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FROM THE MODELING OF THE IMMUNE HALLMARKS OF CANCER TO A BLACK SWAN IN BIOLOGY

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This paper deals with the modeling of the early stage of cancer phenomena, namely mutations, onset, progression of cancer cells, and their competition with the immune system. The mathematical approach is based on the kinetic theory of active particles developed to describe the dynamics of large systems of interacting cells, called active particles. Their microscopic state is modeled by a scalar variable which expresses the main biological function. The modeling focuses on an interpretation of the immune-hallmarks of cancer.

Keywords: Statistical dynamics; active particles; stochastic games; evolution; mutations; system biology; multicellular systems.

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1. Introduction

The scientific community agrees that cancer is a genetic disease and that its evolution is related, since the very early stage, to mutations that give acquired abilities

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to cells. The biological system under consideration appears with multiscale features: genes, cells and the early stage of various cancer phenomena related to the molecular scale, while the dynamics at this scale determines that of cells and hence of tissues. Multiscale issues are described in Ref. 8, which also provides hints to develop a mathematical approach to the modeling of the whole path from the onset of mutated cells to the formation and growth of cancer tissues. The book by Weinberg[53] is a valuable reference regarding the molecular and cell biology of cancer.

The mathematical literature in the field is documented in Ref. 10, in the collection of surveys,[7] as well as in various recent papers in the field, e.g. Refs. 21, 20, 34 and 51. It can be observed that this literature mainly focuses on macroscopic approaches. In some cases, the link between parameters and gene expression is studied. The survey by Eftimie[31] provides an exhaustive report of the state-of-the-art developed at the supermacroscopic scale. On the other hand, the need of modeling cancer dynamics at the low scale, namely molecular and cellular, is documented in the book by Frank[33] and in various papers by Komarova.[43,44] The approach by evolutive games was introduced by Nowak and coworkers,[49,48] while recent developments are due to Gintis[36] and Helbing.[40]

The modeling of the dynamics at the cellular scale is developed by methods of statistical dynamics. The approach is known as the *Kinetic Theory of Active Particles*, for short KTAP method, it was initiated by the pioneer paper[11] and developed and applied by various authors, among others,[2,12–18,25,24,29,42] and therein cited bibliography. The survey by Eftimie[30] offers an interesting overview on the link between kinetic and hyperbolic models. The idea of developing a mathematical approach to modeling mutations followed by Darwinian selection was introduced in Ref. 8. Subsequently, it has been extended in various papers, first to the modeling of virus mutations,[27,28] then to the theory of evolution,[6] and to mutations in multicellular systems.[16] Some ideas of these papers will be exploited in the technical issues of the approach presented in the following.

The present paper aims at putting into a general mathematical framework the seminal paper by Hanahan and Weinberg,[37] which, as already remarked in Refs. 6 and 8, focuses on the critical changes in cell physiology that characterize malignant cancer growth. These changes — self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, evading immune system attack, and tissue invasion and metastasis — incorporate some aspects of genetic mutation, gene expression, and evolutionary selection, leading to malignant progression. In various cases, this evolution is induced by external or concomitant actions (as an example, the effect of therapies, as reported in Ref. 41).

The immune system plays an important role in this dynamics. As a matter of fact immune cells have a strategy to *learn* the presence of carriers of a pathology and attempt to deplete them. It is a complex process, where immune cells, starting from the *innate immunity*, improve their action by learning the so-called *acquired immunity*.[22] The recent paper[19] refers specifically to Refs. 37 and 38 and identifies

the hallmarks of cancer to escape the immune defence. In this dynamics, one has to take into account that immune cells gain new defence abilities, from innate to acquired immunity. Specific therapeutical actions are studied to activate the immune defence.[45]

This complex dynamics has not yet been put into a very general mathematical framework although preceding studies in the field[6,8,9,16] have contributed to this objective. Therefore, the present paper aims at developing a substantial improvement of the theory known in the literature as reviewed in Ref. 8. The dynamics refers to the early stage of the competition, which may end up either with the suppression of cancer cells or with their indefinite growth, which subsequently aggregate into condensed structures.

This objective is developed in the present paper by an approach which needs further developments of the KTAP's methods to introduce learning processes, nonlinearity in the interactions, and Darwinian selection. The contents are presented through four more sections. More in details, Sec. 2 outlines the complexity features of living systems in general and of multicellular systems in particular, and it presents a conceivable representation of the system consistent with the said complexity features. This section also outlines the strategies developed toward both the modeling approach and the validation of models. Section 3 shows how the modeling of interactions at the cellular scale can lead to the derivation of mathematical models suitable to describe the overall dynamics of the multicellular system. Section 4 presents the qualitative analysis of the related Cauchy problem and a variety of simulations to investigate the predictive ability of the model mainly concerning the merging behaviors and some preliminary speculations on therapeutical strategies. This section also presents some reasonings on the prediction of rare events, namely the black swan in biology. Section 5 looks at research perspectives and, in particular, to the modeling of the links between the molecular and the cellular scale, but also on general issues concerning perspectives in the system biology approach.

2. Representation of Multicellular Systems and Modeling Cellular Interactions

The modeling of the complex biological system under consideration requires the use of multiscale methods, where the dynamics at the cellular scale, as reported among others in Ref. 32, is related to the dynamics at the molecular scale, while the structure of tissues is an output of the dynamics at the cellular scale. This paper presents an approach to the dynamics at the cellular scale: cells can progress, namely modify their biological expression and mutate within Darwinian-type selective processes, out of the interaction with other cells.

More precisely, we refer to the interplay, and competition, between cancer and immune cells, where mutations are related, respectively, to the hallmarks of cancer[37] and to those of the immune system.[19] Both types of cells interact with normal epithelial cells, which can undergo a first stage mutation toward cancer progression.

Cells within each population can modify the level of their specific biological expression. The system biology approach finalized to the aforesaid objective is based on the idea that mathematical models should attempt to capture the complexity features of living systems according to the guidelines proposed in Refs. 6 and 23. This section focuses on the first steps of this approach, namely the assessment of the main complexity features that characterize the system under consideration, and its consequent representation. These topics are treated in the next three subsections, while the fourth one proposes a critical analysis on general issues concerning the validation of models and their consistency with the complexity features of living systems.

2.1. *Complexity features of biological systems*

Let us consider the problem of selecting the complexity features of multicellular systems. The first hint to include this strategic ingredient into the modeling approach is arguably due to the celebrated paper by Hartwell and coworkers[39] (soon after the publication of this paper he obtained the award of Nobel laureate). This enlightening paper puts in evidence, from the viewpoint of a biologist, the fundamental differences that distinguish the inert from the living matter. These ideas have been developed by various authors within different research contexts, among others the mathematical approach to the theory of evolution[6] and system biology.[23]

Bearing all above in mind, let us specifically focus on the immune competition and extract from a phenomenological analysis the features that we believe are the most important to insert into the modeling approach. Living entities, e.g. cells, according to Ref. 39, have the ability to develop, without the application of any external organizing principle, *specific strategies* depending both on genetic and epigenetic dynamics. These strategies depend on the search of individuals for their well-being, sometimes just for their survival, and evolve in time. In fact, living systems receive inputs from the environment and have the ability to learn from past experience to adapt themselves to the changing-in-time external conditions.[1,46] Therefore, living entities typically operate out-of-equilibrium in a constant struggle to remain alive.

Additional important features are related to this expression of a strategy, which is *heterogeneously distributed* among cells even when they share the same molecular structure, for instance due to different phenotype expression generated by the same genotype. Moreover, it produces *mutations and selections* generated by net destructive and/or proliferative events. Indeed, all living systems are evolutionary: birth processes can generate individuals that fit better the outer environment, which in turn generate new ones better and better fitted.

The central role in the expression of the strategy is played by *interactions*, which are nonlinear and involve immediate neighbors, but in some cases also distant entities. For instance, cells have the ability to communicate by signaling and can choose different observation paths within networks that evolve in time.

An additional aspect of living systems is the presence of large deviations related to small variations of the parameters. Although some of the qualitative behavior is still preserved, the quantitative one is more likely subject to them. However, in some cases also the qualitative behavior is modified.

Having fixed the aforesaid features, it is worth mentioning two additional technical difficulties challenging the mathematical approach:

(i) Biological systems are characterized by a *large variety of components*, even thousands of different elements. Therefore, the system biology approach needs developing a strategy to reduce this technical complexity feature.
(ii) The study of biological systems needs a *multiscale approach*. For instance, the dynamics at the molecular (genetic) level determines the cellular behaviors; moreover, the structure of macroscopic tissues depends on such dynamics.

