

On a mathematical model of immune competition

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Abstract

This work deals with the qualitative analysis of a nonlinear integro-differential model of immune competition with special attention to the dynamics of tumor cells contrasted by the immune system. The analysis gives evidence of how initial conditions and parameters influence the asymptotic behavior of the solutions.

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1. Introduction

This work deals with the qualitative analysis of a model of competition between progressing (tumor) cells and immune cells. The analysis refers to class of models proposed in [1]—further developed in [2]—which consists of a system of nonlinear integro-differential equations with quadratic type nonlinearity. The structure is somewhat similar to that of classical models of the mathematical kinetic theory [3]. The above model was first proposed to describe the competition between tumor and immune cells, and then developed to model relatively general phenomena of the immune competition. In detail, the model describes the interaction and competition of two cell populations. The first population refers to endothelial cells which, due to DNA corruption, have lost the programmed death cycle and start progressing towards states which are characterized by clonal replication with the feeding contribution of endothelial cells, and are characterized by their ability to inhibit the immune system. The second population is that of immune cells, which contrast (unless inhibited) the progression of the aggressive cells.

Methods of non-equilibrium statistical mechanics and mathematical kinetic theory, as documented in various review papers, e.g. [4], have been developed, following the pioneering paper [5], to describe the evolution of the distribution function over the microscopic state (biological activities or functions) of large complex systems of interacting cells. The literature in the field of biological sciences, with reference to progression phenomena, can be recovered in [6], while general aspects of the immune competition are documented in [7].

The substantial difference of the above models with respect to classical models of population dynamics consists in the fact that the interacting microscopic entities, in this case cells of a vertebrate, are characterized by a microscopic

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state somehow related to the relevant biological functions. Interactions may modify the above states (or functions) and eventually generate birth or death of cells. Mathematical problems consist in the analysis of the influence of microscopic interaction on the qualitative and quantitative behavior of the solutions.

This work deals with the above problem in the particular case of interactions which modify the microscopic state of cells but do not yet generate proliferating and destructive events. This situation corresponds to the very early stage of the immune competition. The analysis should show how the system shifts towards states corresponding to large values of the progression of tumor cells, related to weakening of immune cells, or vice versa. This means evolution towards stages which eventually generate proliferation of tumor cells or destruction of tumor cells by an active immune system. The analysis is developed in two parts: Section 2 briefly describes the mathematical model, while Section 3 develops the qualitative analysis, reporting also some qualitative interpretation of the related analysis.

2. The mathematical model

As already mentioned in Section 1, the model dealt with in this work describes the interaction and competition of two cell populations and is a particular version of a more general model introduced in [1]. The first population of cells refers to endothelial cells which include progressing cells; the second population refers to immune cells, which attempt to contrast the progression of tumor cells. The microscopic state, corresponding to the main biological function, is denoted for each population by the variable $u \in \mathbb{R}$. The physical meaning is as follows:

- For the *first population of cells*, $u \leq 0$ corresponds to normal endothelial cells while $u > 0$ denotes progressing cells.
- For the *second population*, $u \leq 0$ denotes inhibited immune cells whereas $u > 0$ stands for active immune cells.

The intensity of the biological activity identified by the microscopic state is related to the value of the variable u . The state of the system is identified by the distribution function $f_i = f_i(t, u)$ (where the subscript $i = 1$ refers to the endothelial cell population whilst the subscript $i = 2$ stands for the population of immune cells) which is normalized with respect to the number of non-progressing endothelial cells at $t = 0$, denoted by $n_{10}^E = n_1^E(0)$. The model, in the absence of proliferating destructive phenomena, is derived within the following framework [1]:

$$\frac{\partial f_i}{\partial t}(t, u) = \sum_{j=1}^2 \left(\int_{\mathbb{R} \times \mathbb{R}} \eta_{ij}(v, w) \varphi_{ij}(v, w; u) f_i(t, v) f_j(t, w) dv dw - f_i(t, u) \int_{\mathbb{R}} \eta_{ij}(u, w) f_j(t, w) dw \right). \quad (2.1)$$

