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On the Mathematical Modelling of Complex Biological Systems. A Kinetic Theory Approach (*)

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Abstract. – *This paper deals with the mathematical modelling, based on the kinetic theory of active particles, of a complex biological living system constituted by different populations of cells. The modelling refers to the competition between immune and tumor cells. Moreover, a qualitative and quantitative analysis is developed, to show how the models can describe several interesting phenomena related to biological applications. A final section highlights further research perspectives related to the modelling of genetic mutations.*

1. – Introduction.

Methods of the mathematical kinetic theory for active particles have been recently developed to describe the collective behaviour of large systems of interacting entities and has been finalized to model complex systems in applied sciences, namely systems whose collective behaviour is not described only by the knowledge of the dynamics of the individual entities [1]. The microscopic state of the interacting entities, called *active particles*, includes not only mechanical variables (typically position and velocity), but also an additional variable related to their self organized ability. The mathematical approach of the mathematical kinetic theory for active particles leads to the derivation of evolution equations for the one-particle distribution function over the microscopic state, called *activity*.

This is a new kinetic theory that can be applied to derive various models of practical interest in life sciences, and which includes, as particular cases, the classical models of the kinetic theory, namely the Boltzmann and Vlasov equations [1]. The main difference, with respect to the classical theory, is that interactions follow stochastic rules, technically related to the strategy developed by individuals that belong to living systems. This mathematical approach has

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been focused also on the modelling of multicellular systems and, in particular, of the immune competition as documented in several papers, among others [3], [4], [5], [7], and [13].

Several models concerning the biological phenomena have been proposed in the scientific literature, using different mathematical methods and tools; a large bibliography on mathematical methods in cancer modelling is reported in the recent review paper [2].

It is worth to point out that the approach proposed in this paper substantially differs from the approach of population dynamics, e.g. [8], where the state of the system is described by the number of cells expressing a certain biological function, as well as from the approach of population dynamics with internal structure, e.g. [15], expressed in terms of partial differential equations, where the internal structures are regarded as additional independent variables.

This paper deals with the modelling of the evolution of cancer cells and their competition with the immune system. The output may either be the growth of the number of tumor cells, which subsequently aggregate into solid forms, or their progressive destruction, due to the action of the immune system. A *background concept*, to be kept in mind, is that the modelling of living systems needs technically complex mathematical methods, which may be substantially different from those used to deal with inert matter. Therefore, models of multicellular systems should include the *expression of biological functions* of the populations of cells, as well as their role to organize the movement of cells, proliferating and destructive events, the ability to select evolutionary mutations and organize trend towards equilibrium configurations, which do not correspond to those observe in the inert matter. Moreover, systems in biology cannot be simply observed and interpreted at a macroscopic level, because a system constituted by millions of cells shows at the macroscopic level only the output of the cooperative and organized behaviours which may not, or are not, singularly observed. Therefore, generally, all scales are needed to represent real biological systems, and it is necessary a constructive effort to reduce complexity.

The *theory of modules*, proposed by Hartwell [12], provides useful hints to deal with the above mentioned complexity problem. A constructive interpretation of such a theory suggest to consider as a single *module* the collective behaviour of systems of cells which have the ability of expressing certain biological functions.

Accordingly, the modelling approach proposed in this paper deals with biological systems which can be regarded as an assembly of sub-systems, each acting as a module with the ability of expressing a well defined biological function. A module is generally defined at one scale only. A biological system is a network (i.e., a system of systems) of interacting sub-systems, each defined at a different scale. Specifically, a subsystem is an entity which has to be defined with reference to the specific analysis under consideration. Subsequently, equations

of the mathematical kinetic theory for active particles are used to model large systems of interacting cells; for instance, multicellular systems are constituted by different populations, each identified by the expression of a different biological function. Models are specifically focused on the description, by mathematical equations, of the immune competition.

The contents of the paper, after this introductory section, are organized as follows: Section 2 presents the general mathematical framework and derives two specific models of tumor immune competition: Model $\boldsymbol{C}$, corresponding to the early dormant stage when no proliferation or destruction of cells occurs, while interactions only modify the biological functions; and Model $\boldsymbol{P}$ corresponding to the last stage, when the proliferating or destructive events are predominant with respect to biological mutations. Section 3 deals with a qualitative analysis of the initial value problem generated by the application of the above models to the analysis of biological aspects of the competition. Section 4 provides some simulations finalized to visualize phenomena of the immune competition and complete the description offered by the qualitative analysis. Section 5 proposes a critical analysis addressed to show how the mathematical framework may be further developed towards relatively more accurate models including the role of genetic mutations in the evolution of the biological systems.