Therefore it is important, according to the authors' bias, to distinguish between the previous basic features and the technical ones which have been listed above.

2.2. *On the representation of the system*

Let us consider a system made up of a large number of interacting cells, which can be viewed as *active particles*, whose physical microscopic state is described by the variable called *activity*, that represents the individual ability to express a specific biological function.

This approach requires the definition of the terms characterizing the functional subsystems and the related activity variables as well as the interaction, progression and mutation terms.

The identification of the *functional subsystems* is the first step of the modeling approach, which is developed here by analyzing the various stages of selective mutations of cancer cells based on their hallmarks referred to the immune system. The modeling approach needs tackling the problem of reducing the complexity of the system under consideration. The functional system theory approach contributes to such objective by selecting the smallest number of functional subsystems that necessarily have to be taken into account to describe the main features of the competition. Bearing these reasonings in mind, the following decomposition is proposed:

(1) $i = 1$ labels epithelial cells, whose selected function is the ability, supposed uniform for all cells, to feed proliferative phenomena. Proliferative events can generate cells with the same phenotype, but also cells with different phenotype toward the onset of cancer cells. It is supposed that the organism is a source of epithelial cells, so that their quantity can be regarded as constant in time;
(2) $i = 2$ labels cells, generated by the first functional subsystem, that have the ability to thrive in a chronically inflamed micro-environment;
(3) $i = 3$ denotes the functional subsystem of cells, generated by the previous subsystem, that have the ability to evade the immune recognition;

(4) $i = 4$ refers to cells that have acquired the ability of suppressing the immune reaction;
(5) $i = 5$ labels cells of the innate immune system which have the ability to acquire, by a learning process, the capacity of contrasting the development of cancer cells;
(6) $i = 6$ labels cells generated by the innate immune system, which have acquired the ability of contrasting the development of cancer cells labeled by $i = 2$, i.e. cancer cells from the first hallmark;
(7) $i = 7$ labels cells of the immune system generated from the previous two subsystems, which have acquired the ability of contrasting the development of cancer cells labeled by $i = 3$, i.e. cancer cells from the second hallmark;
(8) $i = 8$ labels cells of the immune system generated from the previous three subsystems, which have acquired the ability of contrasting the development of cancer cells labeled by $i = 4$, i.e. cancer cells from the third hallmark.

Remark 2.1. We will refer with the term *cancer cell* to any cell belonging to the functional subsystems $i = 2$, $i = 3$ or $i = 4$, i.e. any cell which is neither epithelial nor immune.

Remark 2.2. We will refer with the term *immune cell* to any cell belonging to the functional subsystems from $i = 5$ to $i = 8$.

Remark 2.3. The decomposition into functional subsystems specifically refers to the hallmarks put in evidence in Ref. 19. In principles, the same idea can be extended to immune cells to take into account their learning ability. However, the approach of the present paper models the learning process by considering only one functional subsystem and confining the learning process to the progression within it. Indeed, the activity expressed in each functional subsystem slowly progresses towards higher values of the activity variable.

In this paper, we refer to the discrete representation of the activity variable, which attains values in the following discrete set:

$$I_u = \{0 = u_1, \dots, u_j, \dots, u_m = 1\},$$

with $u_j < u_{j+1}$, for $j = 1, \dots, m-1$. This variable is heterogeneously distributed and we assume that increasing values of the activity correspond to an increasing ability of the subsystem to express its biological function.

The overall state of the system is described by the *discrete probability distribution function*

$$f_{ij} = f_{ij}(t), \quad i = 1, \dots, 8, \;\; j = 1, \dots, m. \tag{2.1}$$

The index i labels each subsystem, j labels the activity variable, and $f_{ij}(t)$ represents the number of active particles from functional subsystem i that, at time t,

have the state u_j. Therefore,

$$n_i[f](t) = \sum_{j=1}^{m} f_{ij}(t), \quad i = 1, \ldots, 8, \tag{2.2}$$

where $f = \{f_{ij}\}$ gives the number of active particles that, at time t, are in the ith-subsystem.

This representation is consistent with the heterogeneous behavior of cells and with the need of reducing the large number of components.

The mathematical structure for such a system should describe the evolution in time of the probability distribution functions f_{ij}. It is obtained by equating the variation rate of particles, in the corresponding state u_j of functional subsystem i, with the difference between the inlet and outlet fluxes from this state. In this way, the balance equation can be summarized as follows:

$$\frac{df_{ij}(t)}{dt} = J_{ij}[f](t) = C_{ij}[f](t) + P_{ij}[f](t) - D_{ij}[f](t) - L_{ij}[f](t), \tag{2.3}$$

for $i = 1, \ldots, 8$ and $j = 1, \ldots, m$, where J_{ij}, C_{ij}, P_{ij}, D_{ij} and L_{ij} are suitable operators acting over the whole set of probability distribution functions. Specifically,

- $J_{ij}[f](t)$ is the net flux, at time t, of particles that fall into the state u_j of the functional subsystem i;
- $C_{ij}[f](t)$ is the net flux, at time t, into the state u_j of the functional subsystem i, due to conservative interactions that only modify the micro-state;
- $P_{ij}[f](t)$ is the gain, at time t, into the state u_j of the functional subsystem i, due to proliferative events;
- $D_{ij}[f](t)$ is the loss, at time t, in the state u_j of the functional subsystem i, due to destructive events;
- $L_{ij}[f](t)$ is the natural relaxation of the immune system at time t and in the state u_j of the functional subsystem i, to a given healthy state.

This requires the modeling of interactions at the cellular level to compute the balance of particles in the elementary volume of the space of the microscopic states. If the f_{ij}'s are known, the overall behavior of the system is properly described not only by moments, but also by the distribution of biological activity of cells. Accordingly all emerging behaviors are put in evidence.

2.3. *Cellular interactions*

Let us now consider the problem of modeling a multicellular system consistently with the representation that has been given above. The guidelines to pursue such objective are the following:

(i) Interactions involve not only immediate neighbors (short-range interactions) but also the distant ones (long-range interactions). In fact, living systems communicate with each other directly or through media. Consequently, each entity

interacts with all the others in a domain whose elements are able to communicate.

(ii) Each cell plays a game with the surrounding cells lying in its interaction domain. This game modifies the state of the particles, while the strategy it expresses can also be modified by the shape of the heterogeneous distribution of the interacting cells. In some cases it generates net proliferative and/or destructive events.

(iii) Interactions are complex, namely the output of the game is not the linear superposition of its separated interactions, but a complex combination which depends on the strategy that all particles can develop.

(iv) The output of the game can also generate, in the proliferative process, particles with a different structure (for instance, entities with a different phenotype).

(v) The following particles play the game: test particles, whose distribution function is $f_{ij}(t)$, field particles, whose distribution function is $f_{kq}(t)$ and candidate particles, whose distribution function is $f_{hp}(t)$. Candidate particles may acquire, in probability, the state of the test particle by interaction with the field particles. All particles cannot be distinguished individually. Therefore, their state identifies them: more precisely, candidate particles are field particles whose state, after the identification, reaches that of the test particles.

Some guidelines toward the modeling of the quantities related to the interaction terms are suggested here in view of the derivation, in the next section, of the specific model proposed in this paper. A useful reference is that offered by the mathematical approach to the theory of evolution presented in Ref. 6. In order to simplify the notation, let us denote by the abbreviation hp-particle the meaning of particle belonging to the hth-functional subsystem with state u_p.

- η_{hk} is the encounter rate between the hp-candidate particle and the kq-field particle. It is assumed, according to Ref. 26, that it depends on the ability of interacting cells to recognize each other based on the distance between their states and distribution functions. Simple models can be obtained by assuming that it depends on the distances $|u_p - u_q|$ and $\|f_h - f_k\|$, where $\|f_i\| = \sum_j |f_{ij}|$.
- $\mathcal{B}_{ik}^{pq}(j)$ is the transition probability density that the ip-candidate particle falls into the state j of the same functional subsystem after an interaction with a kq-field particle, see Fig. 1. For instance, it can be assumed that the activity variable has a trend toward an increase of progression that depends on the state of the interacting cells and on the overall action of the system.
- $\mu_{hk}^{pq}(ij)$ models the net proliferation rate into the ij-state, due to interactions, occurring with rate η_{hk}, between the hp-candidate particle and the kq-field particle. Interactions can induce net proliferative events, which may generate, although with small probability, a daughter cell that presents genetic modifications with respect to the mother cell, see Fig. 2. In some cases, these different cells represent the first mutation toward the onset of cancer cells.[3] If these cells have the ability

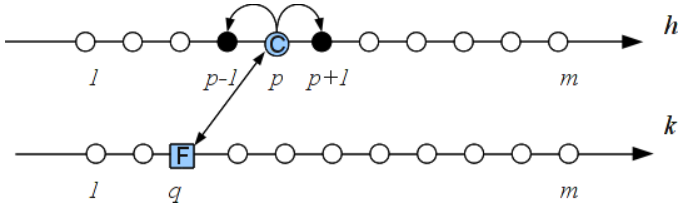

Fig. 1. Dynamics of conservative interactions. A candidate particle from subsystem h with state u_p can experiment a conservative interaction with a field particle from subsystem k. The output of the interaction can be u_{p-1}, u_p or u_{p+1}, depending on the kind of interaction the two are undergoing.

