysis refers to the analysis of the asymptotic behavior of the solution to the initial value problem for the model in the particular case $\alpha_{21} = 0$ in which the immune system cannot be inhibited by the tumor cells, thus the final output, if $\beta_{21} \neq 0$, is always the depletion of the tumor. On the other hand, the behavior can put in evidence the various phenomena which have been outlined above.

Consider, with reference to Ref. 11 for a relatively more detailed analysis, the case in which the nonconservative parameters and the initial conditions are such that $\delta > 0$ and consider the role of the conservative parameters which define the interaction between tumor and immune cell in the case of slow self-progression ($\alpha_{11} \cong 0$). Specifically, considering the problem with the following values of the nonconservative parameters

$$\beta_{11} = 0.9\,, \quad \beta_{12} = 0.1\,, \quad \beta_{21} = 0.9\,,$$

and with Gaussian initial condition, we see two types of evolution: the first when $\alpha_{12} \neq 0$ and $\alpha_{21} \neq 0$. The second when $\alpha_{12} \neq 0$ and $\alpha_{21} = 0$.

- In the first case ($\alpha_{12} \neq 0$ and $\alpha_{21} \neq 0$) simulations show a blow up of tumor cells due to their ability to inhibit the immune ones ($\alpha_{21} \neq 0$) (and of course due to the $\delta > 0$). The asymptotic scenario is shown in Figs. 4 and 5. Tumor progression distribution increases while the immune distribution is partially inhibited (shifts toward the left) and reduced (reduction in high).

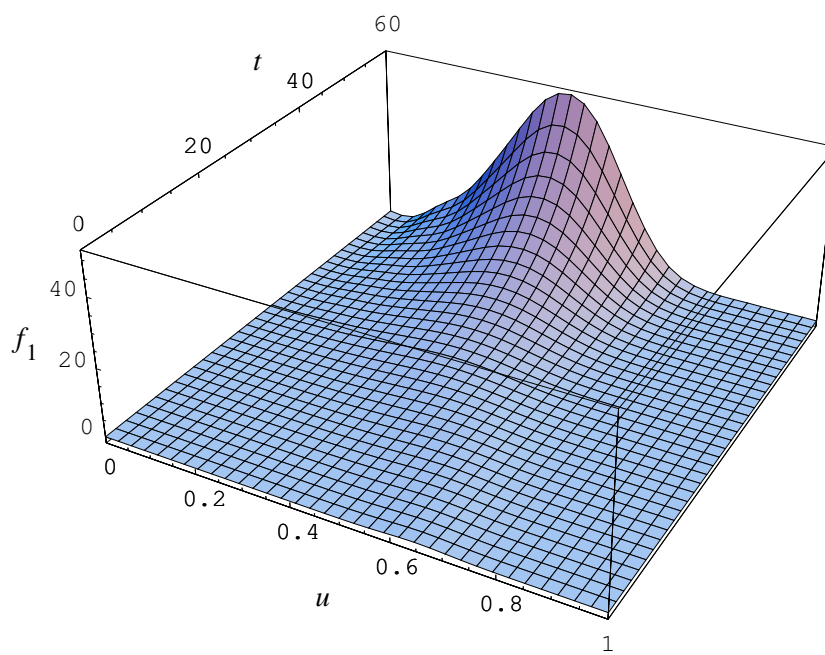

Fig. 4. Tumor cells blow up due to immune inhibition.

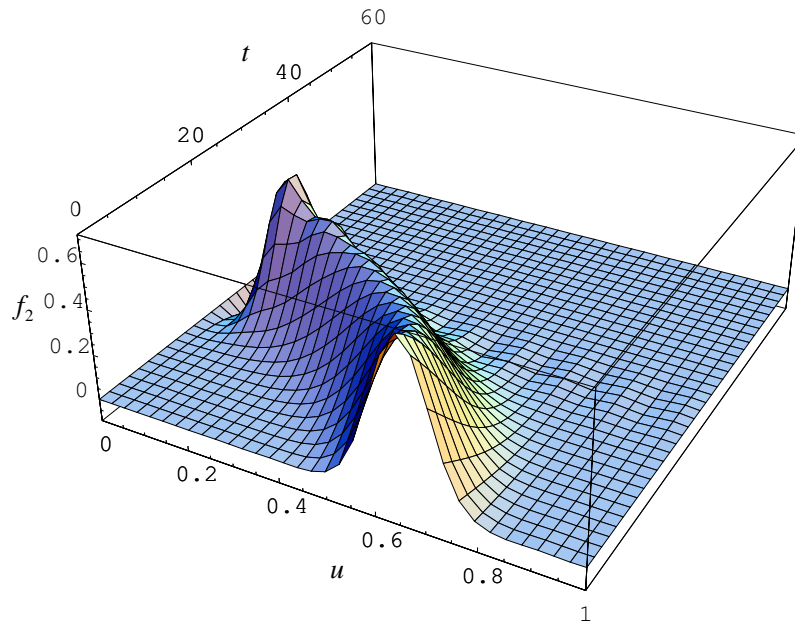

Fig. 5. Inhibition of immune cells.

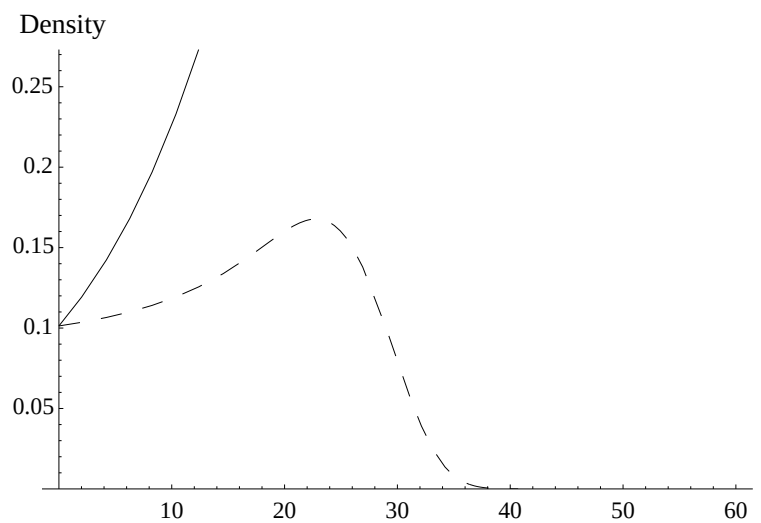

Fig. 6. Tumor blow up and immune inhibition.

Figure 6 shows the evolution in time of the densities. The continuous line is the evolution of the tumor density which increases and the dashed line is the evolution of the immune density which is completely inhibited. This situation, as already mentioned, corresponds to the case in which the immune system is able to "repair"

the progressed cells but in the competition it can be inhibited by the tumor cells. The final output, in a favorable situation for the tumor cells, i.e. considering highly progressing tumors, leads to the total inhibition of the immune cells: the distribution shifts towards negative values of the state corresponding to the inhibition.