2. – Mathematical Framework and Modelling.

This section first derives the *mathematical framework* which can be used to describe the tumor-immune system competition. Subsequently, two specific models of tumor-immune cells competition are derived in view of their qualitative and computational analysis.

2.1 – *The Mathematical Framework.*

Let us consider a large system of n interacting cells populations labelled by the index $i = 1, \ldots, n$. Each population is characterized by a different way of expressing its peculiar activities as well as the interactions with the other populations. Modelling by methods of the mathematical kinetic theory essentially means defining the microscopic state of the cells and deriving an evolution equation for the distribution function over the above state. The analysis is developed in the case of spatial homogeneity.

The variable charged to describe the biological state of each cell, called *activity*, is assumed to be a scalar quantity, $u \in \mathbb{R}$. The heterogeneous distribution over the microscopic state is identified by the distribution function, and writes

as follows:

$$f_i = f_i(t,u)\,, \qquad i = 1,\dots,n\,, \tag{1}$$

where $f_i(t,u)\,du$ denotes the number of cells whose state, at time t, is in the interval $[u, u+du]$.

The evolution equation is obtained equating, in the elementary volume of the state space, the rate of increase of particles with microscopic state u to the net flux of particles which attain such a state due to microscopic interactions that include proliferative and destructive events. The following types of binary interactions are considered:

Conservative interactions, between *candidate* or *test* cells and *field* cells, which modify the microscopic activity of the interacting cells, but not the size of the populations;

Proliferative or destructive interactions, between *test* and *field* cells, which generate death or birth of test cells.

In the space homogeneous case, the corresponding balance equation writes as follows:

$$\partial_t f_i(t,u) = C_i[f](t,u) + P_i[f](t,u)\,, \tag{2}$$

where:

- $C_i[f](t,u)$ models the flow, at the time t, into the elementary volume of the state space of the i^{th} population due to conservative interactions:

$$\begin{aligned} C_i[f](t,u) = &\sum_{j=1}^{n} \eta_{ij} \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \mathcal{B}_{ij}(u_*,u^*;u) f_i(t,u_*) f_j(t,u^*)\,du_*\,du^* \\ &- f_i(t,u) \sum_{j=1}^{n} \eta_{ij} \int_{-\infty}^{\infty} f_j(t,u^*)\,du^*\,, \end{aligned} \tag{3}$$

where η_{ij} is the encounter rate, referred to encounters of a *candidate* cell, with state u_* in the i^{th} population and a *field* cell, with state u^* in the j^{th} population. $\mathcal{B}_{ij}(u_*,u^*;u)$ denotes the probability density (with respect to the variable u) that the candidate particles fall into the state u of the *test* cell remaining in the same populations. Conservative equations modify the microscopic state, but not the number of cells.

- $P_i[f](t,u)$ models the net flow, at the time t, into the elementary volume of the state space of the i^{th} population due to proliferative and destructive interactions:

$$P_i[f](t,u) = f_i(t,u) \sum_{j=1}^{n} \eta_{ij} \int_{-\infty}^{\infty} \mu_{ij}(u,u^*) f_j(t,u^*)\,du^*\,, \tag{4}$$

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

Substituting the expressions (3) and (4) into (2), yields:

$$
\begin{aligned}
\partial_t f_i(t,u) = & \sum_{j=1}^{n} \eta_{ij} \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \mathcal{B}_{ij}(u_*, u^*; u) f_i(t, u_*) f_j(t, u^*)\, du_*\, du^* \\
& - f_i(t,u) \sum_{j=1}^{n} \eta_{ij} \int_{-\infty}^{\infty} f_j(t, u^*)\, du^* \\
& + f_i(t,u) \sum_{j=1}^{n} \eta_{ij} \int_{-\infty}^{\infty} \mu_{ij}(u, u^*) f_j(t, u^*)\, du^* .
\end{aligned} \tag{5}
$$

If f_i is known, then macroscopic gross variables can be computed, under suitable integrability properties, as moments weighted by the above distribution function. For instance, the *size* of the i^{th} population is given by:

$$
n_i = n_i[f_i](t) = \int_{-\infty}^{\infty} f_i(t,u)\, du . \tag{6}
$$

First order moments provide the *linear biological macroscopic* quantities which will be called *activation* at the time t, and are computed as follows:

$$
A_i = A[f_i](t) = \int_{-\infty}^{\infty} u f_i(t,u)\, du . \tag{7}
$$

Specific models can be derived from the above structure (5), by a detailed modelling of microscopic interactions, i.e. defining expressions of the terms η, $\mathcal{B}$, and μ.