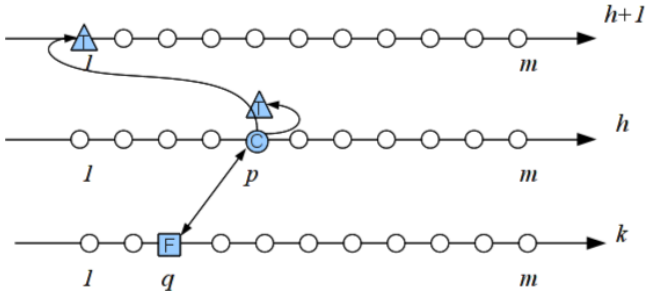

Fig. 2. Dynamics of proliferative interactions. A candidate particle (mother cell) of functional subsystem h, by interacting with a field particle from population k, can proliferate a daughter cell, belonging either to the same functional subsystem with same state, or eventually to the following functional subsystem with the lowest activity value.

to overcome the immune defence, then further mutations can occur[47] toward progression[50] and hallmarks of cancer.[37] The modeling approach is based on the idea that these mutations occur with higher probability when progression increases. The general framework is that of mutations and Darwinian selection.[6,35]

- ν_{ik}^{jq} models the net destruction rate into the ij-state, due to interactions, occurring with rate η_{ik}, between the ij-test particle and the kq-field particle, as shown in Fig. 3. Interactions can induce net destructive events in the sense that the immune system has the ability to kill a cancer cell.
- λ refers to the natural tendency of the immune system to relax to a given healthy state.[25]

The terms appearing in the right-hand side of the evolution equation (2.3) can now be detailed according to the following expressions:

$$C_{ij}[f] = \sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{ik}[f]\mathcal{B}_{ik}^{pq}(j)[f]f_{ip}f_{kq} - f_{ij}\sum_{k=1}^{n}\sum_{q=1}^{m}\eta_{ik}[f]f_{kq}, \qquad (2.4)$$

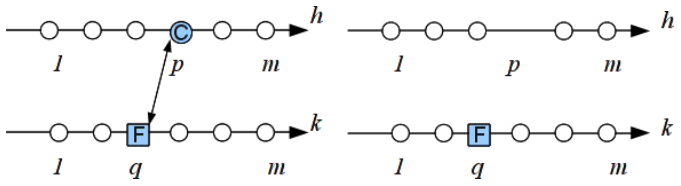

Fig. 3. Dynamics of destructive interactions. A candidate particle from functional subsystem h with state u_p, interacting with a field particle from population k with state u_q, (a), can undergo a destructive action which occurs within the same state of the candidate particle, (b).

$$P_{ij}[f] = \sum_{h=1}^{n}\sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{hk}[f]\mu_{hk}^{pq}(ij)f_{hp}f_{kq}, \tag{2.5}$$

$$D_{ij}[f] = f_{ij}\sum_{k=1}^{n}\sum_{q=1}^{m}\eta_{ik}[f]\nu_{ik}^{jq}f_{kq}, \tag{2.6}$$

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

$$L_{ij}[f] = \lambda(f_{ij} - f_{ij}^0), \tag{2.7}$$

for $i = 5, \dots, 8$ and $j = 1, \dots, m$, namely, in the natural relaxation terms of the evolution equations for the populations of the immune system, we have chosen as healthy state the initial value of the distributions, say f_{ij}^0.

2.4. *Validation of models*

As usual, the validation of models is obtained by comparison of the dynamics depicted by the model and that delivered by empirical data obtained by experiments. A technical difficulty is that empirical data present highly heterogeneous features. Moreover, complex systems generally show collective behaviors that cannot straightforwardly be related to that of a few entities. These emerging behaviors are in most cases repeated only at a qualitative level due to the large amount of events that often appear in the dynamics of living systems.

The validation approach presented in this paper focuses precisely on the simulation of the emerging behaviors that are considered important outputs of the dynamics of the system under consideration. More precisely, the dynamics that the model should take into account is a Darwinian-type evolution of cell phenotypes contrasted by the immune system. The phenotypes correspond to the immune-hallmarks of cancer, while the immune system develops a learning process from innate immunity to acquired immunity.

Generally, this contrast action is sufficient to prevent the indefinite proliferation of cancer cells. However, for some specific mutations, the Darwinian selections can generate highly aggressive cell phenotypes that progress and proliferate with a speed that cannot be contrasted by the learning process of the immune system.

This rare event can even be regarded as a black swan in biology, somehow rare, but with catastrophic outputs. Although, as observed by Taleb,[52] once happened it appears to be predictable. On the other hand, the dynamics that follow this event does not obey the same rules before its onset. In fact, when cells start to grow indefinitely, additional phenomena such as aggregation into tumoral shapes, onset of angiogenesis, and many others should be included into the model. These additional events are not taken into account in the present paper, while a more detailed description of the immune-hallmarks of cancer will be given in the next section focusing on the derivation of a specific model.

3. On the Modeling of the Collective Dynamics

This section is devoted to the modeling of the collective dynamics of the multicellular system based on the mathematical frameworks proposed in Sec. 2, which are formally given by Eq. (2.3), and further particularized by Eqs. (2.4)–(2.7). The modeling needs a detailed description of the interaction terms, so that the mathematical structures can be fully characterized. These take into account some complexity features such as the heterogeneous expression of the cell phenotype characters, nonlinearly additive interactions, competition to survive, generation of new phenotypes and Darwinian selection that determines their surviving or not.

Remark 3.1. In general, a different modeling approach has to be considered for cells of the various different functional subsystems. Briefly, we remember that the tumor cells are distinguished according to their progressive hallmarks, while the immune cells are characterized by the capability to recognize specific hallmarks.

• ***Encounter rate.*** The modeling of the encounter rate η_{hk} needs to take into account the specific functions and expressions of cells, also related to a learning process. Only encounters which lead to progression, mutations and proliferation will be considered, being referred to a (positive) value η_0. This dimensionless parameter, small with respect to one, corresponds to interactions within the subsystem of epithelial cells, and can be included into the time scale. Taking into account the dependence of the encounter rate on the distance between the distribution functions, as already mentioned in Sec. 2.3, we first introduce:

$$\Psi_{hk}[f] = \begin{cases} \exp\left(-\tau \dfrac{\|f_h - f_k\|}{\|f_h\| + \|f_k\|}\right), & \|f_h\|, \|f_k\| \neq 0, \quad \tau > 0, \\ 0, & \|f_h\| = \|f_k\| = 0, \end{cases} \tag{3.1}$$

for each pair of functional subsystems (h, k).

— *Encounter rate of functional subsystems* $h = 1, 2, 3, 4$ *with* $k = 1$. The rate of encounters between tumor and epithelial cells, increases with the hallmark h,

as progressive hallmarks correspond to increasing activation to search nutrients for increasing proliferation:

$$\eta_{h1} = \eta_0 h \Psi_{h1}[f], \quad \forall\, h = 1, 2, 3, 4. \tag{3.2}$$

On the other hand, it is assumed to be equal to zero for encounters involving only cancer cells: $\eta_{hk} = 0$, $\forall\, h, k = 2, 3, 4$.

— *Encounter rate of functional subsystems* $h = 5, 6, 7, 8$ *with* $k = 1, 2, 3, 4$. Immune cells have the ability to identify cancer cells only if they have acquired, after a learning process, this specific ability. The following assumption is proposed:

$$\eta_{hk} = \sigma \eta_0 \Psi_{hk}[f], \quad \sigma > 0, \tag{3.3}$$

for each pair $(h, k) = (5, 2), (6, 2), (6, 3), (7, 2), (7, 3), (7, 4), (8, 2), (8, 3), (8, 4)$.

As we shall see, the innate immune system has the ability to identify cancer cells of the first hallmark to generate progression and mutation processes, but not yet a destructive action, while this specific action is expressed for $h > 5$ toward the hallmarks that have been recognized. On the other hand, the encounter rate between immune and epithelial cells is assumed to be equal to zero.