- Figures 7 and 8 show the evolution with the same condition of the example before where the only difference consists of taking the inhibition ability of tumor cells equal to zero (or equivalently in considering strong immune cells which cannot be inhibited), i.e. $\alpha_{21} = 0$. In this case, after an initial competition which leads to an increase of the density of both immune and tumor cells, asymptotically the tumor starts to be depleted and reduced in aggressiveness once the immune density reaches a certain threshold. The final output is the total depletion of the neoplastic cells. The time evolution of the densities is reported in Fig. 9 and shows an asymptotic behavior just opposite to the one of Fig. 6.

The above simulations show both the behavior of the densities and of the distribution function. It is worth stressing that theorems provide an information on the densities. Simulations enlarge this panorama showing the detailed evolution of the distribution function, thus indicating the statistical activation of inhibition of the functions of cells.

In order to obtain a detailed quantitative description we have to identify, on the basis of experimental data, the parameters of the model and, in particular, the

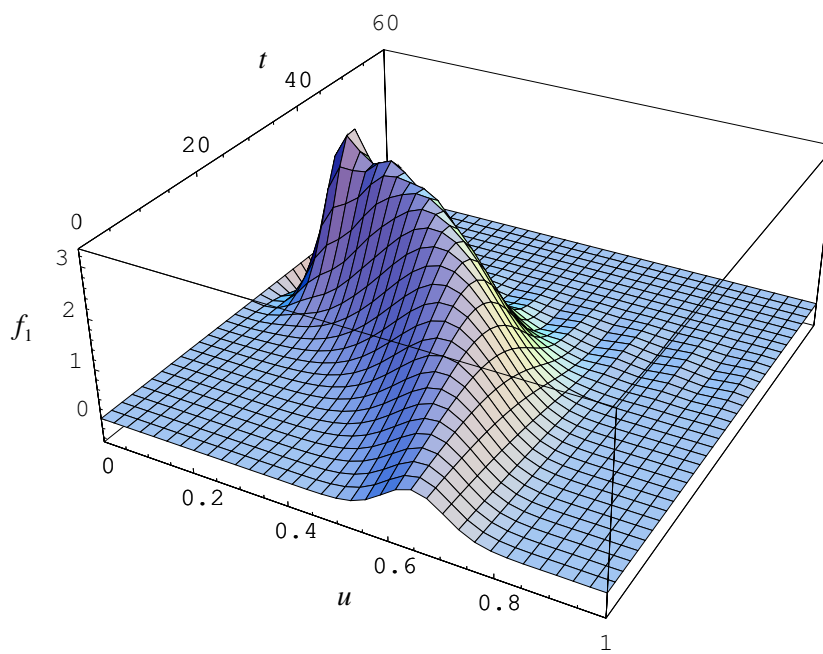

Fig. 7. Weakening and depletion of tumor cells.

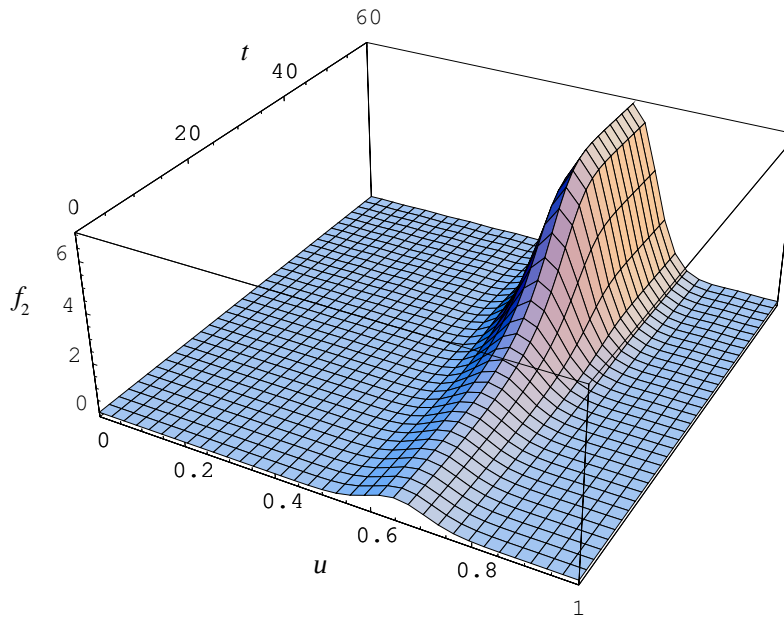

Fig. 8. Activation of immune cells.

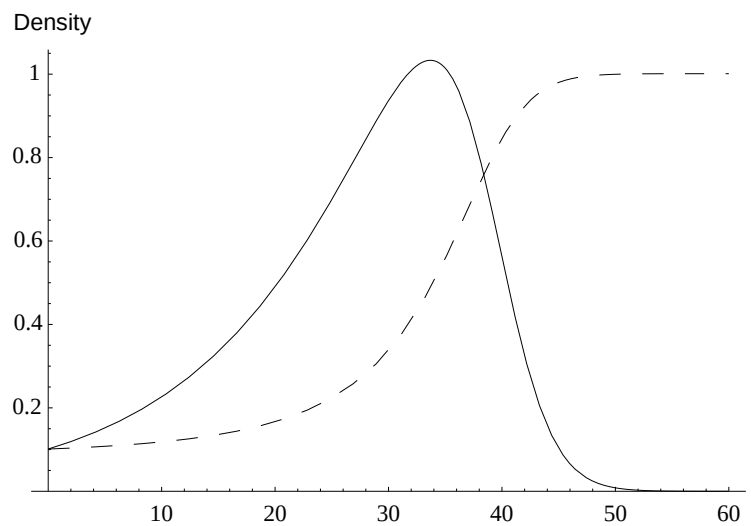

Fig. 9. Tumor competition with immune cells with final depletion of the tumor.

parameters directly related to the growth ability of tumor cells and to the defence ability of immune cells.

The methodology to achieve this result was proposed in Ref. 12. It consists in analyzing the evolution of a tumor induced in a population of immuno-depressed

mice and in a population of normal mice. The experimental results are reported in Fig. 10, indicating by triangular dots the first population and by circular dots the second population. The figure refers to a comparison with experimental results of the model proposed in Ref. 10 and reported in (5.24). A suitable comparison between experimental data and the results provided by the mathematical model allow us an identification of some parameters.

