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Asymptotic analysis of a nonlinear integro-differential system modeling the immune response

A. Bellouquid *, M. CH-Chaoui

Cadi Ayyad University, Ensa Marrakech, Morocco

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ABSTRACT

This paper deals with the qualitative analysis of a nonlinear model of immune response with special attention to the actions applied by cytokine signals to activate the last one, in the framework of the mathematical kinetic theory for active particles. The content focuses on the early stage of the competition before the onset of proliferation. The analysis gives evidence how parameters and initial conditions influence the asymptotic behaviors of solutions.

1. Introduction

This paper presents a qualitative analysis of a system of nonlinear integro-differential equations modeling, at the cellular scale, competition between tumor cells and immune system mediated by cytokine signals. A specific mathematical model was proposed in [1] to describe the competition between epithelial cells which have lost their differentiation and progress towards the state of cancer competence and immune cells that attempt to contrast this progression. Interactions can be mediated by cytokines. The model refers to the early stage of the competition when progressing cells have not yet reached proliferative competence.

Existence of solutions can be proved by application of fixed point theorems in Banach spaces. Quite general results are proposed in [2], while the aforesaid asymptotic analysis is still an open problem, which however, is important to understand if progressing cells are kept under control by the immune system, namely if their number tends to zero or to a finite number, for increasing time. In fact, in the latter case these cells can mutate to cancer cells with proliferative competence [3]. The reader interested in the biological foundations of progression theory is addressed to [4–6].

The content of this paper is presented through three more sections. In detail, Section 2 provides the statement of the initial value problem related to a concise description of the mathematical model referring to the existing literature initiated in [7] and subsequently developed by various authors [1–3,8–10]. The qualitative analysis is presented in Section 3, which is completed by some numerical simulations addressed to show the role of the therapy on the immune response. Finally Section 4 deals with a critical analysis, and some perspectives related to future researches.

2. On the initial value problem

Let us consider the following initial value problem:

$$\begin{cases} \dfrac{\partial f_i}{\partial t}(t,u) = J_i[f](t,u), \\ f_{i0} = f_i(t=0,u), \end{cases} \tag{1}$$

* Corresponding author.
E-mail addresses: a.bellouquid@uca.ma (A. Bellouquid), mohamed.ch-chaoui@edu.uca.ma (M. CH-Chaoui).

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where $f = (f_1, f_2, f_3)^T$. The subscripts $i = 1, 2, 3$ correspond to three populations, specifically $i = 1$ refers to the endothelial cells, $i = 2$ to immune cells, and $i = 3$ to cytokine signals.

Cells and signals are viewed as *active particles* with *activity* identified by a scalar variable $u \in D_u \subseteq \mathbb{R}$ such that for $i = 1$: $u \leq 0$ corresponds to normal endothelial cells, while $u > 0$ denotes cells progressing to cancer states. For the second and the third population: $u \leq 0$ corresponds to inhibited particles, whereas $u > 0$ stands for active cells and cytokine signals. The overall state of each population is described by the distribution function over the activity:

$$f_i = f_i(t, u)\colon [0, T] \times D_u \longrightarrow \mathbb{R}_+. \tag{2}$$

These functions, under suitable integrability assumptions, allow the calculation of the densities:

$$n_1[f_1](t) = n_1^E[f_1](t) + n_1^T[f_1](t), \quad n_1^E[f_1](t) = \int_{-\infty}^{0} f_1(t, u)du,\ n_1^T[f_1](t) = \int_0^{\infty} f_1(t, u)du, \tag{3}$$

$$n_2[f_2](t) = n_2^I[f_2](t) + n_2^A[f_2](t), \quad n_2^I[f_2](t) = \int_{-\infty}^{0} f_2(t, u)du,\ n_2^A[f_2](t) = \int_0^{\infty} f_2(t, u)du, \tag{4}$$

and

$$n_3^A[f_3](t) = \int_0^{\infty} f_3(t, u)\, du, \tag{5}$$

while the so-called *activations* correspond to first order moments:

$$A_1[f_1](t) = \int_{-\infty}^{+\infty} u f_1(t, u)du, \qquad A_2[f_2](t) = \int_{-\infty}^{+\infty} u f_2(t, u)du, \tag{6}$$

$$A_1^T[f_1](t) = \int_0^{+\infty} u f_1(t, u)du \geq 0, \qquad A_1^E[f_1](t) = \int_{-\infty}^{0} u f_1(t, u)du \leq 0, \tag{7}$$

$$A_2^A[f_2](t) = \int_0^{+\infty} u f_2(t, u)du \geq 0, \qquad A_2^I[f_2](t) = \int_{-\infty}^{0} u f_2(t, u)du \leq 0, \tag{8}$$

and

$$A_3^A[f_3](t) = \int_0^{+\infty} u f_3(t, u)du \geq 0. \tag{9}$$

The terms J_i are obtained by suitable models of cell interactions, see [1], which lead to the calculation of the net flow of active particles in the elementary volume of the micro-states. These terms are integral nonlinear operators defined as follows:

$$\begin{aligned} J_1[f] \;=\; & n_1[f_1](t)f_1(t, u + \alpha_{11}) - n_1[f_1](t)f_1(t, u) - f_1(t, u)n_2^A[f_2](t)U_{[0,\infty)}(u) \\ & + n_2^A[f_2](t)f_1(t, u + \alpha_{12})U_{[0,\infty)}(u + \alpha_{12}), \end{aligned} \tag{10}$$

$$\begin{aligned} J_2[f] \;=\; & n_1^T[f_1](t)\, f_2(t, u + \alpha_{21})U_{[0,\infty)}(u + \alpha_{21}) + n_3^A[f_3](t)\, f_2(t, u - \alpha_{23}) \\ & - f_2(t, u)\, n_1^T[f_1](t)U_{[0,\infty)}(u) - n_3^A[f_3](t)\, f_2(t, u), \end{aligned} \tag{11}$$

and

$$J_3[f] = n_2[f_2](t)\big[f_3(t, u + \alpha_{32})U_{[0,\infty)}(u + \alpha_{32}) - f_3(t, u)U_{[0,\infty)}(u)\big], \tag{12}$$

where $U_{[a,b]}(\cdot)$ denotes the stepwise function, and $\alpha_{ij} \in (0, 1]$ stand for positive defined phenomenological parameters.

The reader interested to a deeper understanding of the model under consideration is addressed to Chapters 2 and 3 of [1]. However, a deeper understanding of the model can be obtained by enlightening the meaning of the parameters. In detail:

- α_{11} refers to the inner tendency of a normal cell to degenerate and progress;
- α_{12} refers to the ability of the immune system to reduce the progression of a tumor cell;
- α_{21} indicates the ability of tumor cells to inhibit immune cells;
- α_{23} and α_{32} model, respectively, the progressive decay of cytokines activity and activation of immune cells.

Finally, it is worth mentioning that the mathematical model is derived by the following structure:

$$\frac{\partial f_i}{\partial t}(t, u) = J_i[f](t, u) = \sum_{j=1}^{3}\left[\int_{\mathbb{R}}\int_{\mathbb{R}} \delta(u - m_{ij}(u_*, u^*))f_i(t, u_*)f_j(t, u^*)du_*du^* - f_i(t, u)\int_{\mathbb{R}} f_j(t, u^*)du^*\right], \tag{13}$$

where $m_{ij}(u_*, u^*)$, which depends on the microscopic state of the interacting pair of particles, is the most probable output of the interactions that change the activity variable, but not yet generate proliferative or destructive events. The transition probability density is modeled by a delta function over m_{ij}.