On the kinetic theory for active particles: A model for tumor–immune system competition

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Abstract

This paper deals with the qualitative analysis of a model describing the competition between tumor and immune cells. Such competition is characterized by proliferation–destruction phenomena and the interacting entities are characterized by a microscopic state which is modified by interactions. The model also includes the description of the natural trend of immune cells to reach a healthy or sentinel level, even when they have been involved in the competition with the tumor cells. The model is developed in the mathematical framework of the kinetic theory for active particles.

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1. Introduction

The mathematical kinetic theory of large systems of active particles has been developed, in the last two decades, to model complex systems in biology. One of the papers that first introduced the above mentioned approach was authored by Jager and Segel\textsuperscript{[1]} to model the social behavior of colonies of insects. This method has been subsequently developed by other authors\textsuperscript{[2]}, and the bibliography therein, to model population dynamics of interacting individuals whose microscopic state is related to their social and/or biological behavior.

Following the above line, the modelling of the behavior of large populations of interacting cells has been proposed in\textsuperscript{[3]}, with special attention to the immune competition. The ideas proposed in\textsuperscript{[3]} have been developed by various authors, e.g.\textsuperscript{[4–12]}, with reference to different aspects of the competition including the mathematical description of specific therapies.

Mathematical structures concerning the kinetic theory of active particles are proposed in the book\textsuperscript{[13]} with the aim of overcoming the difficulty to deal with living systems\textsuperscript{[14]}. 

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The term active particles [13] is used to denote microscopic entities whose state includes, in addition to geometrical and mechanical variables, also a microscopic state related to their biological behavior, called activity. Microscopic interactions do not follow rules of mechanics (classical or quantum), but are governed by a somehow organized behavior which cannot be simply modelled by the laws of mechanics. Indeed, this is one of the special features of biological systems, and in general of living systems [15].

The interest of the above approach to cancer modelling is documented in the collection of papers of the special issues [16,17], while additional mathematical structures are reported in [18,19] and the bibliography therein, always looking at new paradigms towards a mathematical theory for complex biological systems [15,20].

The mathematical problem to face is the derivation of an evolution equation for the one particle distribution function over the microscopic state of the active particles. The derivation follows rules with some analogy, but also with various differences, to those of the mathematical kinetic theory of classical particles. A crucial difficulty is the modelling of the onset of tumor cells and their evolution due to genetic degeneration [21–25], which generally occurs during replication [26]. The onset of tumor cells generates the immune competition [27] which involves a complex hiding and learning dynamics [28,29].

This paper deals with a development of the model proposed in [4] to include the trend of immune cells to go back to the sentinel level when tumor cells are successfully eliminated. It is particularly important taking into account this trend in the modelling of therapeutical actions [7]. The objective of this paper is precisely the same as that of Section 3 of [5], while its technical differences with respect to [5] will be analyzed in Section 2.

The contents of this paper are as follows: Section 2 deals with the derivation of the mathematical model. Sections 3 and 4 develop the qualitative analysis of the initial value problem with special attention to the trend of solutions. The analytic results are reported Section 3, while Section 4 deals with the mathematical proof. The biological interpretation of the results is proposed in Section 5.

2. On the derivation of the model

This section deals with a concise description of the model proposed, that is developed in the framework proposed in [4], where the interested reader is directed for more details. This framework may be classified as mean-field modelling, according to the fact that a test cell feels the presence and interacts with the surrounding field cells localized in a suitable volume around the test cell.

**Assumption 2.1.** Cells and particles are homogeneously distributed in space. The system is constituted by the following populations: cells or particles of the aggressive host, immune cells and environmental cells. Each population is labeled, respectively, by the indexes \( i = 1, 2, 3 \).

**Assumption 2.2.** Each cell is characterized by a certain state \( u \in I \subseteq (0, +\infty) \) describing its main activity:

- the progression of the host cells;
- the activation of the immune cells;
- the feeding ability of the environmental cells.

**Assumption 2.3.** The statistical description of the system is described by the number density functions

\[
N_i = N_i(t, u),
\]

which are such that \( N_i(t, u) \, du \) denotes the number of cells per unit volume whose state is, at time \( t \), in the interval \([u, u + du]\). Moreover, if \( n_3^0 \) is the number per unit volume of environmental cells at \( t = 0 \), the description of the system is given by the following normalized distribution functions

\[
f_i = f_i(t, u) = \frac{1}{n_3^0} N_i(t, u).
\]

(This is one of the several possible normalizations we may choose. This choice corresponds to a normalization with respect to what can be considered as the healthy state of the body.)
Remark 2.4. If the distribution function $f_i$ is given, it is possible to compute, under suitable integrability properties, the size of the population still normalized by $n_0$

$$n_i(t) = \int f_i(t, u) \, du,$$

and first order moments such as the activation

$$A_i(t) = A_i[f_i](t) = \int_I u \, f_i(t, u) \, du,$$

of each population.

Assumption 2.5. The inlet from outer environment maintains the same quantity of environmental cells. In this case the corresponding distribution function $f_3(t, u)$ remains constant with time, i.e.

$$f_3(t, u) = f_3(0, u) := f_3^0(u) \quad \forall t > 0.$$

Assumption 2.6. The mathematical model consists in evolution equations for the distribution functions $f_1$ and $f_2$ corresponding to tumor cells and immune system. Microscopic cells interactions are also distributed in space and are capable both to modify the state of the cells (by interactions defined conservative), and the size (by interactions defined nonconservative).

The mathematical structure of the model is as follows:

$$\partial_t f_i(t, u) + \mathcal{F}_i[f](t, u) = S_i[f](t, u) + I_i[f](t, u)$$

for $i = 1, 2$, where $f = (f_1, f_2, f_3)$, $\mathcal{F}_i[f](t, u)$, $S_i[f](t, u)$ and $I_i[f](t, u)$ are defined in the following way.