2.2 – *Derivation of Mathematical Models.*

Let us now consider, as an application, the modelling of the competition among two cellular populations, $n = 2$. The first population is constituted by cells of a specific biological system, or *environmental* cells (i.e. endothelial cells), whose activity denotes how far cells are from the biological normality. The activity of the environmental cells is called *progression*, and is defined by the scalar variable $u \in \mathbb{R}$, where $u \leq 0$ identifies the state of the normal cells, and $u > 0$ the state of abnormal cells. The level of malignancy increases with increasing progression: growth-autonomous, tissue-invasive, metastatically competent.

The second population is constituted by cells of the immune system, whose activity denotes how immune cells contrast cells of the first population. The

activity of the immune cells is called *activation*, and it is defined by the scalar variable $u \in \mathbb{R}$, where $u \leq 0$ identifies the state of the inhibited immune cells, and $u > 0$ the state of the active immune cells. The degree of ability to contrast abnormal cells increases with increasing activation.

Referring to the momenta of the distribution function, we indicate in the sequel with n_1^T the size of abnormal (tumor) cells, and with n_1^E the size of normal cells:

$$n_1^T[f_1](t) = \int_0^\infty f_1(t,u)\,du\,, \qquad n_1^E[f_1](t) = \int_{-\infty}^0 f_1(t,u)\,du\,, \tag{8}$$

while the size of active immune cells, n_2^A, and the size of inhibited immune cells, n_2^I are:

$$n_2^A[f_2](t) = \int_0^\infty f_2(t,u)\,du\,, \qquad n_2^I[f_2](t) = \int_{-\infty}^0 f_2(t,u)\,du\,. \tag{9}$$

The first example, called **Model C**, is related to (prevalent) conservative interactions. It corresponds to a competition where no proliferation or destruction yet occur, while interactions only modify the biological functions of the cells of the two populations. Model C can be applied to analyze latent immune competitions, when cells degenerate before the onset of relevant proliferation phenomena which give evidence of the presence of a pathological state.

The model is derived from the framework (5) by modelling interactions at the cellular level according to the following assumptions:

H.C.1: The most probable output of conservative interactions between cells of the first population is:

$$u_*, u^* \in \mathbb{R} : \; m_{11} = u_* + a_{11}\,.$$

H.C.2: The progression of an abnormal cell decreases due to encounters with an active immune cell, and the most probable output of the microscopic state after the interaction is given as follows:

$$u_*, u^* \geq 0 : \quad m_{12} = u_* - a_{12}\,.$$

H.C.3: The most probable output of the microscopic state of the immune cell after the interaction with progressing cells, with state u^*, is given as follows:

$$u_* \geq 0\,, u^* \geq 0 : \quad m_{21} = u_* - a_{21}\,.$$

All the other interactions give a trivial output, i.e. do not lead to a modification of the microscopic state of the candidate cell. Moreover, assuming that $\mathcal{B}_{ij}$ is a

delta function over the most probable output $m_{ij}(u_*, u^*)$, which depends on the microscopic states u_* and u^* of the interacting pairs.

$$\mathcal{B}_{ij}(u_*, u^*; u) = \delta(u - m_{ij}(u_*, u^*)) \,, \tag{10}$$

and inserting all above assumptions into the framework (5) yields:

$$\begin{cases} \partial_t f_1(t,u) = n_1[f_1](t)[f_1(t, u - a_{11}) - f_1(t,u)] \\ \qquad\qquad + n_2^A[f_2](t) f_1(t, u + a_{12}) U_{[0,\infty)}(u + a_{12}) \\ \qquad\qquad - f_1(t,u) n_2^A[f_2](t) U_{[0,\infty)}(u) \,, \\ \partial_t f_2(t,u) = n_1^T[f_1](t) \big[f_2(t, u + a_{21}) U_{[0,\infty)}(u + a_{21}) \\ \qquad\qquad - f_2(t,u) U_{[0,\infty)}(u) \big] \,. \end{cases} \tag{11}$$

This model is characterized by three phenomenological parameters related to mass conservative encounters. All parameters are positive quantities (eventually equal to zero) small with respect to unity. In details:

– a_{11} is related to the variation of the progression due to encounters between environmental cells. It describes the tendency of a normal cell to degenerate and to increase its progression.