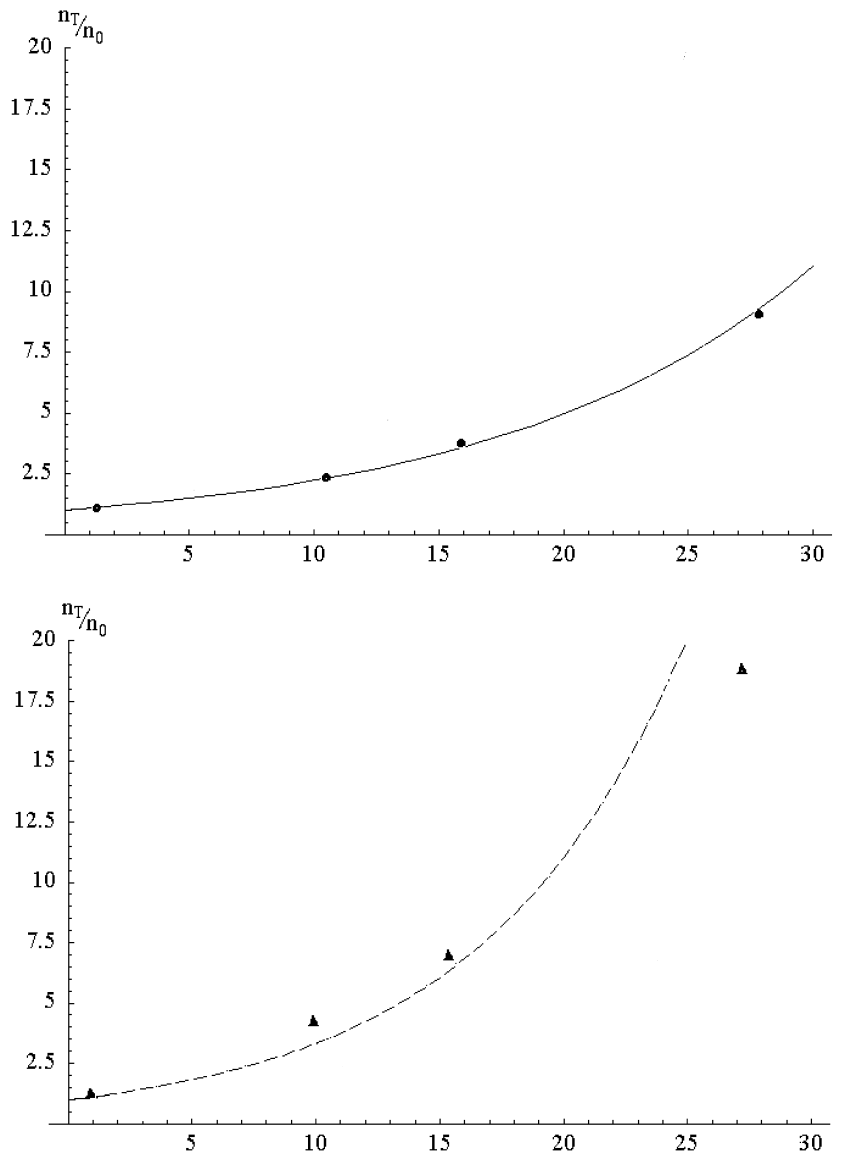

Fig. 10. Comparison between the theoretical results and the experimental data of growth of a tumor in non treated mice (dots) and in irradiated ones (triangles).

In conclusion of this section, one may stress that the model, proposed in Ref. 11, has shown to be able to capture some interesting features of the competition between tumor and immune cells. The model is characterized by six parameters each with a well-defined biological meaning related to specific cellular functions. A proper selection of biological quantities describes either the blow up of immune cells, or the activation of immune cells with progressive suppression of tumor cells. A relevant role in this game is acted by the α-type parameters related to conservative encounters which modify the microscopic state without generating phenomena with proliferation or destruction of cells. Moreover, a particular selection of the parameters may describe interesting phenomena related to the immune competition somehow different from those dealt with in this paper. A further advantage of this model is that it needs a relatively small number of parameters. The qualitative analysis developed in Ref. 11 has shown how methods of nonlinear functional analysis can be applied to predict the asymptotic behavior of the solutions with a detailed analysis of the role of the parameters of the model upon the above behavior. Simulations provide additional information considering that the evolution of the distribution function is shown, while analytic results only refer to the number density of cells. The evolution of the distribution function describes how cells concentrate over certain values of their biological functions.

The above qualitative and computational analysis provide a useful background for the modelling of therapeutical actions. That is an interesting research perspective initiated in Ref. 39 with reference to models with mean field interactions which are described in Sec. 6.

6. Mean Field Models — Prevalent Biological Interactions

This section deals with a survey and critical analysis of models based on long range microscopic interactions in the case of biologically prevalent interactions in the spatially homogeneous case. The general mathematical framework can be derived on the basis of the modelling of microscopic interactions described in Sec. 4. The structure of the evolution equation, again suppressing superscripts, is as follows:

$$\frac{\partial f_i}{\partial t}(t,\mathbf{u}) + \nabla_{\mathbf{u}} \left(\sum_{j=1}^{n} \mathcal{F}_{ij}[f] f_i \right)(t,\mathbf{u}) = f_i(t,\mathbf{u}) \sum_{j=1}^{n} \int_{D_{\mathbf{u}}} [p_{ij} - d_{ij}](\mathbf{u},\mathbf{u}_*) f_j(t,\mathbf{u}_*)\, d\mathbf{u}_* \,, \tag{6.1}$$

where

$$\mathcal{F}_{ij} = \int_{D_{\mathbf{u}}} \mathcal{P}_{ij}(\mathbf{u},\mathbf{u}_*) f_j(t,\mathbf{u}_*)\, d\mathbf{u}_* \,. \tag{6.2}$$

Specific models are obtained after a detailed modelling of the microscopic interaction terms. In particular, let the action $\mathcal{F}_{ij}$ be computed as indicated by Eq. (4.6),

and the source term by Eq. (4.7), then the formal expression of the specific models have been obtained on the basis of a detailed mathematical description of the microscopic interactions terms. In particular, the model proposed in Ref. 36 refers to a system of three interaction populations: tumor, immune and endothelial cells. The assumptions which have generated the model are similar to those described in Sec. 5 with reference to the model based on short range interactions.

A qualitative analysis, proposed in Ref. 37, shows that the parameter related to the ability of tumor cells to inhibit immune cells pays a role analogous to the one we have seen in Sec. 5. Namely, there exists a critical value separating two different asymptotic behaviors:

— blow up of tumor cells with progressive inhibition of immune cells;
— progressive destruction of tumor cells due to an active immune system.

The simulations developed in Ref. 38 visualize the above behavior showing an evolution of the distribution functions qualitatively similar to the one shown in Figs. 4–9. The essential differences between the two classes of models (short and long ranges of interaction) have been critically analyzed in Ref. 41. A revisiting of the model has been proposed in Ref. 32 in order to take into account the natural trend to a sentinel level of immune cells when tumor cells have been eventually destroyed.

On the other hand, the above reviewed models do not take into account the transition of endothelial cells from the state of normal cells to progressing state. Therefore the competition is described only if a suitable initial condition for the tumor cell population is assigned. This consideration suggests to develop models with long range interactions in the framework of the theory of progression dealt with in Sec. 5.

The motivation to develop models in the case of long range interaction is not so obvious in the case of spatially homogeneous case with predominant biological interactions. On the other hand, dealing with phenomena where mechanical interactions play a relevant role may take advantage of the mean field description with the modelling of cell dynamics by interaction potentials. An account of the above modelling will be given in Sec. 7, while the contents of this section are limited to the above survey. The interested reader is referred, as already mentioned, to the review paper Ref. 25 for additional technical information.

7. Models with Space Dynamics and Asymptotic Theory

The analysis developed in the preceding section was essentially devoted to models of cellular populations homogeneously distributed in space. On the other hand, dealing with models including the analysis of cell dynamics in space is important due to various reasons. In particular:

(i) The analysis provides the description of several interesting phenomena related to tumor growth and developments. For instance, aggregation of tumor cells

into solid forms, formation of capillary sprouts from blood vessels, penetration of immune cells into aggregated tumor cells, detachment of metastases, etc.