(i) 

$$\mathcal{F}_i[f](t, u) := \partial_u \left[ f_i(t, u) \sum_{j=1}^3 \int_I \varphi_{ij}(u, w) f_j(t, w) \, dw \right]$$

corresponds to actions of the field cells in the state $w$ of the $j$th population which modify the state $u$ of the test cells of the $i$th population into a new one and are modelled by the conservative action function $\varphi_{ij} = \varphi_{ij}(u, w)$.

(ii)

$$S_i[f](t, u) := \sum_{j=1}^3 \int_I \int_I \psi_{ij}(v, w; u) f_i(t, v) f_j(t, w) \, dv \, dw$$

corresponds to proliferation and/or death phenomena. The nonconservative action function $\psi_{ij} = \psi_{ij}(v, w; u)$ models the generation or the destruction of the cells of the $i$th population in the state $u$ as a consequence of the actions of the field cells in the state $w$ of the $j$th population over test cells of the $i$th population in the state $v$.

(iii) $I_i[f](t, u)$ corresponds to a term describing both phenomena as input or output of external sources or sinks (for example, production of immune cells by the bone marrow or destruction of tumor cells by medical treatment), than phenomena describing the tendency of the body to reach a given healthy state.

This general framework can generate specific models after a detailed modelling of the cell interactions, corresponding to the following phenomenological assumptions:

- The progression of neoplastic cells is not modified by interactions with other cells of the same type: $\varphi_{11} = 0$. On the other hand, it is weakened by interaction with immune cells (linearly depending on their activation state) and it is increased by interactions with environmental cells (linearly depending on their feeding ability). The effect increases with increasing values of the progression: $\varphi_{12} = -\alpha_{12} w u, \varphi_{13} = \alpha_{13} w u$.

- The defense ability of immune cells is not modified by interactions with other cells of the same type and with environmental cells: $\varphi_{22} = \varphi_{33} = 0$. On the other hand, it is weakened by interactions with tumor cells (linearly depending on their activation state) due to their ability to inhibit the immune system: $\varphi_{21} = -\alpha_{21} w u$. 

The nonconservative action function $\psi_{ij}$ is assumed to be a delta function over the state $v$ of the interacting test cell: $\psi_{ij}(v, w; u) = p_{ij}(v, w) \delta(u - v)$.

No proliferation of neoplastic cells occurs due to interactions with other cells of the same type: $p_{11} = 0$. On the other hand, interactions with immune cells generate a destruction linearly depending on their activation state and a proliferation by interactions with environmental cells depending on their feeding ability and the progression of tumor cells: $p_{12} = -\beta_{12}u_1$, $p_{13} = \beta_{13}u_3$.

No proliferation of immune cells occurs due to interactions with other cells of the same type: $p_{22} = 0$. On the other hand, interactions with tumor cells generate a proliferation linearly depending on their defense ability and on the activation state of tumor cells: $p_{21} = \beta_{21}u_1$.

No source or sink terms referred to tumor and environmental cells are considered: $I_1 = I_3 = 0$. On the other hand, we consider in the model a term $I_2$ describing the tendency of the immune system to relax to a given healthy state, represented by a distribution function $f_2^*(\cdot)$. At this phenomenon corresponds the following relaxation term

$$I_2(f)(t, u) =: -\lambda[f_2(t, u) - f_2^*(u)],$$

with $\lambda$ a positive constant. We emphasize that it is the presence of this relaxation term in the equation for $f_2$ that makes the model different from the one already studied in [4]. We include the modelling of the important phenomenon that consists in the natural trend of the immune cells to try to reach a sentinel level, even after being involved in the competition with the tumor cells.

The mathematical model described is characterized by various phenomenologic positive parameters which may be classified into two groups:

- $\alpha$-parameters which refer to conservative encounters and, specifically, to inhibition activity of tumor cells, to the weakening ability of immune cells, and to modifications of the feeding ability of environmental cells. Interactions modify the state of the cells, but not their number;
- $\beta$-parameters which refer to encounters that modify the number of cells due to proliferative or destructive actions.

The seven parameters of the model have to be regarded as positive, small with respect to one and constant. We point out that each of them has a precise biological meaning, referred to a specific role in the competition between immune and tumor cells described by the model.

Based on the above modelling of cell interactions, we are now able to derive the evolution equation (2.3) for $f_1$ and $f_2$:

$$\partial_t f_1(t, u) + \partial_u(-\alpha_{12}u A_2(t) f_1(t, u) + \alpha_{13}u A_3 f_1(t, u)) = -\beta_{12} A_2(t) f_1(t, u) + \beta_{13} A_3 f_1(t, u) \quad (2.4a)$$

and

$$\partial_t f_2(t, u) + \partial_u(-\alpha_{21}u A_1(t) f_2(t, u)) = \beta_{21} u A_1(t) f_2(t, u) - \lambda(f_2(t, u) - f_2^*(u)), \quad (2.4b)$$

for all $t, u \in \mathbb{R}_+$, complemented with initial conditions:

$$f_1(t = 0, u) = f_1^0(u) \quad \text{and} \quad f_2(t = 0, u) = f_2^0(u). \quad (2.5)$$

No boundary condition is needed for $u = 0$ since the transport fields all vanish at this point.

An evolution equation for the immune system including a relaxation term was already considered in Section 3 of [5]. In that paper the model includes the evolution equation (2.4a) for the distribution $f_1$, a slight modification of Eq. (2.4b) for $f_2$, but it also includes an evolution equation for the activity $A_3$ of the environmental cells, so reproducing the production of new cells replacing the dead ones in order to reach the usual healthy state of the body. This makes the mathematical analysis of the system carried out in [5] technically different with respect to the one presented here.