– a_{12} is related to the ability of the active immune cells to reduce the state of abnormal (neoplastic) environmental cells.

– a_{21} is related to the ability of abnormal cells to inhibit the active immune cells.

The second example, called **Model P**, refers to the stage where the distribution over the biological functions reaches a slowly varying value, while the proliferating or destructive events become predominant. This model can be used to analyze the last stage of the competition, when both cell populations have reached a fixed stage of the biological functions, and only proliferating or destructive phenomena are relevant. The model is derived according to the following assumptions:

H.P.1: The proliferation rate of cells of the first populations with $u_* \geq 0$, stimulated by encounters with non-progressing cells $u_* < 0$, is:

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

H.P.2: The proliferation rate of non–progressing cells due to encounters with immune cells, is equal to zero. On the other hand, when $u_* \geq 0$, cells are partially destroyed due to encounters with active immune cells:

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

H.P.3: The proliferation rate of inhibited immune cells due to encounters with cells of the first population is equal to zero. On the other hand, when $u^* \geq 0$, cells proliferate due to encounters with progressing cells:

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

The evolution equation for the distribution function is as follow:

$$\begin{cases} \partial_t f_1(t,u) & = f_1(t,u)\big[\beta_{11} n_1^E[f_1](t) - \beta_{12} n_2^A[f_2](t)\big] U_{[0,\infty)}(u) , \\ \partial_t f_2(t,u) & = \beta_{21} f_2(t,u) n_1^T[f_1](t) U_{[0,\infty)}(u) . \end{cases} \tag{12}$$

This model is characterized by three phenomenological parameters related to proliferative/destructive encounters. Also in this case parameters are positive quantities (eventually equal to zero) small with respect to unity. In details:

– β_{11} is related to the proliferation rate of abnormal cells due to their encounters with normal environmental cells;

– β_{12} is related to the ability of immune cells to destroy abnormal cells;

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

3. – Qualitative Analysis.

The qualitative analysis is focused on the analysis of the well-posedness of the mathematical problem related to the general model and on the study of the asymptotic behaviour of the particular models to analyze the trend of the biological system towards the prevalence of one of the two populations over the other.

Suitable Theorems, followed by interpretation from the biological point of view, are reported in this section while for the proof, the reader is addressed to the already cited book [4]. The analysis, as it can be seen, does not cover the whole panorama of all possible outcomes of the competition. Therefore, the simulations reported in the next section are necessary to complete the analysis.

3.1 – *Local and large time existence.*

Let us consider the initial value problem obtained by linking the initial conditions $f_0 = (f_1(t,0), f_2(t,0))$ with $f_1(t,0) = f_{10}$ and $f_2(t,0) = f_{20}$ to Models **C** and **P**. Local and large time existence of the solutions are proved by application of the classical fixed point theorem. The following function spaces need to be defined:

– $L_1(\mathbb{R})$ 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

$$\| f \| = \| f_1 \|_1 + \| f_2 \|_1 \ . \tag{13}$$

– $\mathcal{X}_+ = \{f = (f_1, f_2) \in \mathcal{X} : f_1 \geq 0, f_2 \geq 0\}$ 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, respectively, in a Banach space $\mathcal{X}$ and $\mathcal{X}_+$, equipped with the norm

$$\| f \|_{\mathcal{Y}} = \sup_{t \in [0,T]} \| f \| \ . \tag{14}$$

Local existence of the solutions is stated by the following:

THEOREM 1. – *There exists a positive constants T and a_0, such that the initial value problem defined linking the models* (11) *and* (12) *with initial conditions $f_0 \in \mathcal{X}_+$, has a unique solution $f \in C([0,T], \mathcal{X}_+)$. The solution f satisfies*

$$f(t) \in \mathcal{X}_+, \quad t \in [0,T] \,, \tag{15}$$

and

$$\| f \| \leq a_0 \| f_0 \|, \quad \forall t \in [0,T] \,. \tag{16}$$

PROOF. – see [4], Chapter 4, pages 60-63.

Large time existence of the solutions, and the analysis of the asymptotic behaviour are obtained analyzing the influence of the parameters of the model on the qualitative behaviour of the solutions.