(ii) The development of an asymptotic theory for cellular systems analogous to that of the mathematical kinetic theory, e.g. Refs. 29 and 74, allows to describe the evolution of locally averaged variables when cells aggregate into solid forms. This derivation should replace the purely phenomenological one which is at present available in the literature.

The existing literature offers a variety of interesting approaches to the macroscopic modelling. Among several ones, some recent contributions can be mentioned (without claim of completeness) with direct reference to the above problems. Specifically, the paper of Levine, Pamuk, Sleeman, and M. Nilsen-Hamilton[61] has the merit of capturing by macroscopic equations a large variety of interesting phenomena such as formation of capillary sprouts from blood vessels; additional developments can be recovered in Ref. 62. At least part of the derivation of the above cited papers is founded on a detailed analysis of microscopic equations. A qualitative analysis of some properties of the solutions is proposed in a paper by Pamuk.[71] De Angelis and Preziosi's paper[35] applies mixture theory (classical in continuum mechanics) to close the conservation equations needed to describe the system. This paper shows how the evolution of the system from the avascular to the vascular case can be described by the same set of equations related to a moving boundary problem. Various papers by Owen and Sherrat, e.g. Refs. 69 and 70, deal with the analysis of coexisting microscopic and macroscopic phenomena, that is the penetration of immune cells into aggregated forms. A computational analysis can be found in the papers by Valenciano and Chaplain.[78,79] All the above approaches need to deal with continuum mechanics problems for variable mass materials, e.g. Refs. 54 and 6. Modelling is occasionally related to the description of therapeutical actions such as the control of angiogenesis.[56]

The above papers have been cited mainly to motivate the development of mathematical methods toward multiscale representation. The interested reader can recover additional bibliography on macroscopic type modelling in the review papers: Refs. 3, 31 and 25. Recently multiscale modelling has been developed with in the framework of cellular automata linked to classical differential models, e.g. Refs. 1 and 33, see also the general background offered in Ref. 34. However, the existing literature on kinetic models with space structure is somehow limited. A technical difficulty, despite the great deal of theoretical and experimental activity in the field, see among others Refs. 28, 80 and 40, refers to modelling the cell motion.[4]

This section, which refers to the contents of boxes β and γ of the flow chart of Fig. 3, is organized into three subsections. The first one deals with the modelling of space dynamics for both classes on equations proposed in the previous sections (short range and mean field interactions); the second one with the methodological approach to derivation of macroscopic equations in the case of models with short range interactions; the third one develops a critical analysis of the gap between

phenomenological derivation of macroscopic equations and the one obtained from an asymptotic theory from the microscopic to the macroscopic description. The above contents critically analyze a few results available in the literature and provide conceivable hints to future research activity.

7.1. *On the modelling space dynamics*

Modelling multicellular systems for cells with a microscopic state which includes the space variables, in addition to the biological functions, is certainly a relevant, however challenging, research target. Indeed, it is the fundamental step to design a mathematical theory of multicellular systems. Models may be able to describe not only the immune competition, but also cell motions, migration with aggregation and fragmentation phenomena.

The main difficulty to deal with the above problem consists of modelling the interactions between mechanical and biological variables to define the overall dynamics of the cell. Due to this difficulty, only some preliminary studies are available in the literature. This subsection reports on two different approaches recently proposed in the literature. The first one refers to short range interactions, while the second one to mean field interactions.

The first model was proposed in Ref. 18, based on the analysis developed in a sequel of papers by Hillen and Othmer,[51,52] and Hillen.[53] The basic assumption is the one already summarized in Sec. 4: cells interact at the biological level with a rate η, while mechanical interactions occur with a rate ν independently superposed to biological interactions. Then, recalling Eq. (4.12), the framework for n-population dynamics, which generalizes to space dynamics the one of Eq. (5.1), is the following:

$$\begin{aligned}
&\frac{\partial}{\partial t} f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) \\
&\quad = \nu \sum_{j=1}^{n} \left[\int_{D_{\mathbf{v}}} T_{ij}(\mathbf{v},\mathbf{v}^*) f_j(t,\mathbf{x},\mathbf{v}^*,\mathbf{u}) - T_{ji}(\mathbf{v}^*,\mathbf{v}) f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) \right] d\mathbf{v}^* \\
&\qquad + \sum_{j=1}^{n} \Bigg(\int_{D_{\mathbf{u}}^2 \times D_{\mathbf{v}}} \eta_{ij}(\mathbf{u}_1,\mathbf{u}_2) A_{ij}(\mathbf{u}_1,\mathbf{u}_2;\mathbf{u}) f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}_1) \\
&\qquad \times f_j(t,\mathbf{x},\mathbf{v}_2,\mathbf{u}_2)\, d\mathbf{v}_2\, d\mathbf{u}_1\, d\mathbf{u}_2 \\
&\qquad - f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) \int_{D_{\mathbf{u}} \times D_{\mathbf{v}}} \eta_{ij}(\mathbf{u},\mathbf{u}_2) f_j(t,\mathbf{x},\mathbf{v}_2,\mathbf{u}_2)\, d\mathbf{v}_2\, d\mathbf{u}_2 \Bigg),
\end{aligned} \tag{7.1}$$

which can be formally written as follows:

$$\partial_t f + \mathbf{v}\cdot\nabla_{\mathbf{x}} f = \nu \mathcal{L} f + \eta \mathcal{N}[f,f] + \alpha S[f]\,, \tag{7.2}$$

In Eqs. (7.1) and (7.2) ν is the turning rate or turning frequency (hence $\tau = \frac{1}{\nu}$ is the mean run time), and $T(\mathbf{v},\mathbf{v}^*)$ is the probability kernel for the new velocity $\mathbf{v} \in D_{\mathbf{v}}$ given the previous velocity was $\mathbf{v}^*$. The above notation corresponds to the

assumptions 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 symmetric (i.e. $\mathbf{v} \in D_{\mathbf{v}} \Rightarrow -\mathbf{v} \in D_{\mathbf{v}}$).

More in details an interesting biological regime is met when quantities ruling the biological dynamics, i.e. η and the parameter α, are of a smaller order with respect to the mechanical one, i.e. ν. Let $\eta = \varepsilon^r$, $\alpha = \varepsilon^q$, with $r \geq 1$, $q \geq 1$ and $\nu = \frac{1}{\varepsilon^p}$, with $p \geq 1$, where ε is dealt with as a small parameter which goes to zero to obtain the continuum mechanics description. In addition, the diffusion scale time $\tau = \varepsilon t$ is used so that the following rescaled equation is obtained:

$$\varepsilon \partial_t f + \mathbf{v} \cdot \nabla_{\mathbf{x}} f = \frac{1}{\varepsilon^p} \mathcal{L} f + \varepsilon^r \mathcal{N}[f, f] + \varepsilon^q S(f)\,. \tag{7.3}$$

It is obvious that the above modelling shows the drawback of the independence between mechanical and biological interactions. This is not always true considering that cells show a different mechanical behavior according to their biological state. Hence model (7.1) [or (7.3)] is meaningful at a formal level, while the general framework may be critically discussed.