3. Main results

We present here the analytic results we shall prove in this paper. Let us assume that the initial data $f_i^0$ ($i = 1, 2, 3$) fulfill the following estimate:

$$\int_0^\infty e^{\tau u} f_i^0(u) du < \infty \quad \text{for all } \tau > 0, \quad (3.1)$$
\[ \mathcal{E}_0 = \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0(u) du < \infty, \tag{3.2} \]

and

\[ \int_0^\infty (1 + u) f_2^0(u) du < \infty. \tag{3.3} \]

Moreover, we assume that

\[ f^*_2(u) \leq f_2^0(u) \quad (u > 0). \]

The existence of solutions to the system (2.4) and (2.5) is provided by the following:

**Theorem 3.1.** Let us assume that \( f_1^0, f_2^0 \) and \( f_3^0 \) satisfy respectively (3.1), (3.2) and (3.3). Then there exist solutions \( f_1, f_2 \in C \left( [0, \infty), L^1((1 + u), du) \right) \) to the initial value problem (2.4) and (2.5) (in the distributional sense). These solutions satisfy the estimates:

\[ \int_0^\infty e^{\tau} f_1(t, u) du \in L^\infty([0, T]), \quad \forall \tau, T > 0, \]

\[ \int_0^\infty \exp(\beta_{21}u/\alpha_{21}) f_2(t, u) du \leq \int_0^\infty \exp(\beta_{21}u/\alpha_{21}) f_2^0(u) du. \tag{3.4} \]

Concerning the time-asymptotic behavior of the solutions to (2.4), one expects, in the spirit of [4], the following dichotomy:

(i) Either the immune system wins and eliminates the tumor cells of the organism. In this case, the immune system goes back to its healthy state corresponding to the sentinel distribution \( f^*_2 \).

(ii) Or the immune system is not able to contract the neoplastic growth. In this case, tumor cells increase their activity and inhibit the activity of the immune cells (the number of immune cells at time \( t > 0 \) being always greater than the initial number of immune cells).

As a first step towards a proof of this conjecture, we present hereafter several partial results concerning the time evolution of some moments of \( f_i \) (\( i = 1, 2 \)). Unfortunately, we have not been able to prove that these two opposite behaviors are the only admissible ones. From the mathematical viewpoint, the complete proof of the dichotomy described here above remains only a conjecture.

Our first result provides sufficient conditions ensuring the blow up as time goes to infinity of the aggressive host. Precisely, we define

\[ \mathcal{E}_* = \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f^*_2(u) du. \]

**Theorem 3.2.**

(1) If \( \alpha_{13} \beta_{21} A_3^0 - \alpha_{21}(\alpha_{12} + \beta_{12})(\mathcal{E}_* - n_2^*) > 0 \) then

\[ \lim_{t \to \infty} A_1(t) = \infty, \quad \lim_{t \to \infty} n_1(t) = \infty \quad \text{and} \quad \liminf_{t \to \infty} A_2(t) = 0. \]

(2) If \( \lim_{t \to \infty} A_2(t) = 0 \), then

\[ \liminf_{t \to \infty} n_2(t) \geq n_2^* + \frac{\beta_{21}}{\alpha_{21}} A_2^*, \]

and

\[ \lim_{t \to \infty} A_1(t) = \infty, \quad \lim_{t \to \infty} n_1(t) = \infty. \]
Remark 3.3. (1) The conclusion of the second item remains valid if one only assumes that \( \int_0^\infty A_2(s)ds < \infty \). Note that, a priori, this does not imply the convergence of \( A_2(t) \) to zero since one cannot exclude oscillations.

(2) Note that the number density \( n_2(t) \) at any time \( t > 0 \) is always greater than \( n^*_2 \) (see Corollary 4.5). The point (2) of the above theorem asserts that, if \( A_2(t) \to 0 \), then \( n_2(t) \) cannot converge to \( n^*_2 \).

On the contrary, one observes that the immune system distribution goes towards the sentinel one provided the activation of the tumor cells is integrable.

Proposition 3.4. If \( \int_0^\infty A_1(t)dt < \infty \) then, for any integer \( k \in \mathbb{N} \),

\[
\lim_{t \to \infty} \int_0^\infty u^k f_2(t, u)du = \int_0^\infty u^k f^*_2(u)du
\]  

(3.5)

and

\[
\lim_{t \to \infty} n_1(t) = 0.
\]  

(3.6)

The following is somehow a converse result to the above proposition. It asserts that, if the number of tumor cells vanishes at infinity and if the relaxation rate \( \lambda \) is large enough, then both the number density and the activity of the immune cell go back to their corresponding values of the sentinel distribution \( f^*_2 \).

Proposition 3.5. Let us assume that \( n_1(t) \) converges to 0 as \( t \) goes to infinity. If

\[
\lambda > \frac{\beta_{12}\alpha_{21}}{\beta_{21}} (\mathcal{E}^* - n^*_2)
\]

then

\[
\lim_{t \to \infty} n_2(t) = n^*_2, \quad \lim_{t \to \infty} A_2(t) = A^*_2 \quad \text{and} \quad \inf_{t \geq 0} A_1(t) = 0.
\]

In the following we present the proofs of the analytical results announced above.

4. Mathematical proofs

Let us give some preliminary result which shall be used in the following. First, one can prove the following lemma, in the spirit of [4, Lemma 5.1]:

Lemma 4.1. Assume that there exists some \( \gamma > 1 \) such that

\[
\int_0^\infty u^\gamma \exp(\beta_{21}u/\alpha_{21}) f^0_2(u)du < \infty.
\]

Then, given \( A_1(\cdot) \in C([0, \infty)) \), consider any weak solution to (2.4b)

\[
f_2 \in C([0, \infty), L^1((1 + u)du)),
\]

one has

\[
\int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2(t, u)du = \mathcal{E}^* + e^{-\lambda t} (\mathcal{E}_0 - \mathcal{E}^*) \leq \mathcal{E}_0, \quad (t \geq 0)
\]  

(4.1)

where \( \mathcal{E}_0 \) is defined by (3.2).