THEOREM 2 **Model C**. – *There exists a unique, nonnegative, strong solution $f(t)$ in $(L_1(\mathbb{R}))^2$ of the problem obtained linking* (11) *with the initial data $f_0 \in \mathcal{X}_+$, for $t \geq 0$, and for every $f_0 \geq 0$ in $(L_1(\mathbb{R}))^2$. Moreover, the equality $\| f \| = \| f_0 \|$ is satisfied.*

PROOF. – see [4], Chapter 4, pages 64.

THEOREM 3 **Model P**. – $\forall\, T > 0$ *there exists a unique solution $f \in C([0,T], \mathcal{X})$ of* (12) *with the initial data, $f_0 \in \mathcal{X}_+$. The solution satisfies*

$$f(t) \in \mathcal{X}_+, \quad \forall t \in [0,T], \tag{17}$$

and, for some constant C_T depending on T and on the initial data,

$$\sup_{t \in [0,T]} f(t) \leq C_T \,. \tag{18}$$

PROOF. – see [4], Chapter 4, pages 63-64.

3.2 – *Asymptotic behaviour.*

Let us now consider the analysis of the *asymptotic behaviour* of the solutions. It is interesting analyzing the influence of the parameters of the model and of the initial conditions on the bifurcation separating two different behaviours:

i) Growth of progressing cells, while the immune cells are inhibited;
ii) Destruction of progressing cells due to the action of the immune system, which remains active.

The analysis of the asymptotic behaviour refers to the time evolution of the densities n_1^T, n_1^E and n_2^A, while simulations visualize the evolution of the distribution function.

Consider first Model **C**. Detailed results can be given after a further specialization obtained by putting equal to zero a_{12} or a_{11}. Here we focus on the case $a_{11} = 0$, which means that the progressing cells do not show a natural trend to increase their progression. This means that either the cells do not show a trend to degenerate at all, either the phenotypic changes occur so rarely that are negligible with respect to the time scale of the model.

The study of the asymptotic behaviour gives the following result:

THEOREM 4. – *Consider the initial value problem for Model* **C** *in the case* $a_{11} = 0$. *The following properties:*

i) $t \uparrow \quad \Rightarrow \quad n_2^A, n_1^T \downarrow$.

ii) $n_1^T(t)$ *and* $n_2^A(t)$ *satisfy, in the limit* $t \to +\infty$, *the following estimates*

$$\lim_{t\to+\infty} n_1^T(t) \leq exp\left(-\frac{n_2^A(0)}{n_1^T(0)}\right) \int_0^{a_{12}} f_{10}(u)du + \int_{a_{12}}^{+\infty} f_{10}(u)du < n_1^T(0)\,,$$

$$\lim_{t\to+\infty} n_2^A(t) \leq exp\left(-\frac{n_1^T(0)}{n_2^A(0)}\right) \int_0^{a_{12}} f_{20}(u)du + \int_{a_{21}}^{+\infty} f_{20}(u)du < n_2^A(0)\,,$$

hold true.

PROOF. – see [4], Chapter 4, pages 80-82.

Referring to the initial value problem corresponding to Model **P**, (12), it is useful introducing the following parameter

$$\delta = \beta_{11} n_1^E(0) - \beta_{12} n_2^A(0)\,. \tag{19}$$

The following result holds:

THEOREM 5. – *Consider the initial value problem for Model* **P**, *as defined by Eqs.* (12):

- *If* $\beta_{21} = 0$, *then* $n_2^A = Cst, n_1^E = Cst$ *and* n_1^T *satisfies the equality*

$$n_1^T(t) = n_1^T(0)\, exp(\delta t),$$

  thus, if $\delta \geq 0$ *then* n_1^T *increases and if* $\delta < 0$ *then* n_1^T *decreases.*
- *If* $\beta_{21} \neq 0$, *then:*
  - *If* $\beta_{12} = 0$, *then* n_1^T *increases,* $n_1^E = Cst$ *and* n_2 *increases.*
  - *If* $\beta_{12} \neq 0$, *then* $n_1^E = Cst$, n_2^A *increases and:*
    - ⋆ *If* $\delta \leq 0$, *then* n_1^T *decreases and satisfies the following estimate*

$$n_1^T(t) \leq n_1^T(0)\, exp(\delta t). \tag{20}$$

    - ⋆ *If* $\delta > 0$: *if* $n_1^T(0) \neq 0$, *then* $\exists t_0$ *such that* n_1^T *increases in* $[0, t_0]$ *and* n_1^T *decreases in* $[t_0, T]$ $\forall T > 0$.