Due to the above remarks and criticism, an alternative framework is proposed in Ref. 20 based on long range interactions. According to Ref. 20, the motion of cells is determined by interaction potentials which identify the mutual actions between cells. When the modelling of microscopic actions generate suitable models of the terms $\mathcal{F}_{ij}$, defined in Eq. (4.6) in a relatively simpler case, then the formal expression of the evolution equation is as follows:

$$\begin{aligned}
&\frac{\partial}{\partial t} f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) + \mathbf{v} \cdot \nabla_{\mathbf{x}} f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \\
&\qquad + \sum_{j=1}^{n} \nabla_{\mathbf{v}} (\mathcal{F}_{ij}^m[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, \mathbf{u}) f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u})) \\
&\qquad + \sum_{j=1}^{n} (\nabla_{\mathbf{u}} \mathcal{F}_{ij}^b[\mathbf{f}](t, \mathbf{x}, \mathbf{u}) f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u})) \\
&= f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \sum_{j=1}^{n} \int_{\mathcal{D}} \sigma_{ij}(\mathbf{u}, \mathbf{u}_*) f_j(t, \mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)\, d\mathbf{x}_*\, d\mathbf{v}_*\, d\mathbf{u}_*\,,
\end{aligned} \tag{7.4}$$

where the transport and source terms have been generalized, under further assumption of superposition of the mechanical and biological actions, as follows:

$$\mathcal{F}_{ij}^m[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, \mathbf{u}) = \int_{\mathcal{D}} \mathcal{P}_{ij}^m(\mathbf{x}, \mathbf{x}_*, \mathbf{v}, \mathbf{v}_*, \mathbf{u}, \mathbf{u}_*) f_j(t, \mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)\, d\mathbf{x}_*\, d\mathbf{v}_*\, d\mathbf{u}_*\,, \tag{7.5}$$

$$\mathcal{F}_{ij}^b[\mathbf{f}](t, \mathbf{x}, \mathbf{u}) = \int_{\mathcal{D}} \mathcal{P}_{ij}^b(\mathbf{u}, \mathbf{u}_*) f_j(t, \mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)\, d\mathbf{x}_*\, d\mathbf{v}_*\, d\mathbf{u}_* \tag{7.6}$$

and

$$\mathcal{S}_{ij}[\mathbf{f}](t, \mathbf{x}, \mathbf{u}) = \int_{\mathcal{D}} \sigma_{ij}(\mathbf{u}, \mathbf{u}_*) f_j(t, \mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)\, d\mathbf{x}_*\, d\mathbf{v}_*\, d\mathbf{u}_*\,. \tag{7.7}$$

Specific models are proposed and analyzed in Ref. 20. In particular, the term $\mathcal{F}_{ij}^m$ is related to the distance between the interacting cells, with a shape identified by the biological state of the interacting pair. Moreover, it is assumed that the following cell pairs: tumor–environmental, tumor–tumor, and tumor–active immune cells, are subject to attractive forces, while the other pairs ignore each other. Additional literature on the modelling of interaction potentials between pairs of cells is given in Ref. 68.

7.2. *On the derivation of macroscopic equations*

The need of developing an asymptotic theory for the biological system we are dealing with was already motivated in the above introduction to this section. It is not an easy task due to various technical difficulties which do not allow a straightforward application of methods of classical kinetic theory commonly used (even recently e.g. Refs. 64, 23 and 24) to obtain hydrodynamic equations from different (classical, quantum, and discrete) models of the kinetic theory of gases. On the other hand, referring to biological systems only a few results are available in the literature, e.g. Refs. 18, 47, 44, 53, 60 and 74, related to very specific models while a general methodological approach is not yet available.

A brief account of the analysis developed in Ref. 18 is given with the aim to show how different scalings lead to different macroscopic equations. This is an interesting result for biological applications somehow in contrast with the heuristic approach that is developed without having selected each class of macroscopic equation on the basis of the rates along which the relevant biological processes effectively evolve. The above result is technically shown, to avoid heavy notations, for a system of one equation only. The generalization to systems of equations can be technically developed following Ref. 21.

Some properties of the operators in (7.3) are needed in order to deal with the asymptotic analysis. Referring to Ref. 18 for the proof, the following properties can be stated:

Property 7.1. Let $h, g, N : D_{\mathbf{v}} \longrightarrow \mathbf{R}$, and let

$$\Psi_1[N] = \frac{T(\mathbf{v}, \mathbf{v}^*)N(\mathbf{v}^*) + T(\mathbf{v}^*, \mathbf{v})N(\mathbf{v})}{2}\,, \tag{7.8a}$$

and

$$\Psi_2[N] = \frac{T(\mathbf{v}, \mathbf{v}^*)N(\mathbf{v}^*) - T(\mathbf{v}^*, \mathbf{v})N(\mathbf{v})}{2}\,. \tag{7.8b}$$

Moreover, let us denote the symmetric and antisymmetric parts of $T(\mathbf{v}, \mathbf{v}^*)N(\mathbf{v}^*)$, respectively; then, operator $\mathcal{L}$ satisfies the following relation

$$\begin{aligned}\int_{D_{\mathbf{v}}} \mathcal{L}(Ng)\frac{h(\mathbf{v})}{N(\mathbf{v})}\,d\mathbf{v} = {} & \frac{1}{2}\int_{D_{\mathbf{v}}}\int_{D_{\mathbf{v}}} \Psi_1[N](g^* - g)\left(\frac{h(\mathbf{v})}{N(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{N(\mathbf{v}^*)}\right) \\ & + \frac{1}{2}\int_{D_{\mathbf{v}}}\int_{D_{\mathbf{v}}} \Psi_2[N](g + g^*)\left(\frac{h(\mathbf{v})}{N(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{N(\mathbf{v}^*)}\right).\end{aligned} \tag{7.9}$$

Moreover, the analysis needs the following assumption on the turning operator:

Assumption 7.1. There exists a bounded velocity distribution $M(\mathbf{v}) > 0$, independent of $\mathbf{x}$, and t, such that the detailed balance

$$T(\mathbf{v}^*, \mathbf{v})M(\mathbf{v}) = T(\mathbf{v}, \mathbf{v}^*)M(\mathbf{v}^*) \tag{7.10}$$

holds. The flow produced by this equilibrium distribution vanishes, and M is normalized:

$$\int_{D_\mathbf{v}} M(\mathbf{v})\, d\mathbf{v} = 1\,, \quad \int_{D_\mathbf{v}} \mathbf{v}M(\mathbf{v})\, d\mathbf{v} = 0\,. \tag{7.11}$$

The kernel $T(\mathbf{v}, \mathbf{v}^*)$ is bounded, and there exists a constant $\sigma > 0$ such that

$$T(\mathbf{v}, \mathbf{v}^*) \geq \sigma M\,, \quad \forall\, (\mathbf{v}, \mathbf{v}^*) \in D_\mathbf{v} \times D_\mathbf{v}\,. \tag{7.12}$$

Property (7.9) with (7.10) give the following:

Property 7.2. The operator $\mathcal{L}$ satisfies the following equality

$$\int_{D_\mathbf{v}} \mathcal{L}(f)\frac{h(\mathbf{v})}{M(\mathbf{v})}\, d\mathbf{v} = -\frac{1}{2}\int_{D_\mathbf{v}}\int_{D_\mathbf{v}} \Psi_1[M]\left(\frac{f(\mathbf{v})}{M(\mathbf{v})} - \frac{f(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right) \times \left(\frac{h(\mathbf{v})}{M(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right) d\mathbf{v}\, d\mathbf{v}^*\,, \tag{7.13}$$

which shows that the operator $\mathcal{L}$ is self-adjoint with respect to the scalar product in the space $L^2(D_\mathbf{v}, \frac{d\mathbf{v}}{M})$.