Proof. The proof follows the line of that of [4, Lemma 5.1] by dealing with the new unknown \( g_2(t, u) = f_2(t, u) - f^*_2(u) \). The details are omitted. ■

Corollary 4.2. The zeroth and first order moments of \( f_2 \) satisfy the following uniform estimate:

\[
0 \leq n^0_2 \leq \frac{\beta_{21}}{\alpha_{21}} A_2(t) + n_2(t) \leq \mathcal{E}_0 < \infty \quad \forall t > 0.
\]
Proof. Using the fact that $X \leq e^X - 1$ for any $X \geq 0$:

$$\frac{\beta_{21}}{\alpha_{21}} A_2(t) \leq \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2(t, u)du - n_2(t)$$  \hspace{1cm} (4.2)

and the corollary follows from (4.1). $\blacksquare$

Remark 4.3. As in [4], it is possible to show that, if $\int_0^\infty e^{\tau u} f_2^0(u)du = \infty$ for any $\tau > 0$, then $f_2(t, \cdot)$ is not integrable.

The existence result Theorem 3.1 can be proved following the arguments of [4]. Precisely, we consider a sequence of weak solution $(f_i)_n$ $(i = 1, 2)$ of a suitably regularized problem. These solutions belong to $C([0, \infty); L^1((1 + u)du))$ and satisfy the estimates (3.4) uniformly with respect to $n \in \mathbb{N}$. Then, each weak limit of the converging subsequence $(f_i)_n$ also belongs to $C([0, \infty); L^1(1 + u)du))$ and is a weak solution to (2.4).

Let us now investigate the asymptotic behavior of the distribution functions $f_1(t, \cdot)$ and $f_2(t, \cdot)$ as $t$ goes to infinity. We first establish the relations between $n_i(t)$ and $A_i(t)$ $(i = 1, 2)$.

Proposition 4.4. The zeroth and first moments of $f_i$ $(i = 1, 2)$ satisfy the following

$$\frac{d}{dt} n_1(t) = -\beta_{12} A_2(t) n_1(t) + \beta_{13} A_3^0 A_1(t)$$

$$\frac{d}{dt} n_2(t) = \beta_{21} A_2(t) A_1(t) - \lambda (n_2(t) - n_2^*)$$  \hspace{1cm} (4.3)

and

$$\frac{d}{dt} A_1(t) + (\alpha_{12} + \beta_{12}) A_2(t) A_1(t) = \beta_{13} A_3^0 \int_0^\infty u^2 f_1(t, u)du + \alpha_{13} A_3^0 A_1(t);$$

$$\frac{d}{dt} A_2(t) + \alpha_{21} A_2(t) A_1(t) = \beta_{21} A_1(t) \int_0^\infty u^2 f_2(t, u)du - \lambda (A_2(t) - A_2^*).$$  \hspace{1cm} (4.4)

Proof. The Eq. (4.3) (respectively (4.4)) can be derived easily in a formal way by integrating (2.4) over $[0, \infty)$ (resp. by multiplying (2.4b) by $u$ and integrating over $[0, \infty)$). This formal derivation can be made rigorous in the following way. We shall restrict ourselves to the second equation of (4.4), the other identities following the same lines. In a weak sense, the second part of (4.4) reads

$$-\int_0^\infty \xi'(t)dt \int_0^\infty uf_2(t, u)du - \xi(0) \int_0^\infty uf_2^0(u)du$$

$$+ \alpha_{21} \int_0^\infty \xi(t) A_1(t)dt \int_0^\infty uf_2(t, u)du - \beta_{21} \int_0^\infty \xi(t) A_1(t)dt \int_0^\infty u^2 f_2(t, u)du$$

$$+ \lambda \int_0^\infty \xi(t)dt \int_0^\infty u(f_2(t, u) - f_2^*(u))du = 0$$  \hspace{1cm} (4.5)

for any test function $\xi \in C_0^\infty(\mathbb{R}_+)$. Obviously, this is equivalent to proving that

$$\lim_{R \to \infty} \Phi(R) = 0$$  \hspace{1cm} (4.6)

where, for any test function $\xi \in C_0^\infty(\mathbb{R}_+)$, the function $\Phi(\cdot)$ is defined by

$$\Phi(R) = -\int_0^\infty \xi'(t)dt \int_0^R uf_2(t, u)du - \xi(0) \int_0^R uf_2^0(u)du + \alpha_{21} \int_0^\infty \xi(t) A_1(t)dt \int_0^R uf_2(t, u)du$$

$$- \beta_{21} \int_0^\infty \xi(t) A_1(t)dt \int_0^R u^2 f_2(t, u)du + \lambda \int_0^\infty \xi(t)dt \int_0^R u(f_2(t, u) - f_2^*(u))du.$$  

Let $\xi \in C_0^\infty(\mathbb{R}_+)$ and $R > 0$ be fixed. Let us multiply (2.4b) by a test function of the form $\xi(t)\psi_R(u)$ where $\psi_R(\cdot) \in C_0^\infty(\mathbb{R})$ is non-negative, compactly supported on $[-2R, 2R]$ and such that

$$\psi_R(u) = u \text{ on } [0, R] \quad \text{and} \quad |\psi_R(u)| \leq u \text{ for all } u \geq 0.$$
Then, integrating by part with respect to \( dt \) and \( du \), and splitting the integral over \([0, 2R]\) into two integrals over \([0, R]\) and \([R, 2R]\) respectively, one checks that

\[
\Phi(R) = \int_0^\infty \xi'(t) dt \int_R^{2R} \psi_R(u) f_2(t, u) du + \xi(0) \int_R^{2R} \psi_R(u) f_2^0(u) du
\]

\[ - \alpha_2 \int_0^\infty \xi(t) A_1(t) dt \int_R^{2R} u \psi_R(u) f_2(t, u) du \]

\[ + \beta_2 \int_0^\infty \xi(t) A_1(t) dt \int_R^{2R} u \psi_R(u) f_2(t, u) du \]

\[ - \lambda \int_0^\infty \xi(t) dt \int_R^{2R} \psi_R(u) (f_2(t, u) - f_2^*(u)) du. \tag{4.7} \]