Remark 3.2. It has been assumed, for simplicity, that η depends only on the different functional subsystems, but not on the activity within each of them. The role of the parameter σ appears to be relevant considering that it models the difference of the rate of action of immune and cancer cells.

• ***Transition probability density.*** Progression phenomena refer, according to Remark 3.1, to an increasing activity within the same functional subsystem. This dynamics is modeled by the terms $\mathcal{B}_{ik}^{pq}(j)$. Only interactions with encounter rate different from zero are considered:

— *Interactions involving functional subsystems* $h = 1, 2, 3, 4$ *with* $k = 1$. Epithelial and cancer cells can increase their state only after an interaction with epithelial cells. Probability of transition is assumed to decrease with the activity state of the candidate particle:

$$\mathcal{B}_{h1}^{pq}(j) = \begin{cases} \alpha(1 - u_p), & j = p + 1, \quad \alpha > 0, \\ 1 - \alpha(1 - u_p), & j = p, \\ 0, & \text{otherwise.} \end{cases} \tag{3.4}$$

— *Interactions of functional subsystem* $h = 1$ *with* $k = 2, 3, 4$. Epithelial cells are assumed to feed progression of cancer cells without changing their own state: $\mathcal{B}_{1k}^{pq}(p) = 1$.

— *Interactions of functional subsystems* $h = 5, 6, 7, 8$ *with* $k = 2, 3, 4$. Immune cells acquire progressively the ability to identify functional subsystems of tumor cells.

As a consequence, immune cells may increase their state and the probability of progression decreases with increasing pth-state:

$$\mathcal{B}_{52}^{pq}(j) = \mathcal{B}_{62}^{pq}(j) = \mathcal{B}_{73}^{pq}(j) = \mathcal{B}_{84}^{pq}(j) = \begin{cases} \alpha(1-u_p), & j = p+1, \\ 1-\alpha(1-u_p), & j = p, \\ 0, & \text{otherwise.} \end{cases} \tag{3.5}$$

— *Interactions between cancer cells from* $h = 2, 3, 4$ *with* $k = 5, 6, 7, 8$. It is assumed that these types of interactions do not induce biological events to cancer cells.

• ***Mutation events.*** These are rare events, related to the rate η_{hk}, where generation of a daughter cell occurs in a functional subsystem different from that of the mother cells. This event is modeled by the term $\mu_{hk}^{pq}(ij)$, where $i = h + 1$ with output into the state $j = 1$:

— *Mutations from cancer subsystems* $h = 1, 2, 3$. These are related to encounters with the first functional subsystem $k = 1$:

$$\mu_{h1}^{pq}(ij) = \begin{cases} \varepsilon_1 u_p, & i = h+1, \quad \text{j=1}, \ \varepsilon_1 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.6}$$

— *Mutations from immune subsystems* $h = 5, 6, 7$. These are related to an increasing capability of the immune cells to recognize a specific hallmark:

$$\mu_{52}^{pq}(6j) = \begin{cases} \varepsilon_{26} u_p, & j = 1, \ \varepsilon_{26} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.7}$$

$$\mu_{63}^{pq}(7j) = \begin{cases} \varepsilon_{27} u_p, & j = 1, \ \varepsilon_{27} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.8}$$

$$\mu_{74}^{pq}(8j) = \begin{cases} \varepsilon_{28} u_p, & j = 1, \ \varepsilon_{28} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.9}$$

• ***Proliferative events.*** Proliferation occurs within the same functional subsystem with rate η_{hk} being modeled by the term $\mu_{hk}^{pq}(ij)$, where $i = h$ and $j = p$. The following assumptions model the dynamics:

— *Proliferation in cancer subsystems* $h = 2, 3, 4$. Proliferation increases with the hallmarks of cancer cells, due to the resulting deregulated proliferation program which is an acquired capability of tumor cells[37]:

$$\mu_{h1}^{pq}(hj) = \begin{cases} \beta_1 h u_p, & j = p, \ \beta_1 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{3.10}$$

— *Proliferation in immune cells subsystems* $h = 6, 7, 8$. Immune cells proliferate due to encounters with cells up to the identified tumor subsystems:

$$\mu_{hk}^{pq}(hj) = \begin{cases} \beta_2, & j = p, \ \ \beta_2 > 0, \\ 0, & \text{otherwise}, \end{cases} \tag{3.11}$$

for each pair $(h, k) = (6, 2), (7, 2), (7, 3), (8, 2), (8, 3), (8, 4)$.

• ***Destruction rate.*** Destructive terms concern only cancer and immune cells. Immune cells have the ability to suppress cancer cells that are identified by them. It is assumed that this ability increases with increasing activity of immune cells:

$$\nu_{26}^{pq} = \nu_{27}^{pq} = \nu_{28}^{pq} = \nu_{37}^{pq} = \nu_{38}^{pq} = \nu_{48}^{pq} = \gamma u_q, \quad \gamma > 0. \tag{3.12}$$

Remark 3.3. Encounter rates are symmetric: $\eta_{hk} = \eta_{kh}, \forall\, h, k, p, q$. However, the other interaction terms do not have this property due to lack of reversibility.

The biological meaning of the parameters introduced in the model is summarized in Table 1.

As a consequence of Eqs. (3.1)–(3.12), for each distribution function f_{ij}, the terms on the right-hand side of Eq. (2.3) given by Eqs. (2.4)–(2.7), for $j = 1, \ldots, m$, read:

$$\begin{aligned} C_{1j}[f] &= \Psi_{11}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{1(j-1)}n_1[f] \\ &\quad + \Psi_{11}[f][1-\alpha(1-u_j)]f_{1j}n_1[f] - \Psi_{11}[f]f_{1j}n_1[f], \end{aligned} \tag{3.13}$$

$$\begin{aligned} C_{2j}[f] &= \Psi_{21}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{2(j-1)}n_1[f] \\ &\quad + \Psi_{21}[f][1-\alpha(1-u_j)]f_{2j}n_1[f] - \Psi_{21}[f]f_{2j}n_1[f], \end{aligned} \tag{3.14}$$

$$\begin{aligned} C_{3j}[f] &= \Psi_{31}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{3(j-1)}n_1[f] \\ &\quad + \Psi_{31}[f][1-\alpha(1-u_j)]f_{3j}n_1[f] - \Psi_{31}[f]f_{3j}n_1[f], \end{aligned} \tag{3.15}$$

$$\begin{aligned} C_{4j}[f] &= \Psi_{41}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{4(j-1)}n_1[f] \\ &\quad + \Psi_{41}[f][1-\alpha(1-u_j)]f_{4j}n_1[f] - \Psi_{41}[f]f_{4j}n_1[f], \end{aligned} \tag{3.16}$$

Table 1. Model parameters.

Parameter	Biological meaning
η_0, σ, τ	Refer to interaction rates
α	Is a parameter of the probability density in conservative progressions
$\varepsilon_1, \varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28}$	Model the mutation rate for cancer and immune cells
β_1, β_2	Model the proliferation rate for cancer and immune cells
γ	Refers to suppression rate
λ	Refers to the relaxation of the immune system

$$C_{5j}[f] = \sigma\Psi_{52}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{5(j-1)}n_2[f] + \sigma\Psi_{52}[f][1-\alpha(1-u_j)]f_{5j}n_2[f] - \sigma\Psi_{52}[\mathbf{f}]f_{5j}n_2[f], \tag{3.17}$$

$$C_{6j}[f] = \sigma\Psi_{62}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{6(j-1)}n_2[f] + \sigma\Psi_{62}[f][1-\alpha(1-u_j)]f_{6j}n_2[f] - \sigma\Psi_{62}[f]f_{6j}n_2[f], \tag{3.18}$$

$$C_{7j}[f] = \sigma\Psi_{73}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{7(j-1)}n_3[f] + \sigma\Psi_{73}[f][1-\alpha(1-u_j)]f_{7j}n_3[f] - \sigma\Psi_{73}[f]f_{7j}n_3[f], \tag{3.19}$$

$$C_{8j}[f] = \sigma\Psi_{84}[f]\alpha(1-u_{j-1})(1-\delta_{1j})f_{8(j-1)}n_4[f] + \sigma\Psi_{84}[f][1-\alpha(1-u_j)]f_{8j}n_4[\mathbf{f}] - \sigma\Psi_{84}[f]f_{8j}n_4[f], \tag{3.20}$$

$$P_{2j}[f] = 4\Psi_{21}[f]\beta_1 u_j f_{2j}n_1[f] + \Psi_{11}[f]\varepsilon_1\delta_{1j}n_1[f]\sum_{p=1}^{m} u_p f_{1p}, \tag{3.21}$$