The parameters $\eta_{ij}(\cdot, \cdot)$ and $\varphi_{ij}(\cdot, \cdot; \cdot)$ have the following meaning:

- $\eta_{ij}(v, w)$ is the *encounter rate* for meetings between the *test* cell with state v belonging to the i th population and the *field* cell with state w belonging to the j th population.
- $\varphi_{ij}(v, w; u)$ is the *transition probability density*, corresponding to *conservative interactions*, which gives the number of test cells with state v belonging to the i th population, which fall into the state u after an interaction with a field cell, belonging to the j th population, with state w . Detailed assumptions reported also in the review [4] generate the following model:

$$\begin{cases} \frac{\partial f_1}{\partial t}(t, u) = \frac{1}{1 + \alpha_{11}} n_{10} f_1 \left(t, \frac{u}{1 + \alpha_{11}} \right) - f_1(t, u) n_{10} - n_2^A(t) f_1(t, u) \chi_{[0, \infty)}(u) \\ \quad + \frac{1}{1 - \alpha_{12}} n_2^A(t) f_1 \left(t, \frac{u}{1 - \alpha_{12}} \right) \chi_{[0, \infty)}(u), \\ \frac{\partial f_2}{\partial t}(t, u) = n_1^T(t) [f_2(t, u + \alpha_{21}) \chi_{[0, \infty)}(u + \alpha_{21}) - f_2(t, u) \chi_{[0, \infty)}(u)], \end{cases} \quad (2.2)$$

where the total number of cells in each population, *by assumption*, is constant in time:

$$n_1(t) = \int_{-\infty}^{\infty} f_1(t, u) du, \quad n_1(0) =: n_{10} \quad \text{and} \quad n_2(t) = \int_{-\infty}^{\infty} f_2(t, u) du = n_2(0) =: n_{20} \quad \forall t \geq 0,$$

while the other densities

$$n_1^E(t) = \int_{-\infty}^0 f_1(t, u) du, \quad n_1^T(t) = \int_0^{\infty} f_1(t, u) du, \quad n_2^I(t) = \int_{-\infty}^0 f_2(t, u) du, \quad n_2^A(t) = \int_0^{\infty} f_2(t, u) du$$

depend a priori on time due to modification of the microscopic state related to cell interactions. Here above, $\chi_I(\cdot)$ stands for the characteristic function of some set $I \subset \mathbb{R}$. The model is characterized by three phenomenological parameters related to mass conservative encounters: α_{11} is referred to as the variation of the progression due to encounters between endothelial cells and describes the tendency of a normal cell to degenerate and to increase its progression; α_{12} is the parameter corresponding to the ability of the active immune cells to reduce the progression of tumor cells; α_{21} is the parameter corresponding to the ability of tumor cells to inhibit the active immune cells. All the parameters α_{ij} are positive and less than one. Throughout the remainder, $n_{10}^E, n_{10}^T, n_{20}^I$ and n_{20}^A will denote respectively $n_1^E(0), n_1^T(0), n_2^I(0)$ and $n_2^A(0)$, so $n_{10}^E + n_{10}^T = n_{10}$ and $n_{20}^A + n_{20}^I = n_{20}$.