Now, to prove (4.6), it suffices to show that each term of the above sum vanishes as \( R \to \infty \). Let us prove it for the last term, i.e.

\[
\lim_{R \to \infty} \int_0^\infty \xi(t) dt \int_R^{2R} \psi_R(u) (f_2(t, u) - f_2^*(u)) du = 0.
\]

According to (3.4), one has

\[
\left| \int_0^\infty \xi(t) dt \int_R^{2R} \psi_R(u) (f_2(t, u) - f_2^*(u)) du \right|
\]

\[ \leq \sup_{u \in (R, 2R)} |u \exp(-\beta_2 u/\alpha_2)| \int_0^\infty \xi(t) dt \int_R^{2R} \exp(\beta_2 u/\alpha_2) |f_2(t, u) - f_2^*(u)| du
\]

\[ \leq 2 \sup_{u \in (R, 2R)} |u \exp(-\beta_2 u/\alpha_2)| \|\xi(\cdot)\|_{L^1(\mathbb{R}^+)} \int_R^{2R} \exp(\beta_2 u \alpha_2) f_2^0(u) du.
\]

Since

\[
\lim_{R \to \infty} \sup_{u \in (R, 2R)} |u \exp(-\beta_2 u/\alpha_2)| = \lim_{R \to \infty} R \exp(-2\beta_2 R/\alpha_2) = 0,
\]

one sees that the last term of (4.7) vanishes as \( R \to \infty \). One proves in the same way that the other terms in (4.7) converges to 0 as \( R \) goes to \( \infty \). This achieves to prove (4.4). We point out that, to prove (4.3), one should make use of the estimate (3.4) on \( f_1(t, \cdot) \). The details are left to the reader who may consult also [5].

A direct consequence of the above proposition is the following result which means that the number of immune cells (at any time \( t > 0 \)) is always greater than \( n_2^* \).

**Corollary 4.5.** For any \( t \geq 0 \),

\[
n_2(t) - n_2^* = \beta_2 \int_0^t \exp(-\lambda (t-s)) A_1(s) A_2(s) ds + \exp(-\lambda t)(n_2^0 - n_2^*). \tag{4.8}
\]

In particular, \( n_2(t) \geq n_2^* \). Moreover,

\[
A_2(t) \geq A_2^* - \frac{\alpha_2}{\beta_2} (n_2(t) - n_2^*) \quad \forall t > 0. \tag{4.9}
\]

**Proof.** The first part of the corollary is a direct consequence of (4.3). Now, from (4.4),

\[
\frac{d}{dt} A_2(t) + \alpha_2 A_2(t) A_1(t) \geq -\lambda (A_2(t) - A_2^*).
\]

Further, from (4.3),

\[
A_2(t) A_1(t) = \frac{1}{\beta_2} \left( \frac{dn_2(t)}{dt} + \lambda (n_2(t) - n_2^*) \right).
\]
so that
\[
\frac{d}{dt} A_2(t) + \frac{\alpha_{21}}{\beta_{21}} \left( \frac{dn_2(t)}{dt} + \lambda(n_2(t) - n_2^*) \right) \geq -\lambda (A_2(t) - A_2^*).
\]

Setting \( F(t) = (A_2(t) - A_2^*) + \frac{\alpha_{21}}{\beta_{21}}(n_2(t) - n_2^*) \), one sees that
\[
\frac{dF}{dt}(t) \geq -\lambda F(t) \quad \text{and} \quad F(0) \geq 0,
\]
so that \( F(t) \geq 0 \) for any \( t \geq 0 \). \( \blacksquare \)

One can complement the above Corollary by the following:

**Lemma 4.6.** Assume that \( n_2(t) \) converges to \( n_2^* \) as \( t \) goes to infinity. Then,
\[
\liminf_{t \to \infty} A_2(t) \geq A_2^* \quad \text{and} \quad \inf_{t \geq 0} A_2(t) > 0.
\]

As a consequence, \( \int_0^\infty A_1(t)A_2(t)dt < \infty \) if and only if \( \int_0^\infty A_1(t)dt < \infty \).

**Proof.** The first part of the lemma is immediately deduced from (4.9). Now, let
\[
a_2 := \inf_{t \geq 0} A_2(t).
\]

If \( a_2 \geq A_2^* \), then obviously \( a_2 > 0 \). If \( a_2 < A_2^* \), the first part of the Lemma implies that there is a \( T > 0 \) such that
\[
\inf_{0 < t < T} A_2(t) = \inf_{t \geq 0} A_2(t).
\]

Therefore, there is a \( t_0 \in (0, T) \) such that
\[
\inf_{t \geq 0} A_2(t) = A_2(t_0) = A_2^* \quad \text{and} \quad \frac{d}{dt} A_2(t_0) = 0.
\]

From (4.4),
\[
\alpha_{21} A_2(t_0) A_1(t_0) \geq -\lambda (A_2(t_0) - A_2^*) = \lambda (A_2^* - a_2) > 0
\]
so that \( a_2 \neq 0 \). This achieves to prove the second assertion. Now, one sees from the proof of the Proposition 3.4 that, if \( \int_0^\infty A_1(t)A_2(t)dt < \infty \) then \( n_2(t) \to n_2^* \). From the first part of the lemma, \( A_2(t) \) is bounded from below. The integrability of \( A_1(\cdot)A_2(\cdot) \) implies then that of \( A_1(\cdot) \). The necessary part comes from the fact that \( A_2(\cdot) \) is bounded according to Corollary 4.2. \( \blacksquare \)

**Remark 4.7.** Note that the above estimate (4.9) is valid without any assumption. In particular, if \( n_2(t) \) converges as time goes to infinity to some \( N_2 \geq n_2^* \) such that \( \beta_{21} A_2^* \geq \alpha_{21}(N_2 - n_2^*) \), then \( A_2(t) \) is bounded from below. In the same way, if \( \liminf_{t \to \infty} A_2(t) \geq A_2^* \), then \( \liminf_{t \to \infty} A_2(t) > 0 \).