PROOF. – see [4], Chapter 4, pages 66-72.

The qualitative analysis, although it offers a variety of interesting results, still needs the additional support of computational simulations, as analysis refers to the evolution of the density of the cell populations, while computational simulations can focus directly on the distribution functions, thus enlarging the picture and showing the evolution of the heterogeneity of the distribution functions over the microscopic variable.

4. – Simulations.

This section deals with the computational analysis of Models **C** and **P**, showing how simulations complete and enlarge the asymptotic scenario depicted by theorems of the previous section.

4.1 – *Conservative Model.*

The number of cells in Model **C** is constant in time since the observation time is short and no proliferation phenomena occurs, while the distribution function over the microscopic state shifts toward higher or lower values. The evolution is ruled only by the evolution of the states, and the expected behaviour strongly depends of the ability of the cells of a population to inhibit the competitor cells of the other population, and thus on the ratio between a_{21} and a_{12}. An additional role is played by the parameter a_{11} related to the tendency to degenerate of the cells of the first population. Thus, it is expected a complex scenario, dependent on the values of the conservative parameters.

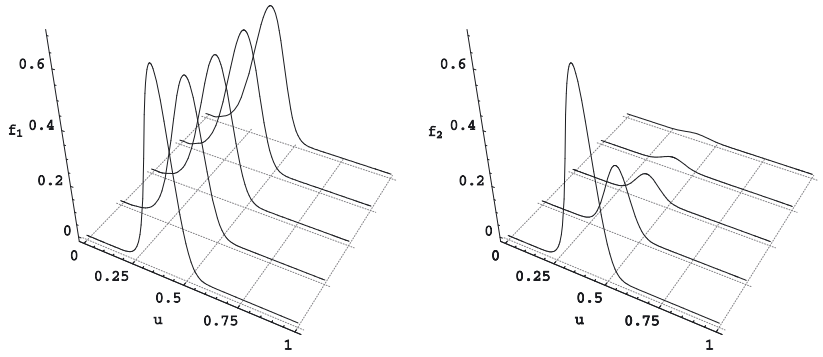

Fig. 1. – $a_{11} = 0$, $a_{12} = 0.1$, $a_{21} = 0.9$. Model C. Evolution in time of the distribution functions. Evolution of neoplastic cells (on the left) and immune suppression (on the right).

The qualitative scenario studied in Theorem 4 refers to the Model in which no degeneration occurs, $a_{11} = 0$, and only the parameters a_{21} and a_{12} are different from zero. The Theorem states that:

$$n_2^A \downarrow \qquad \text{and} \qquad n_1^T \downarrow .$$

As it is expected, simulations show that both neoplastic and immune cells are reduced during the competition (since no proliferation may occur). However, simulations complete the results of the qualitative analysis showing that asymptotically only one cell population survives and the other is completely depleted. Moreover the survival or the defeat of each population depends on the ratio between the values of a_{21} and a_{12}, as well as on the initial conditions.

Let us now consider the same initial condition for neoplastic and immune cells. If $a_{21} > a_{12}$, the ability of neoplastic cells to inhibit immune cells is greater

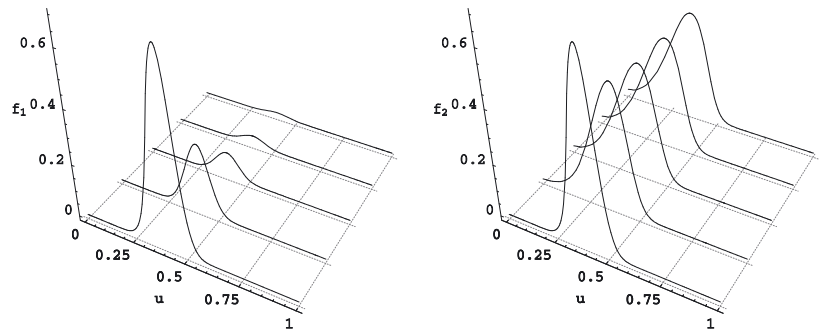

Fig. 2. – $a_{11} = 0$, $a_{12} = 0.9$, $a_{21} = 0.1$. Model C. Evolution in time of the distribution functions. Reduction of neoplastic cells (on the left) and immune survival (on the right).

than the ability of immune cells to reduce the state of neoplastic cells. The final output is a complete inhibition of immune cells and a final survive of neoplastic cells, as reported in Figure (1).