$$P_{3j}[f] = 9\Psi_{31}[f]\beta_1 u_j f_{3j}n_1[f] + 2\Psi_{21}[f]\varepsilon_1\delta_{1j}n_1[f]\sum_{p=1}^{m} u_p f_{2p}, \tag{3.22}$$

$$P_{4j}[f] = 16\Psi_{41}[f]\beta_1 u_j f_{4j}n_1[f] + 3\Psi_{31}[f]\varepsilon_1\delta_{1j}n_1[f]\sum_{p=1}^{m} u_p f_{3p}, \tag{3.23}$$

$$P_{6j}[f] = \sigma\Psi_{62}[f]\beta_2 f_{6j}n_2[f] + \sigma\Psi_{52}[f]\varepsilon_{26}\delta_{1j}n_2[\mathbf{f}]\sum_{p=1}^{m} f_{5p}u_p, \tag{3.24}$$

$$P_{7j}[f] = \sigma\Psi_{72}[f]\beta_2 f_{7j}n_2[f] + \sigma\Psi_{73}[f]\beta_2 f_{7j}n_3[f] + \sigma\Psi_{63}[f]\varepsilon_{27}\delta_{1j}n_3[f]\sum_{p=1}^{m} f_{6p}u_p, \tag{3.25}$$

$$P_{8j}[f] = \sigma\Psi_{82}[f]\beta_2 f_{8j}n_2[f] + \sigma\Psi_{83}[f]\beta_2 f_{8j}n_3[f] + \sigma\Psi_{84}[f]\beta_2 f_{8j}n_4[f] + \sigma\Psi_{74}[f]\varepsilon_{28}\delta_{1j}n_4[f]\sum_{p=1}^{m} f_{7p}u_p, \tag{3.26}$$

while $P_{1j}[f] = P_{5j}[f] = 0$. Moreover,

$$D_{2j}[f] = \sigma\gamma f_{2j}\sum_{q=1}^{m} u_q(\Psi_{26}[f]f_{6q} + \Psi_{27}[f]f_{7q} + \Psi_{28}[f]f_{8q}), \tag{3.27}$$

$$D_{3j}[f] = \sigma\gamma f_{3j}\sum_{q=1}^{m} u_q(\Psi_{37}[f]f_{7q} + \Psi_{38}[f]f_{8q}), \tag{3.28}$$

$$D_{4j}[f] = \sigma\gamma f_{3j}\sum_{q=1}^{m} u_q\Psi_{48}[f]f_{8q}, \tag{3.29}$$

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

$$L_{ij}[f] = \lambda(f_{ij} - f_{ij}^0), \quad i = 5, \dots, 8, \tag{3.30}$$

while $L_{ij}[f] = 0$ for $i = 1, \dots, 4$, as it was already stated in Eq. (2.7).

We used the standard notation $\delta_{ij} = 1$ if $i = j$ and $\delta_{ij} = 0$ otherwise. The rate η_0 has been inserted into the time scale.

4. Qualitative Analysis, Simulations and Emerging Behaviors: Looking for the Black Swan

Let us first consider the following initial value problem:

$$\begin{cases} \dfrac{df_{ij}(t)}{dt} = J_{ij}[f](t), \\ f_{ij}(0) = f_{ij}^0, \end{cases} \tag{4.1}$$

where $J_{ij}[f](t) = C_{ij}[f](t) + P_{ij}[f](t) - D_{ij}[f](t) - L_{ij}[f](t)$, for $i = 1, \dots, n$ and $j = 1, \dots, m$, and $f = \{f_{ij}\}$, under the condition that all the terms $L_{ij}[f](t)$ are nonzero, i.e. all the n populations admit a relaxation term in the corresponding evolution equation. The analysis of existence of solutions for problem (4.1) is a useful preliminary step forward in the qualitative analysis of the corresponding Cauchy problem for Eqs. (2.3)–(2.7).

Therefore the initial value problem (4.1) consists of $n \times m$ ordinary differential equations in the unknown $f_{ij} : \mathbb{R}^+ \to \mathbb{R}^+$, supplemented by $n \times m$ initial conditions f_{ij}^0. The proof of existence and uniqueness of a global in time solution of the Cauchy problem can be obtained by taking advantage of the Lipschitz properties of the right-hand side of (4.1).

In order to study the well-posedness of problem (4.1), let M_{nm} be the set of real $n \times m$ matrices. We endow M_{nm} with the 1-norm,

$$\|f\|_1 = \sum_{i=1}^{n} \sum_{j=1}^{m} |f_{ij}|, \quad f = \{f_{ij}\} \in M_{nm}. \tag{4.2}$$

Moreover, we introduce the linear space $X = C_b([0, +\infty); M_{nm})$ of the matrix-valued bounded and continuous functions

$$f = f(t) : [0, +\infty) \to M_{nm},$$

equipped with the infinity norm

$$\|f\|_\infty = \sup_{t \in [0, +\infty)} \|f\|_1.$$

Note that $(X, \|\cdot\|_\infty)$ is a real Banach space. We will denote by X_+ the positive cone of space X. For $T > 0$, we denote $X_T = C([0, T]; M_{nm})$.

Well-posedness of the spatially homogeneous problem means global-in-time existence and uniqueness of a solution $f = f(t)$ to the Cauchy problem (4.1). To show these results, it is usual to make some assumptions which are necessary for the proof.

Assumption H.1. In Sec. 2.3, $\mathcal{B}_{ik}^{pq}(j)$ is defined as a transition probability density, and this implies:

$$\sum_{j=1}^{m} \mathcal{B}_{ik}^{pq}(j)[f] = 1 \quad \forall\, i,k = 1,\dots,n,\ \ \forall\, p,q = 1,\dots,m.$$

Assumption H.2. There exists $C_\eta > 0$ such that:

$$0 < \eta_{ik}[f] \le C_\eta \quad \forall\, i,k = 1,\dots,n.$$

Assumption H.3. Both the encounter rate $\eta_{ik}[f]$ and the transition probability $\mathcal{B}_{ik}^{pq}(j)[f]$ satisfy that there exist constants L_1, L_2 such that:

$$|\eta_{ik}[f] - \eta_{ik}[g]| \le L_1 \frac{\|g_i - f_i\| + \|g_k - f_k\|}{\|g_i\|} \quad \forall\, f,g \in M_{nm} \tag{4.3}$$

and

$$|\mathcal{B}_{ik}^{pq}(j)[f] - \mathcal{B}_{ik}^{pq}(j)[g]| \le L_2 \frac{\|g_i - f_i\| + \|g_k - f_k\|}{\|g_i\|} \quad \forall\, f,g \in M_{nm}, \tag{4.4}$$

for all $i,k = 1,\dots,n$ and $j,p,q = 1,\dots,m$.

Remark 4.1. (1) By inverting the role of f and g one gets easily from (4.3) the following:

$$|\eta_{ik}[f] - \eta_{ik}[g]| \le L_1 \frac{\|f_i - g_i\| + \|f_k - g_k\|}{\|f_i\|}. \tag{4.5}$$

(2) The function Ψ_{hk} given by (3.1) satisfies Assumption H.3, namely (4.3). Indeed, by Taylor formula, one has:

$$|\Psi_{ik}[f] - \Psi_{ik}[g]| = \tau \left| \frac{\|g_i - g_k\|}{\|g_i\| + \|g_k\|} - \frac{\|f_i - f_k\|}{\|f_i\| + \|f_k\|} \right| \exp(-c),$$

where c is a positive constant such that:

$$c \in \left(\min\left(\tau \frac{\|g_i - g_k\|}{\|g_i\| + \|g_k\|}, \tau \frac{\|f_i - f_k\|}{\|f_i\| + \|f_k\|} \right), \max\left(\tau \frac{\|g_i - g_k\|}{\|g_i\| + \|g_k\|}, \tau \frac{\|f_i - f_k\|}{\|f_i\| + \|f_k\|} \right) \right).$$

Then,

$$\begin{aligned} |\Psi_{ik}[f] - \Psi_{ik}[g]| \le{}& \tau \left| \frac{\|g_i - g_k\| - \|f_i - f_k\|}{\|g_i\| + \|g_k\|} \right| \\ &+ \tau \|f_i - f_k\| \frac{|\|f_i\| - \|g_i\|| + |\|f_k\| - \|g_k\||}{(\|g_i\| + \|g_k\|)(\|f_i\| + \|f_k\|)}. \end{aligned}$$

Using the inequality $|\|f\| - \|g\|| \leq \|f - g\|$ yields:

$$|\Psi_{ik}[f] - \Psi_{ik}[g]| \leq 2\tau \frac{\|g_i - f_i\| + \|g_k - f_k\|}{\|g_i\| + \|g_k\|} \leq 2\tau \frac{\|g_i - f_i\| + \|g_k - f_k\|}{\|g_i\|}.$$

Under Assumptions H.1, H.2 and H.3, one obtains the following.