In particular, from (7.13), the following equality is obtained:

$$\int_{D_\mathbf{v}} \mathcal{L}(h)\frac{h(\mathbf{v})}{M(\mathbf{v})}\, d\mathbf{v} = -\frac{1}{2}\int_{D_\mathbf{v}}\int_{D_\mathbf{v}} \Psi_1[M]\left(\frac{h(\mathbf{v})}{M(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right)^2 d\mathbf{v}^* \tag{7.14}$$

which holds true for $h \in L^2(V, \frac{d\mathbf{v}}{M})$, and the equation $\mathcal{L}(h) = f$ has a unique solution $h \in L^2(D_\mathbf{v}, \frac{d\mathbf{v}}{M})$ satisfying

$$\int_{D_\mathbf{v}} h d\mathbf{v} = 0 \quad \text{if and only if} \quad \int_{D_\mathbf{v}} f d\mathbf{v} = 0\,. \tag{7.15}$$

In particular, as a consequence, the following equation:

$$\mathcal{L}(\theta) = \mathbf{v}M(\mathbf{v}) \tag{7.16}$$

has a unique solution $\theta \in L^2(V, \frac{d\mathbf{v}}{M})$. This is due to (7.11).

The diffusive/hydrodynamics asymptotic limit of Eq. (7.3) can be investigated, as shown in Ref. 18, by different methods. Nevertheless, the method of moments has shown relatively greater generality. Let $f_\varepsilon(t, \mathbf{x}, \mathbf{v}, \mathbf{u})$ be a sequence of solutions to the scaled kinetic equation (7.3) such that f_ε converges in the distributional sense to a function f as ε goes to zero. Furthermore, assume that all moments of $f_\varepsilon, \mathcal{N}[f_\varepsilon, f_\varepsilon]$ and $S(f_\varepsilon)$ converge to the corresponding moments in the distributional sense. Multiplying Eq. (7.3) by ε^p, letting ε go to zero, and using the moment

convergence assumptions yields the relation $\mathcal{L}(f) = 0$, which implies that $f \in \mathrm{Ker}(\mathcal{L})$ and thus it can be written as $f(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) = M(\mathbf{v})\rho(t, \mathbf{x}, \mathbf{u})$. Integrating Eq. (7.3) in $\mathbf{v}$, and using the fact that $\int_{D_\mathbf{v}} \mathcal{L} f_\varepsilon \, d\mathbf{v} = 0$, one obtains

$$\partial_t \langle f_\varepsilon \rangle + \left\langle \frac{\mathbf{v} \cdot \nabla_\mathbf{x} f_\varepsilon}{\varepsilon} \right\rangle = \varepsilon^{r-1} \langle \mathcal{N}[f_\varepsilon, f_\varepsilon] \rangle + \varepsilon^{q-1} \langle S(f_\varepsilon) \rangle \,. \tag{7.17}$$

The asymptotic limit of $\langle \frac{\mathbf{v} \cdot \nabla_\mathbf{x} f_\varepsilon}{\varepsilon} \rangle$ has to be estimated to recover the limit in (7.17). Therefore, consider the identity

$$\left\langle \frac{\mathbf{v} \cdot \nabla_\mathbf{x} f_\varepsilon}{\varepsilon} \right\rangle = \nabla_\mathbf{x} \cdot \left\langle \frac{M(\mathbf{v}) \mathbf{v} f_\varepsilon}{\varepsilon M(\mathbf{v})} \right\rangle . \tag{7.18}$$

Then, using identity (7.16), and recalling from Property 7.2 that $\mathcal{L}$ is self-adjoint in $L^2(D_\mathbf{v}, \frac{d\mathbf{v}}{M(\mathbf{v})})$, yields

$$\left\langle \frac{\mathbf{v} \cdot \nabla_\mathbf{x} f_\varepsilon}{\varepsilon} \right\rangle = \nabla_\mathbf{x} \cdot \left\langle \frac{\mathcal{L}(\theta) f_\varepsilon}{\varepsilon M(\mathbf{v})} \right\rangle = \nabla_\mathbf{x} \cdot \left\langle \frac{\theta \mathcal{L}(f_\varepsilon)}{\varepsilon M(\mathbf{v})} \right\rangle . \tag{7.19}$$

Eliminating $\mathcal{L} f_\varepsilon$ and using Eq. (7.3), yields

$$\frac{1}{\varepsilon} \mathcal{L}(f_\varepsilon) = \varepsilon^p \partial_t f_\varepsilon + \varepsilon^{p-1} \mathbf{v} \cdot \nabla_\mathbf{x} f_\varepsilon - \varepsilon^{p+r-1} \mathcal{N}[f_\varepsilon, f_\varepsilon] - \varepsilon^{p+q-1} S(f_\varepsilon) \,. \tag{7.20}$$

Finally, combining (7.19) and (7.20), the following identity is obtained

$$\left\langle \frac{\mathbf{v} \cdot \nabla_\mathbf{x} f_\varepsilon}{\varepsilon} \right\rangle = \nabla_\mathbf{x} \cdot \left\langle \frac{\theta}{M} (\varepsilon^p \partial_t f_\varepsilon + \varepsilon^{p-1} \mathbf{v} \cdot \nabla_\mathbf{x} f_\varepsilon \right.$$
$$\left. - \varepsilon^{p+r-1} \mathcal{N}[f_\varepsilon, f_\varepsilon] - \varepsilon^{p+q-1} S(f_\varepsilon)) \right\rangle . \tag{7.21}$$

Developing the moment analysis leads to the following:

Theorem 7.1. *Let $f_\varepsilon(t, \mathbf{x}, \mathbf{v}, \mathbf{u})$ be a sequence solutions to the scaled kinetic equation (7.3) such that f_ε converges in the distributional sense to a function f as ε goes to zero. Furthermore, assume that the moments*

$$\langle f_\varepsilon \rangle \,, \quad \left\langle \frac{\theta(\mathbf{v})}{M(\mathbf{v})} \otimes \mathbf{v} f_\varepsilon \right\rangle , \quad \langle \mathcal{N}[f_\varepsilon, f_\varepsilon] \rangle \,, \quad \langle S(f_\varepsilon) \rangle \,,$$

converge in $D'(t, \mathbf{x}, \mathbf{u})$ to the corresponding moments

$$\langle f \rangle \,, \quad \left\langle \frac{\theta(\mathbf{v})}{M(\mathbf{v})} \otimes \mathbf{v} f \right\rangle , \quad \langle \mathcal{N}[f, f] \rangle \,, \quad \langle S(f) \rangle \,,$$

and, in addition, all small terms formally vanish. Then the asymptotic limit has the form:

$$f(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) = M(\mathbf{v}) \rho(t, \mathbf{x}, \mathbf{u}) \,, \tag{7.22}$$

where $\rho(t, \mathbf{x}, \mathbf{u})$, *in different cases, is the weak solution of the following equations*:

$$p = q = r = 1 : \partial_t \rho + \nabla_{\mathbf{x}} \cdot \langle \mathbf{v} \otimes \theta(\mathbf{v}) \cdot \nabla_{\mathbf{x}} \rho \rangle = \langle M^2 \rangle_{\mathbf{v}} \mathcal{N}[\rho, \rho] + \langle S(M\rho) \rangle_{\mathbf{v}} \,, \quad (7.23)$$

$$p = r = 1 \,, \quad q > 1 : \partial_t \rho + \nabla_{\mathbf{x}} \cdot \langle \mathbf{v} \otimes \theta(\mathbf{v}) \cdot \nabla_{\mathbf{x}} \rho \rangle = \langle M^2 \rangle_{\mathbf{v}} \mathcal{N}[\rho, \rho] \,, \quad (7.24)$$

$$p = q = 1 \,, \quad r > 1 : \partial_t \rho + \nabla_{\mathbf{x}} \cdot \langle \mathbf{v} \otimes \theta(\mathbf{v}) \cdot \nabla_{\mathbf{x}} \rho \rangle = \langle S(M\rho) \rangle_{\mathbf{v}} \,, \quad (7.25)$$

$$r > 1 \,, \quad q > 1 \,, \quad p = 1 : \partial_t \rho + \nabla_{\mathbf{x}} \cdot \langle \mathbf{v} \otimes \theta(\mathbf{v}) \cdot \nabla_{\mathbf{x}} \rho \rangle = 0 \,, \quad (7.26)$$

$$r = q = 1 \,, \quad p > 1 : \partial_t \rho = \langle M^2 \rangle_{\mathbf{v}} \mathcal{N}[\rho, \rho] + \langle S(M\rho) \rangle_{\mathbf{v}} \,, \quad (7.27)$$

$$p > 1 \,, \quad q > 1 \,, \quad r = 1 : \partial_t \rho = \langle M^2 \rangle_{\mathbf{v}} \mathcal{N}[\rho, \rho] \,, \quad (7.28)$$

$$p > 1 \,, \quad r > 1 \,, \quad q = 1 : \partial_t \rho = \langle S(M\rho) \rangle_{\mathbf{v}} \,, \quad (7.29)$$

$$p > 1 \,, \quad q > 1 \,, \quad r > 1 : \partial_t \rho = 0 \,. \quad (7.30)$$

The biological interpretation is that the diffusion process, which may generate invasion, only occurs when biological interactions become predominant with respect to mechanical ones. It is plain that further useful information can be obtained by an analysis where the rate of activity of the source term, corresponding to the parameter η, is different from the one of the other biological interaction.

Theorem 7.1 can be exploited, using the same technique of Ref. 18, to find the possible asymptotic limit equations. In details, let $M\rho(t, \mathbf{x}, u)$ be an approximation of f_ε, then some specific cases, among several ones, of different evolution equations for the density ρ are reported in what follows. Specifically, the result of the technical application of the above method is reported for three different regimes. As we shall see, the more the biological interaction rate grows with respect to the mechanical one, the more the macroscopic evolution equation shifts from a diffusion process to a local mass evolution.

I. The following nonlinear diffusion equation is derived for $p = q = r = 1$, $\eta \cong \alpha \cong \varepsilon$, $\nu \cong \frac{1}{\eta} \cong \frac{1}{\varepsilon}$:

$$\partial_t \rho + \nabla_{\mathbf{x}} \cdot \langle \mathbf{v} \otimes \theta(\mathbf{v}) \cdot \nabla_{\mathbf{x}} \rho \rangle = \langle M^2 \rangle_{\mathbf{v}} \mathcal{N}[\rho, \rho] + \langle S(M\rho) \rangle_{\mathbf{v}} \,, \quad (7.31)$$

where the function θ is given by (7.16).

II. Linear diffusion is obtained for $r > 1$, $q > 1$, and $p = 1$ with $\eta \cong \alpha \cong \varepsilon^r$, $\nu \cong \frac{1}{\varepsilon}$:

$$\partial_t \rho + \nabla_{\mathbf{x}} \cdot \langle \mathbf{v} \otimes \theta(\mathbf{v}) \cdot \nabla_{\mathbf{x}} \rho \rangle = 0 \,. \quad (7.32)$$

This means that the ratios with respect to ν of rates of biological interactions are of a smaller order with respect of the one which generates Eq. (7.31). This means that the diffusion process takes place only if the rate of biological interactions overcomes a critical value.

III. Nonlinear evolution equations are obtained for $r = q = 1$, and $p > 1$ with $\eta \cong \alpha \cong \varepsilon$, $\nu \cong \frac{1}{\eta^p} \cong \frac{1}{\varepsilon^p}$:

$$\frac{\partial \rho}{\partial t} = \langle M^2 \rangle_{\mathbf{v}} \mathcal{N}[\rho, \rho] + \langle S(M\rho) \rangle_{\mathbf{v}} \,. \tag{7.33}$$

This corresponds to the opposite situation with respect to the previous two cases: the rate of mechanical interactions become relatively greater than those corresponding to Cases I and II.

7.3. *Critical analysis*

A critical analysis needs to be developed with reference to the mathematical problems dealt with in this section. The main criticisms is that the problem of modelling the dynamical behavior of cells is not yet solved in a satisfactory way. Indeed models which describe the mechanics of cell motion by a stochastic jump process, such as those reported in Sec. 7.1, should be replaced by a relatively more detailed description based on a microscopic analysis such as the one qualitatively reported in the same subsection.

An additional technical difficulty, which cannot be hidden, is that the modelling should also be able to describe aggregation and fragmentation phenomena which, as documented in a broad literature, e.g. Ref. 65, and therein cited papers, can be modelled by kinetic type equations. Again, the main difficulty consists in referring the above phenomena to the biological properties of cells. Then, the derivation of the macroscopic equation may follow the same methodological lines reported in Sec. 7.2. In any case, the structure of macroscopic equations depends on the scaling related to the mechanical and biological processes. This essentially means that, although transferring this idea into a proper research program is not a simple task, a microscopic analysis is absolutely necessary to recover the correct macroscopic equations otherwise obtained by the reasoning typical of continuum mechanics.[6,54] Finally, let us remark that a relevant target of the interaction between mathematics and biology is also to look at the modelling of cellular and macroscopic phenomena in the presence of therapeutical actions, which play a relevant role at both scales.

8. Perspectives

The contents of this paper deal with a critical analysis of the mathematical results available in the literature concerning models which describe multicellular systems with special attention to the modelling by methods of the mathematical kinetic theory. The main aim was, all along the paper, the analysis of a mathematical theory to model complex biological systems constituted by several interacting cell populations. The analysis of the passage from the microscopic to the macroscopic description is one of the relevant aspects of the above topics.

The above analysis clearly indicates the great complexity of the system we are dealing with, and that a variety of analytical and modelling problems are still open despite the effort of applied mathematicians who have dedicated a great deal of their research activity to the above problems.

A general question can be naturally posed: *Which are the relevant research perspectives that can be identified out of the above critical analysis*?

Rather than providing a list of open problems (it has to be recognized that almost all topics are somehow still open to further developments), it can be stated that the main effort should be addressed to develop a mathematical theory suitable to describe the relevant phenomena related to complex biological systems with special attention to the specific one dealt with in this paper.