**Remark 4.8.** From (4.8), one sees immediately that, if \( \lim_{t \to \infty} n_2(t) = n_2^* \) then \( A_2(\cdot)A_1(\cdot) \) cannot be bounded from below.

**Proposition 4.9.** Let \( \ell = \limsup_{t \to \infty} A_2(t) \). If \( \alpha_{13} A_3^0 > (\alpha_{12} + \beta_{12})\ell \), then
\[
\lim_{t \to \infty} A_1(t) = \infty, \quad \lim_{t \to \infty} n_1(t) = \infty.
\]

**Proof.** Let \( \varepsilon > 0 \) be fixed and let \( T > 0 \) be such that
\[
0 \leq A_2(t) < \varepsilon + \ell \quad \text{for any} \quad t \geq T.
\]

Then, from (4.4),
\[
\frac{d}{dt} A_1(t) \geq [\alpha_{13} A_3^0 - (\alpha_{12} + \beta_{12})A_2(t)]A_1(t)
\]
\[
\geq [\alpha_{13} A_3^0 - (\alpha_{12} + \beta_{12})(\varepsilon + \ell)]A_1(t) \quad \forall t \geq T.
\]
Choosing $\varepsilon > 0$ such that $\alpha_{13}A_{3}^{0} - (\alpha_{12} + \beta_{12})(\varepsilon + \ell) = \delta > 0$, one gets that
\[ A_{1}(t) \geq A_{1}(T)e^{\delta(t-T)} \quad \forall t \geq T \]
so that
\[ \lim_{t \to \infty} A_{1}(t) = \infty. \]

Further, from (4.3)
\[ \frac{d}{dt} n_{1}(t) \geq -\beta_{12}(\varepsilon + \ell)n_{1}(t) + \beta_{13}A_{3}^{0}A_{1}(T)e^{\delta(t-T)} \quad t \geq T \]
so that
\[ \frac{d}{dt} \left[ e^{\beta_{12}(\varepsilon + \ell)t}n_{1}(t) \right] \geq \beta_{13}A_{3}^{0}A_{1}(T)e^{\delta(t-T)}e^{\beta_{12}(\varepsilon + \ell)t} \quad t \geq T. \]
Straightforward computations yield
\[ n_{1}(t) \geq n_{1}(T)e^{-\beta_{12}(\varepsilon + \ell)(t-T)} + \frac{\beta_{13}A_{3}^{0}A_{1}(T)}{\delta + \varepsilon\beta_{12}}(e^{\delta(t-T)} - e^{-(\varepsilon + \ell)\beta_{12}(t-T)}) \quad (t \geq T), \]
which completes the proof of the proposition. ■

We are now in position to prove Theorem 3.2:

Proof of (1). Let us first assume that $\alpha_{13}\beta_{21}A_{3}^{0} - \alpha_{21}(\alpha_{12} + \beta_{12})(\mathcal{E}_{*} - n_{2}^{*}) > 0$. From Eqs. (4.1) and (4.2)
\[ \ell = \limsup_{t \to \infty} A_{2}(t) \leq \alpha_{21}/\beta_{21}(\mathcal{E}_{*} - n_{2}^{*}), \]
and the first two assertions follow from Proposition 4.9. In particular, arguing as in the above proof, for any $\varepsilon > 0$, there exists $T_{1} > 0$ such that
\[ \frac{d}{dt} A_{1}(t) \geq \left[ \alpha_{13}A_{3}^{0} - (\alpha_{12} + \beta_{12})\varepsilon - \alpha_{21}(\alpha_{12} + \beta_{12})(\mathcal{E}_{*} - n_{2}^{*})/\beta_{21} \right] A_{1}(t) \quad \forall t \geq T. \]
Choosing $\varepsilon > 0$ such that $\rho = \alpha_{13}A_{3}^{0} - (\alpha_{12} + \beta_{12})\varepsilon - \alpha_{21}(\alpha_{12} + \beta_{12})(\mathcal{E}_{*} - n_{2}^{*})/\beta_{21} > 0$, we get
\[ A_{1}(t) \geq \exp(\rho(t - T_{1}))A_{1}(T_{1}) \quad \forall t > T_{1}. \quad (4.10) \]
Now, let us assume that
\[ \ell_{0} = \liminf_{t \to \infty} A_{2}(t) > 0. \]
Then, there exists $T_{2} > 0$ such that $A_{2}(t) \geq \ell_{0}/2$ for any $t \geq T_{2}$. According to (4.3) and (4.10),
\[ \frac{d}{dt} \left[ \exp(\lambda t)(n_{2}(t) - n_{2}^{*}) \right] \geq \frac{\beta_{21}e^{-\rho T_{1}}A_{1}(T_{1})\ell_{0}}{2} \exp(\lambda + \rho)t \quad (t \geq \max(T_{1}, T_{2})). \]
This implies that
\[ \lim_{t \to \infty} n_{2}(t) = \infty \]
which contradicts the fact that $n_{2}(t) \leq \mathcal{E}_{0}$ for any $t \geq 0$ (see Corollary 4.2).