Theorem 4.1. *Let Assumptions* H.1, H.2 *and* H.3 *hold. Then there exists* $f_0^0 > 0$ *such that if* $\|f_0\|_1 \leq f_0^0$, *there exists a strictly positive constant a such that problem* (4.1) *admits a unique non-negative global solution* $f \in X$ *satisfying the following estimate*:

$$\|f(t)\|_1 \leq a\|f_0\|_1, \quad t \in (0, \infty). \tag{4.6}$$

Remark 4.2. The smallness condition on the initial condition can be avoided by using the parameter λ large enough and the result can be stated as follows.

Theorem 4.2. *Let Assumptions* H.1, H.2 *and* H.3 *hold and let* $f_0 \in M_{nm}$. *Then there exists* λ^0 *such that if* $\lambda \geq \lambda^0$, *there exists a strictly positive constant a such that the problem* (4.1) *admits a unique non-negative global solution* $f \in X$ *satisfying the following estimate*:

$$\|f(t)\|_1 \leq a\|f_0\|_1, \quad t \in (0, \infty). \tag{4.7}$$

Coming back to our model, i.e. Eqs. (2.3)–(2.7) and $n = 8$, due to the fact that we have $L_{ij}[f](t) = 0$ for $i = 1, \ldots, 4$ and $\forall\, j = 1, \ldots, m$, we obtain the following local existence theorem.

Theorem 4.3. *Let Assumptions* H.1, H.2 *and* H.3 *hold and let* $f_0 \in M_{nm}$. *Then there exists* T *such that if* $t \leq T$, *there exists a strictly positive constant a such that the problem* (4.1) *admits a unique non-negative global solution* $f \in X_T$ *satisfying the following estimate*:

$$\|f(t)\|_1 \leq a\|f_0\|_1, \quad t \in [0, T]. \tag{4.8}$$

To prove Theorems 4.1–4.3 we need some preliminary estimates on the nonlinear operator $J^\star$ given by

$$J_{ij}^\star = J_{ij} + L_{ij}, \tag{4.9}$$

which are given in the following lemma.

Lemma 4.1. *Let Assumptions* H.1, H.2 *and* H.3 *hold. Then the following estimates are satisfied*: *there exists* $C_1 > 0$ *such that*:

$$\|J^\star[f]\|_1 \leq C_1\|f\|_1^2, \tag{4.10}$$

$$\|J^\star[f] - J^\star[g]\|_1 \leq C_1(\|f\|_1 + \|g\|_1)\|f - g\|_1. \tag{4.11}$$

Proof. Note that $J^\star = C_{ij} + P_{ij} - D_{ij}$. Therefore to prove Lemma 4.1, one has to establish the estimate (4.10), (4.11), for the terms C_{ij}, P_{ij} and D_{ij} given by (2.4)–(2.6). Using Assumptions H.1 and H.2, and summing over i, j yields:

$$\begin{aligned}
\sum_{i=1}^{n}\sum_{j=1}^{m}|C_{ij}| &\le \sum_{i=1}^{n}\sum_{j=1}^{m}\sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}|\eta_{ik}[f]|\mathcal{B}_{ik}^{pq}(j)[f]|f_{ip}||f_{kq}| \\
&\quad + \sum_{i=1}^{n}\sum_{j=1}^{m}|f_{ij}|\sum_{k=1}^{n}\sum_{q=1}^{m}|\eta_{ik}[f]||f_{kq}| \\
&\le C_\eta \sum_{i=1}^{n}\sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}\left(\sum_{j=1}^{m}\mathcal{B}_{ik}^{pq}(j)[f]\right)|f_{ip}||f_{kq}| \\
&\quad + C_\eta \sum_{i=1}^{n}\sum_{j=1}^{m}|f_{ij}|\sum_{k=1}^{n}\sum_{q=1}^{m}|f_{kq}| \\
&\le 2C_\eta \|f\|_1^2.
\end{aligned}$$

Note that:

$$\begin{aligned}
C_{ij}[f] - C_{ij}[g] &= \sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}\eta_{ik}[f]\mathcal{B}_{ik}^{pq}(j)[f](f_{ip}(f_{kq}-g_{kq}) + g_{kq}(f_{ip}-g_{ip})) \\
&\quad + \sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}((\eta_{ik}[f]-\eta_{ik}[g])\mathcal{B}_{ik}^{pq}(j)[g] \\
&\quad + \eta_{ik}[g](\mathcal{B}_{ik}^{pq}(j)[f] - \mathcal{B}_{ik}^{pq}(j)[g]))g_{ip}g_{kq} \\
&\quad + f_{ij}\sum_{k=1}^{n}\sum_{q=1}^{m}(\eta_{ik}[g](g_{kq}-f_{kq}) + (\eta_{ik}[g]-\eta_{ik}[f])f_{kq}) \\
&\quad + (g_{ij}-f_{ij})\sum_{k=1}^{n}\sum_{q=1}^{m}\eta_{ik}[g]g_{kq} \\
&= S_{ij} + T_{ij}. \qquad (4.12)
\end{aligned}$$

Then using Assumptions H.1, H.2 and summing over i, j yields:

$$\begin{aligned}
\sum_{i=1}^{n}\sum_{j=1}^{m}|S_{ij}| &\le C_\eta \sum_{i=1}^{n}\sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}(|f_{ip}||f_{kq}-g_{kq}| + |g_{kq}||f_{ip}-g_{ip}|) \\
&\quad + \sum_{i=1}^{n}\sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}|\eta_{ik}[f]-\eta_{ik}[g]||g_{ip}||g_{kq}| \\
&\quad + C_\eta \sum_{i=1}^{n}\sum_{j=1}^{m}\sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m}|\mathcal{B}_{ik}^{pq}(j)[f] - \mathcal{B}_{ik}^{pq}(j)[g]||g_{ip}||g_{kq}| \\
&= I + J + K. \qquad (4.13)
\end{aligned}$$

The first term I is estimated as follows:

$$I \leq C_\eta(\|f\|_1 + \|g\|_1)\|f-g\|_1. \tag{4.14}$$

Now using (4.3), yields:

$$\begin{aligned} J &\leq L_1 \sum_{i=1}^n \sum_{k=1}^n \sum_{p=1}^m \sum_{q=1}^m \frac{\|g_i - f_i\| + \|g_k - f_k\|}{\|g_i\||g_{ip}||g_{kq}|} \\ &\leq L_1 \sum_{i=1}^n \sum_{k=1}^n \sum_{q=1}^m \frac{\|g_i - f_i\| + \|g_k - f_k\|}{\|g_i\|} \sum_{p=1}^m |g_{ip}||g_{kq}| \\ &= L_1 \sum_{i=1}^n \sum_{k=1}^n \sum_{q=1}^m (\|g_i - f_i\| + \|g_k - f_k\|)|g_{kq}| \\ &\leq 2L_1 n^2 \|f-g\|_1 \|g\|_1. \end{aligned} \tag{4.15}$$

By the same arguments, using (4.4) for the transition probability $\mathcal{B}_{ik}^{pq}(j)[f]$, yields

$$K \leq C\|g\|_1\|f-g\|_1. \tag{4.16}$$

Using Assumptions H.1, H.2 and H.3 and (4.5), and summing over i, j yields

$$\sum_{i=1}^n \sum_{j=1}^m |T_{ij}| \leq C_\eta \|f\|_1\|f-g\|_1 + L_1\|f\|_1\|f-g\|_1 + C_\eta\|g\|_1\|f-g\|_1. \tag{4.17}$$

Finally combining (4.12)–(4.17), one deduces the estimate (4.11) for the term C_{ij}.

The same arguments can be used to prove (4.10)–(4.11) for P_{ij} and D_{ij}. Indeed,

$$\begin{aligned} \sum_{i=1}^n \sum_{j=1}^m |P_{ij}[f]| &\leq C_\eta \sum_{h=1}^n \sum_{k=1}^n \sum_{p=1}^m \sum_{q=1}^m \sum_{i=1}^n \sum_{j=1}^m \mu_{hk}^{pq}(ij) f_{hp} f_{kq} \\ &\leq C_\eta C_\mu \sum_{h=1}^n \sum_{k=1}^n \sum_{p=1}^m \sum_{q=1}^m f_{hp} f_{kq} = C_\eta C_\mu \|f\|_1^2, \end{aligned}$$

where $C_\mu = \max_{h,k,p,q} \sum_{i=1}^n \sum_{j=1}^m \mu_{hk}^{pq}(ij)$. In the same way, one has

$$\sum_{i=1}^n \sum_{j=1}^m |D_{ij}[f]| \leq C_\eta C_\nu \|f\|_1^2,$$

where $C_\nu = \max_{i,j,k,q} \nu_{ik}^{jq}$. This completes the proof of the lemma. □

Define the following operator ψ as follows:

$$\psi(f)(t) = \int_0^t \exp(\lambda(s-t))J^\star[f](s)ds.$$

Then the next lemma gives the following estimate for ψ.