The mathematical results reported in the preceding sections already contain features which are typical of a mathematical theory. On the other hand, the general framework is not yet complete. Bearing this in mind, consider a few specific aspects (among several ones) which have to be properly developed toward the above objective.

- Starting from the idea that the statistical representation by methods of the mathematical kinetic theory is the proper way of representing the system, some related topics still have to be developed. For instance, the complexity of the system needs to be reduced without losing the relevant information. Specifically, the number of populations has to be selected in the model. Such number is certainly lower than those populations which play the game, however the model should still be able to describe the qualitative and quantitative behavior of the phenomena which are typical of multicellular systems. The same reasoning applies to cell interactions: the relevant events concerning cell interactions have to be selected among a large variety of interactions, still without losing the ability to describe the most relevant phenomena.
- Modelling of cell interactions should be developed by theoretical methods rather than various phenomenological descriptions available in the literature. Indeed, it is an unavoidable passage to go through if one has in mind the objective of the development of a mathematical theory.
- Two types of conceivable kinetic representations have been analyzed, specifically related to short range and mean field interactions. Suitable criteria have still to be defined to select the relatively more correct representation. Actually, both of them appear to be equivalent in the spatially homogeneous case. On the other hand, mean field interactions may intuitively appear consistent with the ability of cells to feel the presence of other cells even at a certain distance. The analysis of this topic should be related to the modelling of microscopic interactions mentioned in the preceding item.
- The multiscale representation is definitely a crucial aspect of the development of a mathematical theory. The contents of Sec. 7 have shown how kinetic equations lead, at least in a formal way, to the corresponding macroscopic equations. Still one has to develop an analysis directly referred to models existing in the literature. This means selecting for both representations the various populations which play the game and deriving the macroscopic representation for each of them. On the other hand, even when the proper macroscopic evolution equations

are derived, the system often shows the presence of phenomena coexisting at different representation scales.

Definitely the above problems are dealt with in the near future and some of them will be hopefully solved. Waiting for these mathematical results, we wish to revisit some of the sentences proposed in the first part of this paper to show how the contents of this paper is effectively related to the suggestions proposed there.

- Referring to the paper by Hartwell *et al.*[50]:
  Although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiate biology from other natural sciences.

  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. More important, what really distinguish biology from physics are survival and reproduction, and the concomitant notion of function.

A conceivable way to model the above-mentioned functions has been realized by introducing the biological state **u** into the set of variables modelling the microscopic state. Selecting a limited number of populations which play the game has to be interpreted as a way to reduce complexity. Reproduction and destruction events have been modelled based on a direct connection with the biological state. This aspect identifies the substantial difference between classical models of population dynamics, e.g. Refs. 66 and 67, and the class of models dealt with in this paper.

- Referring to some sentences that can be quoted from the paper by Gatenby and Maini.[46] The first one refers to the so-called Vogelgram theory:
  These models might, for example, adapt methods of game theory and population biology to frame the "Vogelgram" mathematically as a sequence of competing populations that are subject to random mutations while seeking optimal proliferative strategies in a changing adaptative landscape. The phenotypic expression of each mutation interacts with specific environmental selection factors that confer a proliferative advantage or disadvantage. Such models will generate far less predictable (and more biologically realistic) system behavior, including multiple possible genetic pathways and timeliness in the somatic evolution of invasive cancer.

Cells play a game with complex rules to be defined after a deep analysis of biological phenomena. Providing a detailed description of these rules means understanding the overall behavior of the biological system. Section 5 has reported about two specific models developed on the basis of a phenomenological modelling

of the above rules. Hopefully an immuno-mathematical theory can be developed exploiting the above preliminary approach.

Going on into the contents of this interesting paper, one may recover again various motivations and suggestions to develop an immuno-mathematical theory for multicellular systems.

Existing mathematical models may not be entirely correct. But they represent the necessary next step beyond simple verbal reasoning and linear intuition. As in physics, understanding the complex, nonlinear systems in cancer biology will require ongoing interdisciplinary, interactive research in which mathematical models, informed by extant data and continuously revised by new information, guide experimental design and interpretation.

It is plain that cells do not follow the rules of Newtonian mechanics. Indeed, cells organize their dynamics and play a collective game which may end up either with the blow up of cells or their destruction due to the action of the immune defense.

- Referring finally to the paper by Greller, Tobin and Poste[49]:
  The modelling paradigm provides conceptual foundation not only for modelling progression and heterogeneity phenomena, but acts as a language for describing their complex phenomena.

  Tumor cellular populations are characterized by progression distributions, progression velocities and progression dependent growth rates. Major genetic changes after the tumor dynamics as each subpopulation moves further away from genetic normality.

  To the degree that a model is an adequate representation of biological reality, it can be used to perform "experiments" that are impossible or impractical in the laboratory. The danger of discovering phenomena that are artifacts of the model must always be scrutinized, but the properties of a model may also foretell genuine biological situations that are yet to be observed.

Also this paper motivates the concept of socio-biological state in addition to the microscopic mechanical state. While such a variable is added, one has to be aware that interactions between the biological and the mechanical quantities may occur. Therefore, at least in some cases, the whole set of microscopic variables shows a significant interplay. Moreover, working on theories appear to be an essential key to the development and understanding of experiments. This topic is well documented in the above sentences.

The complexity of interactions is definitely the main difficulty in deriving mathematical models. Complexity was reduced and constrained into the so-called transition distribution functions, but one has to be aware that such reduced description may not be, at least in some cases, satisfactory. This reasoning also applies to the simplification of binary interactions which may be affected by the presence of a third interacting subject.

The mathematical interpretation of the various hints proposed in Refs. 50, 46 and 49 was developed along this paper which was essentially focused on

mathematical aspects related to the modelling of complex biological systems. The analysis has shown that severe difficulties still have to be solved and can be proposed as research perspectives to applied mathematicians. While the trend to equilibrium is rather well understood for classical particles, this topic still has to be properly analyzed in the case of socio-biological systems. Often a trend to equilibrium is observed by experimental computation, but a rigorous proof and/or a deep understanding on the asymptotic behavior has been reached only for specific models.

The main point essentially refers to the modelling of microscopic interactions to be developed by a theoretical approach rather than by phenomenological assumptions as in the two models proposed in Sec. 6. A first step toward this matter was already given in the last part of Sec. 4.

The above statement essentially means that the formal mathematical framework still remains the same, to be used for improvements of specific models to be obtained by a relatively more refined description of microscopic interactions. When finally these interactions will be delivered by a theory, then a statistical mechanics theory for complex biological systems will be effectively available.

The final remarks of this paper refer to theoretical problems posed by the contents of the above sections. Essentially, we refer to the qualitative analysis of mathematical problems: initial value problems in the spatially homogeneous case, and initial-boundary value problems in the space dependent case. In addition to these problems, a highly challenging problem refers to the development of an asymptotic theory to obtain macroscopic equations for the microscopic description. As we have seen, some of the above problems have been properly dealt with in the literature, while a large variety of problems appears to be still open. Applied mathematicians should be attracted by them and by their difficulty. Although some models will be improved in the next years, still mathematical methods can be referred to the general mathematical structure which is claimed to remain valid, so that mathematical methods can be technically generalized to new models.

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