Proof of (2). The first assertion follows easily from Remark 4.7 whereas the two last assertions can be easily deduced from Proposition 4.9.

Remark 4.10. Proposition 4.9 and Theorem 3.2 can be interpreted as follows. For given $A_{3}^{0}$ and $f_{2}^{0}$, Proposition 4.9 asserts that, if $A_{2}(t)$ does not grow too much, then the activity and the number density of the tumor system grow up to infinity (exponentially). On the contrary, according to Theorem 3.2, for a given $f_{2}^{0}$, there exists $A_{3}^{0}$ large enough to make $A_{1}(t)$ and $n_{1}(t)$ such that the activity and the number density of the tumor system grow up to infinity (exponentially). This means that the immune system can win only if the activity of the endothelial cells is less than a
threshold value which is explicitly computable. Note that both the results are independent of the (non-trivial) initial data $f_1^0$.

Let us give now the proof of Proposition 3.4. Assume that $A_1(\cdot)$ is integrable over $\mathbb{R}_+$. Since $A_2(\cdot)$ is bounded from Corollary 4.2, it implies that $\int_0^\infty A_1(t)A_2(t)dt < \infty$. Then, using (4.8), one gets that

$$n_2(t) - n_2^0 - e^{-\lambda t}(n_2^0 - n_2^*) = \beta_21 \left( \int_0^{t/2} \exp(-\lambda(t-s))A_2(s)A_1(s)ds + \int_{t/2}^t \exp(-\lambda(t-s))A_1(s)A_2(s)ds \right)$$

$$\leq \beta_21 \left( \exp(-\lambda t/2) \int_0^\infty A_2(s)A_1(s)ds + \int_{t/2}^t A_2(s)A_1(s)ds \right).$$

so that

$$\lim_{t \to \infty} n_2(t) = n_2^*.$$ 

Now, for any $k \in \mathbb{N}$, let us denote by $A_k(t)$ and $A_k^*$ the $k$th order moment of $f_2(t, u)$ and $f_2^*(u)$ respectively:

$$A_k(t) = \int_0^\infty u^k f_2(t, u)du, \quad A_k^* = \int_0^\infty u^k f_2^*(u)du.$$ 

According to (4.1), one sees immediately that, for any $k \in \mathbb{N}$,

$$M_k := \sup_{t \geq 0} A_k(t) < \infty \quad \text{(depending on $k$).}$$

Arguing as in the proof of Proposition 4.4, one can prove that $A_k$ satisfies

$$\frac{d}{dt} A_k(t) + \alpha_{21} k A_1(t) A_k(t) = \beta_{21} A_1(t) A_{k+1}(t) - \lambda (A_k(t) - A_k^*),$$

i.e.

$$\frac{d}{dt} A_k(t) \leq \beta_{21} M_{k+1} A_1(t) - \lambda (A_k(t) - A_k^*).$$

Multiplying by $\exp(\lambda t)$ and integrating over $(0, t)$ leads to

$$e^{\lambda t} (A_k(t) - A_k^*) \leq (A_k(0) - A_k^*) + \beta_{21} M_{k+1} \int_0^t e^{\lambda s} A_1(s)ds.$$

Arguing as in (4.11), one gets that

$$A_k(t) \leq A_k^* + e^{-\lambda t} (A_k(0) - A_k^*) + \beta_{21} M_{k+1} \left( e^{-\lambda t/2} \int_0^t A_1(s)ds + \int_{t/2}^t A_1(s)ds \right).$$

Letting $t \to \infty$, and using the fact that $A_1(\cdot)$ is integrable, one gets

$$\limsup_{t \to \infty} A_k(t) \leq A_k^*.$$ 

In the same way,

$$\frac{d}{dt} A_k(t) \geq -\alpha_{21} k A_1(t) A_k(t) - \lambda (A_k(t) - A_k^*)$$

which implies that

$$A_k(t) - A_k^* \geq e^{-\lambda t} (A_k(0) - A_k^*) - \alpha_{21} k \int_0^t e^{-\lambda (t-s)} A_k(s)A_1(s)ds$$

$$\geq e^{-\lambda t} (A_k(0) - A_k^*) - \alpha_{21} k M_k \int_0^t e^{-\lambda (t-s)} A_1(s)ds.$$
Consequently, arguing as above (see (4.11))

\[ A_k(t) - A_k^* \geq e^{-\lambda t} \left( A_k(0) - A_k^* \right) - kM_k \left( \int_{t/2}^{t} A_1(s) ds + e^{-\lambda t / 2} \int_{0}^{\infty} A_1(s) ds \right). \]

Letting \( t \to \infty \) one gets that

\[ \lim_{t \to \infty} \inf A_k(t) \geq A_k^*. \]

This shows (3.5) for any integer \( k \in \mathbb{N} \). In particular, \( A_2(t) \) is bounded from below. Then, as in [4], one deduces from

\[ n_1(t) = \exp \left\{ -\beta_{12} \int_{0}^{t} A_2(s) ds \right\} \left[ n_1^0 + \beta_{13} A_3^0 \int_{0}^{t} A_1(s) \exp \left\{ -\beta_{12} \int_{0}^{s} A_2(\tau) d\tau \right\} ds \right] \]

(4.13)

that

\[ n_1(t) \leq M \left( e^{-ct} + \int_{0}^{t} A_1(s) e^{-c(t-s)} ds \right) \]

\[ \leq M \left( e^{-ct} + e^{-ct / 2} \int_{0}^{t} A_1(t) dt + \int_{t/2}^{t} A_1(s) ds \right), \]

where \( c = \inf_t A_2(t) \beta_{12} \) and \( M = \max \{ n_1^0, \beta_{13} A_3^0 \} \). This leads to (3.6).