3. Qualitative analysis and biological interpretation

The goal of this section is to develop a suitable qualitative analysis of the initial value problem associated with (2.2). First, we briefly deal with the existence, uniqueness and continuity of the solutions of model (2.2). The abstract formulation of the initial value problem can be stated in the spirit of [1]. Let $L_1(\mathbb{R})$ denote the Lebesgue space of (real-valued) integrable functions on \mathbb{R} with its usual norm $\|\cdot\|_1$ and let $X = L_1(\mathbb{R}) \times L_1(\mathbb{R})$ be equipped with its natural norm. We define the positive cone of X as

$$X_+ = \{f = (f_1, f_2) \in X : f_1 \geq 0, f_2 \geq 0\}.$$

Now, let $Y = C([0, \infty), X_+)$ be the space of continuous functions on $[0, \infty)$ with values on X_+ , endowed with the uniform norm $\|f\|_Y = \sup_{t \geq 0} \|f(t)\|$. The following existence and uniqueness result is a consequence of [1, Theorem 4.1]:

Theorem 3.1 (Well-posedness). *Let $f_0 \in X_+$. Then, the initial value problem (2.2) has a unique solution $f \in Y$ with $f(t) \in X_+$ for any $t \geq 0$ and $\|f(t)\| = \|f_0\|, \forall t \geq 0$.*

Proof. Arguing as in [1, Theorem 4.1], one gets the local existence, namely, there exists a positive time $T > 0$ and a constant $a_0 > 0$ (which depends on T) such that the initial value problem (2.2) has a unique solution $f \in C([0, T], X)$ with $f(t) \in X_+$ for any $t \in [0, T]$ and $\sup_{t \in [0, T]} \|f(t)\|_X \leq a_0 \|f_0\|$. Actually, as already mentioned, the total number of cells in each population is constant in time, which reads, for any $t \in [0, T]$, $\|f(t)\| = \|f_0\|$ for any $t \in [0, T]$. This last identity guarantees the global existence of the solution $f(t)$ since it prevents the blow-up of $\|f(t)\|$ from occurring in finite time. \square

From now on, we assume $f_0 = (f_{10}, f_{20}) \in X_+$ to be fixed with $f_{10} \neq 0, f_{20} \neq 0$. We are now in a position to investigate the asymptotic behavior of the solution $f(t)$ of (2.2) as $t \rightarrow \infty$. To be precise, we are interested in the evolution of the zeroth order moment $n_1^E(t), n_1^T(t), n_2^A(t)$ and $n_2^I(t)$ and the first order moments, related to the activity of each population:

$$A_i(t) = \int_{-\infty}^{\infty} u f_i(t, u) du, \quad i = 1, 2;$$

and

$$\begin{aligned} A_1^T(t) &= \int_0^{\infty} u f_1(t, u) du \geq 0, & A_1^E(t) &= \int_{-\infty}^0 u f_1(t, u) du \leq 0, \\ A_2^A(t) &= \int_0^{\infty} u f_2(t, u) du \geq 0, & \text{and} & \quad A_2^I(t) = \int_{-\infty}^0 u f_2(t, u) du \leq 0. \end{aligned}$$

As above, we use the following notation for the initial activations: $A_{10}, A_{20}, A_{10}^T, A_{10}^E, A_{20}^A$ and A_{20}^I denote respectively $A_1(0), A_2(0), A_1^T(0), A_1^E(0), A_2^A(0)$ and $A_2^I(0)$. Direct computations show that the zeroth order moment of $f_i(t, u)$ fulfills the following:

$$\begin{cases} \frac{d}{dt} n_1^T(t) = \frac{d}{dt} n_1^E(t) = 0, \\ \frac{d}{dt} n_2^A(t) = -\frac{d}{dt} n_2^I(t) = -n_{10}^T \int_0^{\alpha_{21}} f_2(t, u) du, \quad (t \geq 0), \end{cases} \tag{3.1}$$

while the evolution of the first order moments is given by

$$\begin{cases} \frac{d}{dt} \mathbf{A}_1(t) = \alpha_{11} n_{10} \mathbf{A}_1(t) - \alpha_{12} n_2^A(t) \mathbf{A}_1^T(t), \\ \frac{d}{dt} \mathbf{A}_2(t) = -\alpha_{21} n_2^A(t) n_{10}^T \end{cases} \quad (t \geq 0). \tag{3.2}$$