Lemma 4.2. *Let Assumptions* H.1, H.2 *and* H.3 *hold. Then ψ is a continuous map from X into X and there exists $C1 > 0$ such that*:

$$\|\psi(f)\|_\infty \leq \frac{C_1}{\lambda}\|f\|_\infty^2, \tag{4.18}$$

$$\|\psi(f) - \psi(g)\|_\infty \leq \frac{C_1}{\lambda}(\|f\|_\infty + \|g\|_\infty)\|f-g\|_\infty. \tag{4.19}$$

Proof. Using (4.10), yields

$$\|\psi(f)(t)\|_1 \leq C_1\|f\|_\infty^2 \int_0^t \exp(\lambda(s-t))ds \leq \frac{C_1}{\lambda}\|f\|_\infty^2(1-\exp(-\lambda t)),$$

which gives (4.18). By the same argument, taking into account (4.11), one has easily (4.19).

To prove the continuity of ψ, let $t_1, t_2 \in [0, +\infty)$ such that $t_1 < t_2$. Write

$$\begin{aligned}\psi(t_2) - \psi(t_1) = &\int_{t_1}^{t_2} \exp(\lambda(s-t_2))J^\star[f](s)ds \\ &+ \int_0^{t_1} (\exp(\lambda(s-t_2)) - \exp(\lambda(s-t_1)))J^\star[f](s)ds.\end{aligned}$$

Therefore, using (4.10), yields

$$\begin{aligned}\|\psi(t_2) - \psi(t_1)\|_1 &\leq C_1\|f\|_\infty^2 \int_{t_1}^{t_2} \exp(\lambda(s-t_2))ds \\ &\quad + C_1\|f\|_\infty^2 \int_0^{t_1} |\exp(\lambda(s-t_2)) - \exp(\lambda(s-t_1))|ds \\ &\leq C_1\|f\|_\infty^2|t_2-t_1| \\ &\quad + \lambda C_1\|f\|_\infty^2|t_2-t_1| \int_0^{t_1} \exp(c)ds,\end{aligned} \tag{4.20}$$

where $c \in (\lambda(s-t_2), \lambda(s-t_1))$. Noting that as $c < \lambda(s-t_1)$, then

$$\int_0^{t_1} \exp(c)ds \leq \int_0^{t_1} \exp(\lambda(s-t_1))ds = \frac{1}{\lambda}(1-\exp(-\lambda t_1)) \leq \frac{1}{\lambda}. \tag{4.21}$$

Combining (4.20), (4.21), yields

$$\|\psi(t_2) - \psi(t_1)\|_1 \leq 2C_1\|f\|_\infty^2|t_2-t_1|.$$

This completes the proof of lemma. □

Proof of Theorems 4.1 and 4.2. First, by multiplying the equation in (4.1) by $\exp(\lambda t)$, yields

$$\begin{cases} \dfrac{d}{dt}(\exp(\lambda t) f_{ij}) = \exp(\lambda t) J^{\star}_{ij}(t) + \lambda \exp(\lambda t) f^0_{ij}, \\ f_{ij}(0) = f^0_{ij}, \end{cases} \tag{4.22}$$

where $J^{\star}$ is given by (4.9).

Therefore (4.22) can be written in the form of the integral equation:

$$f = N(f),$$

where $N(f)$ is given by

$$\begin{aligned} (N(f))_{ij} &= f^0_{ij} + \int_0^t \exp(\lambda(s-t)) J^{\star}_{ij}[f](s) \\ &= f^0_{ij} + \psi(f)(t). \end{aligned} \tag{4.23}$$

Then, the proof can be obtained by application of classical fixed point methods. Using Lemma 4.2 one has:

$$\|N(f)\|_\infty \leq \|f_0\|_1 + \frac{C_1}{\lambda}\|f\|^2_\infty,$$

$$\|N(f) - N(g)\|_\infty \leq \frac{C_1}{\lambda}(\|f\|_\infty + \|g\|_\infty)\|f - g\|_\infty.$$

Take f_0 and λ such that:

$$\frac{4C_1}{\lambda}\|f_0\|_1 < 1,$$

and let

$$d = \sqrt{1 - \frac{4C_1}{\lambda}\|f_0\|_1}.$$

Consider

$$a = \lambda \frac{1 - \sqrt{d}}{2C_1\|f_0\|_1}.$$

This implies that N is a contraction on a ball in X of radius $a\|f_0\|_1$ if $\|f_0\|_1 \leq f^0_0 = \frac{\lambda}{4C_1}$ or equivalently if $\lambda \geq \lambda^0 = 4C_1\|f_0\|_1$. Thus, there exists a unique global solution $f(t)$ of Eq. (4.1) on $[0, +\infty)$.

Let

$$C^1_{ij}[f] = \sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m} \eta_{ik}[f]\mathcal{B}^{pq}_{ik}(j)[f] f_{ip} f_{kq},$$

$$C_i[f] = \sum_{k=1}^{n}\sum_{q=1}^{m} \eta_{ik}[f] f_{kq}$$

and

$$D_i[f] = \sum_{k=1}^{n}\sum_{q=1}^{m} \eta_{ik}[f]\nu_{ik}^{jq} f_{kq}.$$

The solution f_{ij} satisfies the following identity:

$$(N(f))_{ij} = (f_{ij}) = \exp\left(-\int_0^t (\lambda + C_i + D_i)(s)ds\right) f_{ij}^0 + \int_0^t \exp\left(\int_t^\tau (\lambda + C_i + D_i)(s)ds\right)(C_{ij}^1 + P_{ij})(\tau)d\tau.$$

It is clear that N maps X_+ into itself if the initial datum (condition) is positive. To complete the proof, the fixed point theorem in X_+ can be applied again using Lemma 4.1. This completes the proof. □

Remark 4.3. Global existence does not mean that the dynamics of the competition can be studied by the present model globally in time. In fact, when tumor cells grow monotonically, they start to aggregate into condensed form. Then model change of type namely into continuum model with space structure, which can be derived from the underlying description delivered by our kinetic approach.

Proof of Theorem 4.3. In this case, i.e. for Eqs. (2.3)–(2.7), $n = 8$ and $L_{ij}[f](t) = 0$ for $i = 1, \ldots, 4$ and $\forall\, j = 1, \ldots, m$, Eq. (4.23) can be written in the form:

$$f = N(f),$$

where $N(f)$ is given by:

$$(N(f))_{ij} = f_{ij}^0 + \int_0^t J_{ij}(f, f)(s), \quad i = 1, \ldots, 4, \tag{4.24}$$

$$(N(f))_{ij} = f_{ij}^0 + \int_0^t \exp(\lambda(s-t))J_{ij}^\star[f](s), \quad i = 5, \ldots, 8. \tag{4.25}$$

Then, the proof can be obtained by application of classical fixed point methods. Using Lemma 4.1 one has:

$$\|N(f)\|_{X_T} \leq \|f_0\|_1 + C_1 T\|f\|_{X_T}^2,$$
$$\|N(f) - N(g)\|_{X_T} \leq C_1 T(\|f\|_{X_T} + \|g\|_{X_T})\|f - g\|_{X_T}.$$

Let T such that

$$4C_1 T\|f_0\|_1 < 1,$$

and let

$$d = \sqrt{1 - 4C_1 T\|f_0\|_1}.$$

Consider

$$a = \frac{1 - \sqrt{d}}{2C_1 T \|f_0\|_1}.$$

This implies that N is a contraction on a ball in X_T of radius $a\|f_0\|_1$ if $T \leq \frac{1}{4C_1\|f_0\|_1}$. Thus, there exists a unique local solution $f(t)$ of Eq. (4.1) on $[0, T]$. This completes the proof of theorem. □

The above qualitative analysis allows to apply computational methods to obtain simulations. As we have seen, the model is characterized by 10 parameters, which is still a small number considering the complexity of the phenomenon under consideration. A detailed sensitivity analysis, suitable to put in evidence the aforesaid phenomenon concerning the growth or depletion of tumor cells, needs a variety of calculations scheduled in a forthcoming paper. However, a somehow limited analysis is proposed in the present paper, which focuses on a detailed study of the parameters ε_1 and ε_{2i} $(i = 6, 7, 8)$. More precisely, simulations aim at investigating if there exists a critical value $\varepsilon_c = \frac{\varepsilon_1}{\varepsilon_{28}}$ of the ratio between these two parameters such that for $\varepsilon < \varepsilon_c$ the immune system has the ability to prevent the growth of cancer cells, namely cells of the fourth functional subsystem, while for $\varepsilon > \varepsilon_c$ the opposite behavior is depicted.