**Remark 4.11.** According to (3.4) and (3.5)

\[ \lim_{t \to \infty} \hat{f}_2(t, \eta) = \hat{f}_2^\ast(\eta) \]

uniformly with respect to \( |\eta| \leq \beta_{21} / \alpha_{21} \),

where \( \hat{f}_2(t, \eta) \) denotes the Fourier transform (over \( \mathbb{R}_+ \)) of \( f_2(t, \cdot), \eta \in \mathbb{R} \). This means that \( f_2(t, \cdot) \) converges to the sentinel distribution in some weak \( L^1 \)-sense.

We end this section with the proof of **Proposition 3.5**: first, from (4.13), one notes that

\[ n_1(t) \geq \beta_{13} A_3^0 \int_{0}^{t} \exp \left\{ -\beta_{12} \int_{s}^{t} A_2(r) dr \right\} A_1(s) ds, \quad t \geq 0. \]

Let \( \lambda^* = \frac{\beta_{12} \alpha_{21}}{\beta_{21}} (E_* - n_2^*) \). Clearly, for any \( t, s \geq 0 \),

\[ \beta_{12} \int_{s}^{t} A_2(r) dr \leq \lambda^*(t - s) \]

so that

\[ n_1(t) \geq \beta_{13} A_3^0 \int_{0}^{t} \exp\{ -\lambda^*(t - s)\} A_1(s) ds, \quad t \geq 0. \]

This last integral goes therefore to 0 as \( t \) goes to infinity. Since \( \lambda > \lambda^* \), one gets that

\[ \lim_{t \to \infty} \int_{0}^{t} \exp\{ -\lambda(t - s)\} A_1(s) ds = 0. \] \hfill (4.14)

One deduces from (4.8) and from the boundedness of \( A_2(t) \) that

\[ \lim_{t \to \infty} n_2(t) = n_2^*. \]

**Lemma 4.6** asserts then that \( \lim \inf_{t \to \infty} A_2(t) \geq A_2^* \). Moreover, from (4.4),

\[ \frac{dA_2(t)}{dt} \leq \beta_{21} A_1(t) \int_{0}^{\infty} u^2 f_2(t, u) du - \lambda (A_2(t) - A_2^*). \]
Since $\int_0^\infty u^2 f_2(t, u)du \leq c < \infty$, one obtains

$$A_2(t) \leq A_2^* + c\beta_{21} \int_0^t \exp\{-\lambda(t-s)\}A_1(s)ds$$

and (4.14) leads to

$$\limsup_{t \to \infty} A_2(t) \leq A_2^*.$$

Finally, the fact that $\inf_{t \geq 0} A_1(t) = 0$ is a direct consequence of (4.14).

**Remark 4.12.** Let us note that, according to Theorem 3.2, the assumption $n_1(t) \to 0$ as $t \to \infty$ may only occur if

$$\frac{\alpha_{12}}{\beta_{21}}(\alpha_{11} + \beta_{11})(\mathcal{E}_* - n_2^*) \geq \alpha_{13}A_3^0.$$

### 5. Biological interpretation

We summarize some of the analytical results presented in Sections 3 and 4. These results essentially deal with the time evolution of the size and the activation of both the populations under consideration. Our results indicate two different behaviors: the trend of the immune system towards a sentinel level (healthy state) which implies the progressive depletion of the aggressive cells (Proposition 3.4) and the opposite one: the growth of the activity of the tumor cells and, as a consequence, the inhibition of the activity of the immune system (Theorem 3.2). In more details,

- Proposition 3.4 asserts that the immune system goes towards a sentinel level provided the activation of tumor cells is somehow controllable (the mathematical condition is integrability with respect to time).
- Proposition 3.5 can be considered partially a converse result to the Proposition 3.4, because it asserts that the number density and the activity of the immune cells go back to the corresponding values of the sentinel distribution if the number of tumor cells goes to zero at infinity and if $\lambda$, the relaxation-rate parameter, is large enough.
- Moreover, for a given activation of the endothelial cells and an initial distribution of immune cells, Proposition 4.9 asserts that, if the activation of the immune cells does not grow too much, then the activity and the number density of the tumor system grows to infinity (exponentially).
- According to Theorem 3.2, for a given initial distribution of immune cells, there always exists a distribution of endothelial cells large enough to make possible that the activity and the number density of the tumor system grows exponentially to infinity. This means that the *immune system can win* only if the activity of the endothelial cells is less than a threshold value which is *explicitly computable*. In other words, for given initial distributions of immune and tumor cells, the immune system may control the neoplastic growth only if the activity of endothelial cells is less than a (explicit) threshold value (see Theorem 3.2-(1) and Remark 4.10). For therapeutical perspectives, this means that a first (necessary) step toward the control of the neoplastic growth is to avoid the organism to provide too much nutriment.

As we have seen in Sections 3 and 4, a specific objective of the analysis of the model presented in this paper has been to relate the behavior of the solutions to the values of the constants of the model. In the spirit of [4,5], we have conjectured that different values of the parameters give rise to only two different possible asymptotic behaviors of the solutions: regression of progressed cells due to an effective action of the immune system, and the opposite case, with the blow up of progressed cells and the progressive inhibition of the immune system. The importance of this aspect lies in the relation between these results and the development of specific therapies. This kind of relation corresponds to a well defined medical motivation related to the action of cytokine signals: one is interested in understanding whether a suitable action on the immune system may make it able to recognize and possibly destroy the tumor cells.

The qualitative analysis presented in Sections 3 and 4 provides useful information especially on the zeroth and first order moments of the distribution functions. We recall that the activities are proportional to the mean progression speed, describing the velocity of evolution toward larger or lower values of the cells states. In detail, this means, for tumor system, evolution toward higher or lower degree of malignity, while for immune system toward higher or lower activation. When tumor cells are progressing, not only their number increases but also their progression values move toward higher values. On the other side, immune cells may increase in time, but their effective action is significant only if their activation also increases.
References