More precisely,

$$\begin{cases} \frac{d}{dt} \mathbf{A}_1^E(t) = \alpha_{11} n_{10} \mathbf{A}_1^E(t), \\ \frac{d}{dt} \mathbf{A}_1^T(t) = \alpha_{11} n_{10} \mathbf{A}_1^T(t) - \alpha_{12} n_2^A(t) \mathbf{A}_1^T(t), \end{cases} \quad (t \geq 0) \tag{3.3}$$

and

$$\begin{cases} \frac{d}{dt} \mathbf{A}_2^I(t) = n_{10}^T \int_0^{\alpha_{21}} (u - \alpha_{21}) f_2(t, u) du, \\ \frac{d}{dt} \mathbf{A}_2^A(t) = -n_{10}^T \int_0^{\alpha_{21}} (u - \alpha_{21}) f_2(t, u) du - \alpha_{21} n_{10}^T n_2^A(t), \end{cases} \quad (t \geq 0). \tag{3.4}$$

The zeroth order moments of $f_2(t, \cdot)$ enjoy the following property:

Lemma 3.1. *The integral $\mathbf{I}_2 := \int_0^\infty n_2^A(s) ds$ is finite. In particular, $\lim_{t \rightarrow \infty} n_2^A(t) = 0$, and $\lim_{t \rightarrow \infty} n_2^I(t) = n_{20}$.*

Proof. According to (3.4) and using that $0 \geq \int_0^{\alpha_{21}} (u - \alpha_{21}) f_2(t, u) du \geq -\alpha_{21} \int_0^{\alpha_{21}} f_2(t, u) du$, one has

$$\frac{d}{dt} \mathbf{A}_2^A(t) \leq \alpha_{21} n_{10}^T \int_0^{\alpha_{21}} f_2(t, u) du - \alpha_{21} n_{10}^T n_2^A(t) \leq 0.$$

Now, using that $\int_0^{\alpha_{21}} f_2(t, u) du = -\frac{1}{n_{10}^T} \frac{d}{dt} n_2^A(t)$, we get $\frac{d}{dt} \mathbf{A}_2^A(t) \leq -\alpha_{21} \frac{d}{dt} n_2^A(t) - \alpha_{21} n_{10}^T n_2^A(t)$. Integrating over $(0, t)$ leads to

$$\mathbf{A}_2^A(t) - \mathbf{A}_{20}^A \leq -\alpha_{21} (n_2^A(t) - n_{20}^A) - \alpha_{21} n_{10}^T \int_0^t n_2^A(s) ds$$

so $0 \leq \mathbf{A}_2^A(t) \leq \mathbf{A}_{20}^A + \alpha_{21} n_{20}^A - \alpha_{21} n_{10}^T \int_0^t n_2^A(s) ds$. In other words,

$$\alpha_{21} n_{10}^T \int_0^t n_2^A(s) ds \leq \mathbf{A}_{20}^A + \alpha_{21} n_{20}^A. \tag{3.5}$$

Therefore $\mathbf{I}_2 := \int_0^\infty n_2^A(s) ds$ is finite. The conclusion then follows easily from the identity $n_2^A(t) + n_2^I(t) = n_2(t) = n_{20}$ for any $t \geq 0$. \square

We are now in a position to state the main result of this section.

Theorem 3.2. *Let $f_0 \in X_+$ be given and let $f = (f_1, f_2)$ be the unique solution to (2.2). Then,*