If $a_{21} < a_{12}$, the final scenario is a reduction of the state of the neoplastic cells, until their complete depletion and the final survival of immune cells, as reported in Figure (2).

Simulations may also investigate how this asymptotic behaviour is modified if also the tendency of cells to degenerate, i.e. $a_{11} \neq 0$, is considered.

4.2 – *Proliferative Model.*

The Model P is such that proliferating/destructing events are predominant. Simulations aim at completing the qualitative analysis proposed in the previous section.

Let define a **weighted critical immune density** $n_{2_C}^A = \beta^*$ with

$$\beta^* = \frac{\beta_{11}}{\beta_{12}}\, n_1^E(0)\,, \tag{21}$$

product between the initial number of environmental cells and the ratio of the proliferation rate of abnormal cells and the ability of immune cells to destroy them. The results of Theorem 5 can be summarized as follows.

$$\text{If } \; n_2^A(0) \geq n_{2_C}^A = \beta^* \; (\delta \leq 0) \; : \begin{cases} n_2^A(t) \uparrow\,, \\ n_1^T(t) \downarrow\,; \; \exists \delta \leq 0 : n_1^T(t) \leq n_1^T(0)\, exp\,(\delta t)\,. \end{cases}$$

$$\text{If } \; n_2^A(0) < n_{2_C}^A = \beta^* \; (\delta > 0) \; : \quad \begin{cases} n_2^A(t) \uparrow\,, \\ \exists t_0 \; : \; n_1^T \uparrow\,, \forall\, t \in [0, t_0] \text{ and} \\ \qquad n_1^T \downarrow\,, \forall\, t \in [t_0, T]\,, \forall T > 0 \end{cases}$$

Therefore, the immune system is stimulated to grow by the presence of abnormal (aggressive) cells, and its density increases, while the following two behaviours are predicted by the Model:

– If $n_2^A(0) \geq \beta^*$, i.e. $\delta \leq 0$, the number of abnormal cells decreases with the rate of decreasing is given by Estimate (20).

– If $n_2^A(0) < \beta^*$, i.e. $\delta > 0$, at the beginning the number of abnormal cells grows, since the number of immune cells is not sufficient to contrast them. Nevertheless, since the immune cells are stimulated to proliferate, after a certain critical time t_0 their number will be large enough to reduce the number of abnormal cells.

Some computational analysis may be useful to complete the above interpretation. Indeed, simulations show the evolution of the distribution functions,

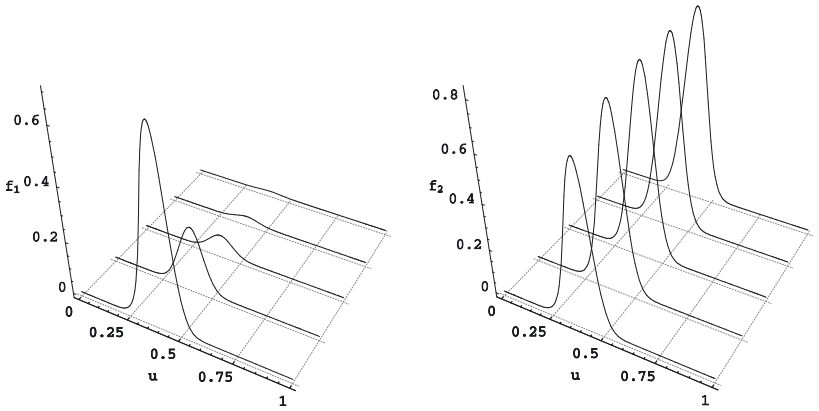

Fig. 3. – $\beta_{11} = 0.1$, $\beta_{12} = 0.9$, $\beta_{21} = 0.1$, $\delta \leq 0$. Model P. Evolution in time of the distribution functions. Depletion of neoplastic cells (on the left) and immune cell proliferation (on the right).

thus providing a deeper glance on the inner structure of the system, giving additional information with respect to the theorems on the asymptotic behaviour which refer to the evolution of the densities. Therefore, if $n_2^A(0) \leq \beta^*$, i.e. $\delta \leq 0$, a decrease from the beginning of the number of neoplastic cells and an increase for of the number of immune ones, see Figure (3), occurs.