Moreover, simulations should put in evidence how the state of the various functional subsystems evolve in time along the said different dynamics. More precisely, normally differentiated epithelial cells generate with small probability daughter cells with the first hallmark of cancer. These newborn cells can generate, despite the contrast of the immune system, newborn cells with the subsequent hallmarks. The previous generations are suppressed, while the last one can continue to proliferate. In several cases the learning action of the immune system is sufficient to contrast this process. However, for some values of the parameter, tumor cells may continue to grow.

Of course, the specific value of ε_c depends on the value of the other parameters. However, we look for a preliminary analysis of the aforesaid bifurcation problem in view of the more detailed analytic and computational investigation that was announced before.

Simulations are developed for the following values of parameters: $\sigma = 0.5$, $\tau = 1$, $\alpha = 10^{-2}$, $\beta_1 = 10^{-3}$, $\beta_2 = 10^{-1}$, $\gamma = 1$, $\lambda = 0.02$, $\varepsilon_1 = 10^{-3}$, $\varepsilon_{26} = \varepsilon_{27} = 10^{-1}$, and different values of ε_{28}, which models the transition of immune cells to the last hallmark. We choose null initial conditions except for f_{1j} and f_{5j}. We select f^0_{1j} and f^0_{5j} linearly decreasing with respect to the activity.

The objective of the simulations aims at depicting the following emerging behaviors:

cancer cells cannot be suppressed for low values of the said parameter. Therefore these will end up to aggregate into compact multicellular

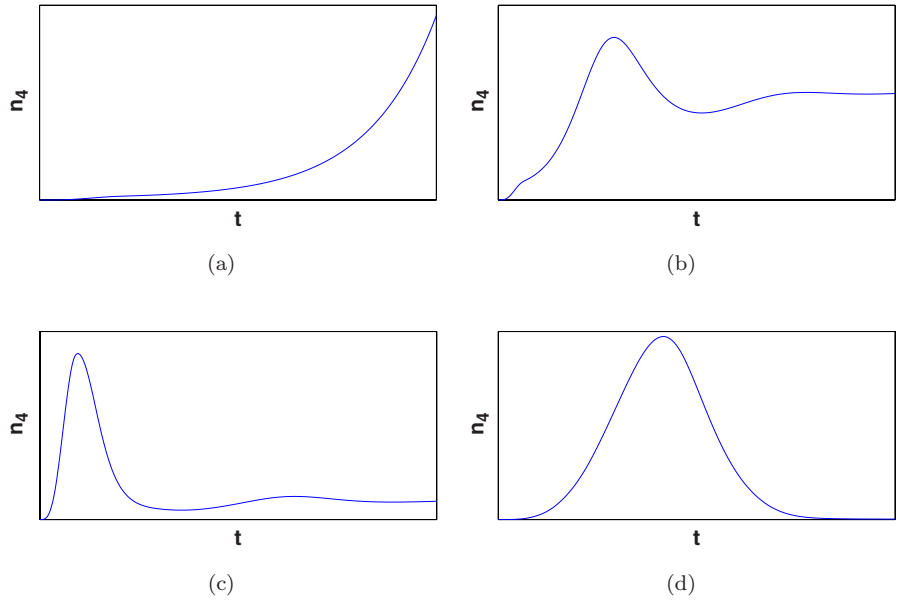

Fig. 4. Evolution of the density of functional subsystem 4 for different values of parameter ε_{28}: (a) $\varepsilon_{28} = 0$, (b) $\varepsilon_{28} = 10^{-4}$, (c) $\varepsilon_{28} = 10^{-3}$, (d) $\varepsilon_{28} = 10^{-2}$.

structures, while for high values immune cells have the ability to learn the presence of cancer cells, which are progressively depleted.

Figure 4 shows different behavior which cancer cells with the most aggressive hallmark experiment for different values of ε_{28}. Figure 5 shows the evolution of n_2 and n_3 that is equal for any choice of ε_{28}, as expected.

As already mentioned, further simulations are planned in a proper research program. However, the specific analysis of the present paper already confirms the following:

- Figure 4 shows that the number density of cancer cells of the last hallmark have an increasing behavior for $\varepsilon_{28} = 0$ as the immune cell is not able to deplete them, while an asymptotic value is reached for increasing value of ε_{28}. Finally, for $\varepsilon_{28} = 10^{-2}$ cancer cells are suppressed. This occurs because as ε_{28} takes greater values, the immune system becomes stronger.
- Figure 5 shows how the number density of preceding hallmarks after a temporary increase decay due to the selection of cells of the highest hallmark.

Referring now to the comments on the black swan[52] reported in Sec. 2.4, we stress that the rare event is the growth of cancer cells, which is generated by a mutation into the highest hallmarks where the immune cells have not anymore the ability to identify the presence of cancer cells and suppress them. As we have seen, it is a Darwinian selective process ruled by cellular properties and specifically on

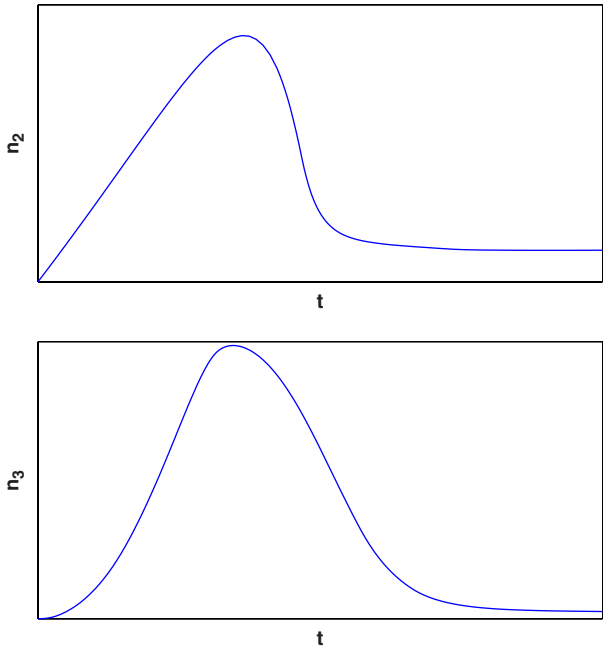

Fig. 5. Evolution of the density of functional subsystems 2 and 3.

the mutation rate. Hence the rare event is related to a mutation that is already a rare event which can cause disaster for the vertebrate carrier of such mutation.

5. Critical Analysis on the Scaling Problem

A mathematical model of immune competition has been proposed in this paper, including mutations and Darwinian selection, based on an extended development of the tools of the kinetic theory for active particles and game theory. Preliminary simulations have shown that the model has the ability to depict some important emerging behaviors of the competition. The approach was developed at the cellular scale by taking advantage of a phenomenological interpretation of cell interactions.

It is plain that this specific modeling can be further refined to obtain an improved model. Empirical data and simulations can contribute to this objective. However, the important problem that remains is the study of the links between the lower and the higher scale. As already mentioned, cancer is a genetic disease. The onset of cancer cells are induced by DNA modifications related to low expression of genes, namely at the molecular scale. Empirical data can indicate groups of genes that cause specific diseases. On the other hand, it is plain that the process is dynamical being ruled by interactions involving genes and the outer environment.

It was argued in Ref. 8 that the same approach to model cellular dynamics can be properly generalized to model the dynamics at the molecular scale. On the other hand, although this conjecture is convincing, it has not yet been transferred into effective models. Therefore the validity of models can be based, at present, on their ability to depict emerging behaviors as described by the modeling of the aforesaid interactions. Moreover, they should describe not only the qualitative behaviors that are repeated and observed, but also those appearing in rare circumstances and that are, at least apparently, not predictable.

On the other hand, the link between the cellular scale and the macroscopic one of tissues has recently given encouraging results as documented in the survey[5] and in the therein cited bibliography. In particular, it has been shown that classical and improved Keller–Segel model can be obtained from the underlying description at the cellular scale.[4] This approach can be possibly extended to the derivation of tissue models for time-evolving cancer phenomena. The classical derivation of models by conservation equations implemented by reaction diffusion description[20] can possibly take advantage of these micro–macro methods.[16]

An additional interesting perspective consists in modeling genetic therapies or activation of the immune system.[45] This aim can be pursued by including external actions in the general mathematical structure.

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