$$\begin{cases} n_1^T(t) = n_{10}^T, \quad n_1^E(t) = n_{10}^E, \quad n_1(t) = n_{10} = n_{10}^E + n_{10}^T, \quad \text{for any } t \geq 0, \\ \lim_{t \rightarrow \infty} n_2^A(t) = 0, \quad \lim_{t \rightarrow \infty} n_2^I(t) = n_{20} = \lim_{t \rightarrow \infty} n_2(t), \\ \lim_{t \rightarrow \infty} \mathbf{A}_2(t) = \mathbf{A}_{20} - \alpha_{21} n_{10}^T \mathbf{I}_2 = \lim_{t \rightarrow \infty} \mathbf{A}_2^I(t), \quad \lim_{t \rightarrow \infty} \mathbf{A}_2^A(t) = 0, \\ \lim_{t \rightarrow \infty} \mathbf{A}_1^E(t) = -\infty, \quad \lim_{t \rightarrow \infty} \mathbf{A}_1^T(t) = \infty, \end{cases}$$

and

$$\lim_{t \rightarrow \infty} \mathbf{A}_1(t) = \begin{cases} -\infty & \text{if } \mathbf{A}_{10}^E + \mathbf{A}_{10}^T \exp(-\alpha_{21} \mathbf{I}_2) < 0, \\ +\infty & \text{if } \mathbf{A}_{10}^E + \mathbf{A}_{10}^T \exp(-\alpha_{21} \mathbf{I}_2) > 0, \end{cases}$$

where $\mathbf{I}_2 = \int_0^\infty n_2^A(t)dt < \infty$ is such that

$$\max\left(0, \frac{\mathbf{A}_{20}}{\alpha_{21}n_{10}^T}\right) \leq \mathbf{I}_2 \leq \frac{\mathbf{A}_{20} + \alpha_{21}n_{20}^A}{\alpha_{21}n_{10}^T}. \tag{3.6}$$

Finally, if $\mathbf{A}_{10}^E \mathbf{A}_{10}^T \exp(-\alpha_{21}\mathbf{I}_2) = 0$, $\liminf_{t \rightarrow \infty} \mathbf{A}_1(t) \geq 0$.

Proof. The asymptotic behavior of the zeroth order moments of $f_1(t, \cdot)$ and $f_2(t, \cdot)$ is provided by Lemma 3.1. Direct integration of (3.3) and (3.4) yields, for any $t \geq 0$,

$$\mathbf{A}_1^E(t) = \mathbf{A}_{10}^E \exp(\alpha_{11}n_{10}t) \quad \text{and} \quad \mathbf{A}_1^T(t) = \mathbf{A}_{10}^T \exp\left(\alpha_{11}n_{10}t - \alpha_{12} \int_0^t n_2^A(s)ds\right).$$

Since $\int_0^t n_2^A(s)ds \rightarrow \mathbf{I}_2 < \infty$ as $t \rightarrow \infty$, the limits as $t \rightarrow \infty$ of $\mathbf{A}_1^E(t)$, $\mathbf{A}_1^T(t)$ and $\mathbf{A}_1(t) = \mathbf{A}_1^E(t) + \mathbf{A}_1^T(t)$ easily follow. More specifically, if $\mathbf{A}_{10}^E + \mathbf{A}_{10}^T \exp(-\alpha_{21}\mathbf{I}_2) = 0$, then

$$\mathbf{A}_1(t) = \mathbf{A}_{10}^T \exp(\alpha_{11}n_{10}t) \left(\exp\left(-\alpha_{12} \int_0^t n_2^A(s)ds\right) - \exp\left(-\alpha_{21} \int_0^\infty n_2^A(s)ds\right) \right) \geq 0, \quad t \geq 0,$$

so $\liminf_{t \rightarrow \infty} \mathbf{A}_1(t) \geq 0$. On the other hand, one deduces easily from Eq. (3.4) and Lemma 3.1 that

$$\lim_{t \rightarrow \infty} \mathbf{A}_2(t) = \mathbf{A}_{20} - \alpha_{21}n_{10}^T \mathbf{I}_2.$$