The opposite behaviour is obtained if $n_2^A(0) > \beta^*$, i.e. $\delta > 0$, where immune cells are stimulated to proliferate, while neoplastic ones increase at the beginning and after a certain critical time start to be depleted, see Figure (4).

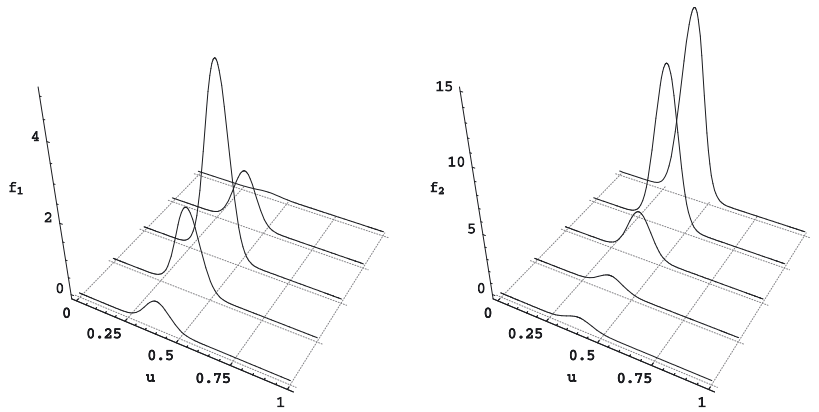

Fig. 4. – $\beta_{11} = 0.9$, $\beta_{12} = 0.1$, $\beta_{21} = 0.1$, $\delta > 0$. Model P. Evolution in time of the distribution functions. Initial increase and final depletion of neoplastic cells (on the left) and immune proliferation (on the right).

5. – Perspectives.

According to the biological literature, e.g. [11], the onset of cancer is caused by genetic instability that generates low or over-expression of the genes which are responsible of tumorigenesis. Such instability can occur during DNA replication, or can be caused by interaction with other mutated genes, or with the external environment. Therefore, the onset of cancer is a multistep, multipath and multiscale process in which the accumulation of genetic mutations causes increasing cell malignity. A deeper insight into the dynamics at the molecular level seems to be necessary to capture the essence of the complexity of the system which may be viewed as an evolutionary process, [14].

As documented in the review paper [2], different mathematical approaches have been proposed to deal with this evolutionary perspective of gene mutations and tumorigenesis. Among others, the paper [9] proposes a population model where the competition of interacting cells is ruled by a Darwinian evolution. Thus, "winner" cells proliferate, retaining the phenotypic properties which give their competitive advantage, at the expense of "loser" cells.

The above models are described by deterministic interactions, while stochastic events are typical in the phenomena under consideration, see for instance paper [10], which is focused on the stochastic dynamics of gene interaction as the pattern in cancer initiation and progression related to mutations. This observation encourages to look at the use of developments of the classical methods of statistical and quantum mechanics.

A recent work, still in progress, [6], starting from the above suggestions, attempts to describe, by methods of the kinetic theory for active particles, the role of genetic mutations in the onset and progressive development of cancer.

The above paper focuses on the competition between tumor and immune cells, with progressive genetic mutations from an initial normal state to a final neoplastic state. The mutations are assumed to cause the *transition of populations*, which describes the proliferation of cells in a new population with a larger level of malignancy, with respect to the mother cell. The jump of population is introduced to model the mutations which will give a competitive advantage to the tumor cells, like the acquisition of a specific *hallmark*, [11].

To describe these type of phenomena, the mathematical framework proposed in Section 3, (2), should be generalized to include the *proliferation with population transition*. The proliferating term (4) should be modified as follows:

$$P_i[f](t,u) = \sum_{h=1}^{n}\sum_{k=1}^{n} \eta_{hk} \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \mu_{hk}^{i}(u_*,u^*;u) f_h(t,u_*) f_k(t,u^*)\, du_*\, du^*\,, \tag{22}$$

where $\mu_{hk}^{i}(u_*,u^*;u)$ models the net proliferation, into the i^{th} population, due interactions, which occur with rate η_{hk}, of the *candidate particle*, with state u_*, of

the h^{th} population and the *field particle*, with state u^*, of the k^{th} population. It is worth to point out that the above expression includes, as a particular case, the proliferation without population transition, i.e. $\mu_{hk}^{i=h}$.

The above structure acts as a paradigm for derivation of specific models including genetic mutations, to be obtained after a detailed modelling of the terms related to the microscopic interactions accordingly to the evolutionary dynamics of the system.

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