Now, since $\mathbf{A}_2^I(\cdot)$ is a decreasing function, the limit $\lim_{t \rightarrow \infty} \mathbf{A}_2^I(t)$ exists in $[-\infty, \mathbf{A}_{20}^I]$. Since both $\mathbf{A}_2^I(t)$ and $\mathbf{A}_2(t)$ converge to finite limits, one also gets that $\lim_{t \rightarrow \infty} \mathbf{A}_2^A(t) = \mathbf{A}_2^A(\infty)$ exists and

$$0 \leq \mathbf{A}_2^A(\infty) \leq \mathbf{A}_{20}^A + \alpha_{21}n_{20}^A - \alpha_{21}n_{10}^T \mathbf{I}_2 < \infty.$$

Actually, let us show that $\int_0^\infty \mathbf{A}_2^A(s)ds < \infty$ which would imply that $\mathbf{A}_2^A(\infty) = 0$. Let us write $B(t) = \int_0^\infty u^2 f_2(t, u)du$; one can check that

$$\frac{d}{dt} B(t) = - \int_0^{\alpha_{21}} (u - \alpha_{21})^2 f_2(t, u)du + \alpha_{21}^2 n_2^A(t) - 2\alpha_{21} \mathbf{A}_2^A(t).$$

Therefore,

$$\frac{d}{dt} B(t) \leq \alpha_{21}^2 n_2^A(t) - 2\alpha_{21} \mathbf{A}_2^A(t).$$

Integrating over $(0, t)$ leads to $B(t) - B(0) \leq \alpha_{21}^2 \int_0^t n_2^A(s)ds - 2\alpha_{21} \int_0^t \mathbf{A}_2^A(s)ds$. Since $B(t) \geq 0$, one gets that

$$2\alpha_{21} \int_0^\infty \mathbf{A}_2^A(s)ds \leq B(0) + \alpha_{21}^2 \mathbf{I}_2 < \infty.$$

This concludes the proof. The estimate on \mathbf{I}_2 comes from Eq. (3.5) and from the fact that $\mathbf{A}_2^I(t) \geq 0$ for any $t \geq 0$. \square

Remark 3.1. The above Theorem leaves open the case $\mathbf{A}_{10}^E + \mathbf{A}_{10}^T \exp(-\alpha_{21}\mathbf{I}_2) = 0$. To conclude in this case, one should have a precise estimate of the rate of convergence of $\int_0^t n_2^A(s)ds$ to \mathbf{I}_2 as t goes to infinity. Note however, that, if $\mathbf{A}_{10} \leq 0$, then $\lim_{t \rightarrow \infty} \mathbf{A}_1(t) = -\infty$.

Remark 3.2. The asymptotic behaviors of $\mathbf{A}_1(t)$ and $\mathbf{A}_2(t)$ depend on the quantity \mathbf{I}_2 which is not a given data of the problem. Nevertheless, this quantity can be estimated from known data of the system thanks to (3.6). Note also that the right-hand side of (3.6) provides useful information only if $\mathbf{A}_{20} \geq 0$. In particular, in this case,

$$\mathbf{A}_{10}^E + \mathbf{A}_{10}^T \exp\left(-\frac{\mathbf{A}_{20} + \alpha_{21}n_{20}^A}{n_{10}^T}\right) \leq \mathbf{A}_{10}^E + \mathbf{A}_{10}^T \exp(-\alpha_{21}\mathbf{I}_2) \leq \mathbf{A}_{10}^E + \mathbf{A}_{10}^T \exp\left(-\frac{\mathbf{A}_{20}}{n_{10}^T}\right).$$

In conclusion, let us stress that the analysis developed in this work is limited to a simplified model where the outset of nonconservative interactions is not yet relevant. In this relatively simple case, the qualitative analysis provides information on the *first order moments*. Note that this is relevant information towards the biological interpretation considering that the zeroth order moments simply give the number of cells, while the first order moments also take into account the biological activities of the cells. The various results reviewed in [4] were limited to the analysis of the evolution of the number of cells. Certainly an interesting research perspective is the generalization of our analysis to the case of models including the description of nonconservative events.

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