

# A Mathematical Model of Immune Competition Related to Cancer Dynamics

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## Abstract

This paper deals with the qualitative analysis of a model describing the competition among cell populations each of them expressing a peculiar cooperating and organizing behaviour. The mathematical framework in which the model has been developed is the kinetic theory for active particles. The main result of this paper is concerned with the analysis of the asymptotic behavior of the solutions. We prove that, if we are in the case when the only equilibrium solution is the trivial one, the system evolves in such a way that the immune system, after being activated, goes back towards a physiological situation while the tumor cells evolve as a sort of progressing travelling waves, characterizing a typical equilibrium/latent situation.

Keywords: kinetic theory for active particles, Cauchy problem, travelling waves, complex systems, biological systems, cell population, tumour-immune competition, tumor dormancy.

## 1 Introduction

This paper deals with the qualitative analysis of a model describing the competition among cell populations each of them expressing a peculiar cooperating and organizing behaviour. In detail, the object of our study are some aspects of the competition between tumor and immune cells, in presence of environmental (i.e. endothelial) cells. Such competition is a part of the complex evolutionary process that is the cancer progression and represents a tumor-defence and tumour-suppressive mechanism, at least at the early stage of the process.

The term progression related to cancer cells, as reported in the pioneer paper [10], describes the biological state of the cells and concisely represents a way to describe how far from the healthy (free from disease) state the cells are. We also refer to [14]

for a review of the developing knowledge and the understanding of the many different aspects of the phenomenon of tumor progression.

As reported in [3], tumour survival and metastasis necessitate overcoming immune surveillance and regulation, extracellular matrix barriers and limiting nutrients.

The crucial role of the immune system in shaping cancer development and controlling tumour growth has been recognized for decades, see for example [1] and [12]. An active immune system can detect early lesions and can keep the proliferating tumor cells at low numbers. It can also prevent the expansion of proliferating tumor cells and can eliminate them. A tumour mass, although angiogenesis competent, might be prevented from expanding and kept dormant (i.e. in a non-dividing state and with quiescent physiological functions, a state of equilibrium) by an active immune response, [1]. This is the mechanism of the immunosurveillance.

On the other hand, evasion of the immune system causes tumour mass expansion: tumor cells with increased capacity to attenuate the immune response can escape equilibrium and may progress. This process as a whole is termed cancer immunoediting, see [12].

Another important aspect of tumor progression consists in the evolution of tumour cell populations through sequential genetic and epigenetic changes. In clinical trials, one of the possible strategy to contrast such evolution consists in mobilizing the immune system against a crucial self antigen that is upregulated in the tumour (active immunotherapy), [11].

At the moment, an interdisciplinary and a multiscale approach to the study of cancer progression and evolution seems a reality more than a challenge, as mentioned in [4], [5], [2], [15]. More generally, an interdisciplinary approach to the study of complex systems, as cancer dynamics can be considered, is needed in order to capture the main essence of the such kind of problems. Among different disciplines, the mathematical approach in general and the mathematical modelling approach in particular, is addressed to the phenomenological description of some aspects of the biology of the system we are dealing with.

The aim of this paper is just to present and to carry out a qualitative analysis of a model describing some particular features of the immune competition related to cancer dynamics. More in detail, we propose and analyze a model describing the relevant phase of the cancer dormancy that is the immunosurveillance.

Cancer dormancy is a complex stage of the disease progression and therapeutic response, but it is still poorly understood. The immunosurveillance is one important phase of this stage. Other phases are angiogenic dormancy and cellular dormancy.

Presently, the details of the entire mechanisms controlling each single phase of tumor dormancy are still unknown as well as the intersections among the different phases. From a clinical point of view, it is crucially important to understand the mechanisms of the cancer dormancy, because metastases and local recurrences derived from these dormant cells. Additionally, dormant cells are resistant to chemotherapy so that they escape the drug treatments to induce cell death, [1].

The mathematical framework in which the model has been developed is the kinetic theory for active particles: we refer to [4] for a complete overview of the mathematical framework and a comprehensive list of papers devoted to models describing the immune

competition with specific focus on cancer. The main result of this paper is concerned with the analysis of the asymptotic behavior of the solutions. We prove that, if we are in the case when the only equilibrium solution is the trivial one, the system evolves in such a way that the immune system, after being activated, goes back towards a physiological situation while the tumor cells evolve as a sort of progressing travelling waves, characterizing a typical equilibrium/latent situation.

The contents of this paper are proposed in four sections, following this Introduction:

- Section 2 deals with the presentation of the model;
- Section 3 deals with the presentation of the analytical results and with their biological interpretation;
- Section 4 presents the proofs of the analytical results;
- Section 5 deals with some numerical simulations, with the main aim to give information on functions linked to the asymptotic behaviour of the tumor cells that we have not got theoretically.

## 2 The model

As already mentioned in the Introduction, our model consists in the evolution equations for a three population system developed in the framework of the kinetic theory for active particles. In detail, we consider the following three populations: endothelial (or environmental) cells, immune cells and tumor cells, labelled respectively by the indexes  $i = 1, 2, 3$ , homogeneously distributed in space. Each population is characterized by a peculiar way of expressing both its self-organizing ability and its capability to interact with the entities of the other populations.

We are mainly interested in describing a situation of relative competition among the three populations, with the specific aim of capturing the progression of the tumor cells toward a situation of latent/equilibrium state.

As already mentioned in the Introduction, the term progression related to cancer cells represents a way to describe how far from the healthy (free from disease) state the cells are. Clinical and biological aspects of tumor progression include clonal evolution and genetic alterations, such that the genes involved cover a variety of functions, [14].

From a mathematical point of view, we describe this biological characterization at the cellular level with a scalar variable  $u \in I = [0, +\infty)$ . Let  $f_3 = f_3(t, u)$  be the dependent variable describing the tumor cells population as depending on time  $t$  and progression  $u$ .

Referring to the other two populations involved in the system, i.e. endothelial cells and immune cells, we are just interested in the effects of such populations in the competition with the tumor cells. Let  $A_1 = A_1(t)$  and  $A_2 = A_2(t)$  be the dependent variables able to describe the behavior of such populations, as function of time  $t$ .

Based on the above modelling principles, we are now ready to present the evolution equations for  $A_1$ ,  $A_2$  and  $f_3$ :

$$\frac{d}{dt}A_1 = -A_1(t)A_3(t) + \alpha(A_1)A_1(t) \quad (2.1)$$

$$\frac{d}{dt}A_2 = A_2^* - A_2(t) + A_3(t) \quad (2.2)$$

$$\partial_t f_3 + \partial_u f_3 = r(u)f_3(t, u) - A_2(t)f_3(t, u), \quad (2.3)$$

for all  $t, u \in \mathbb{R}^+$ , where by definition

$$A_3(t) = A_3[f_3](t) = \int_I u f_3(t, u) du.$$

Equation (2.1) describes the evolution of the environmental cells under the hypothesis that no proliferation occurs due to interactions with other cells of the same type or with immune cells. On the other hand, interactions with tumor cells generate a destruction, as is described by the first term on the right hand side of the equation. The second term on the right hand side is a reproduction term and suitable hypotheses on function  $\alpha$  will be given in the next section.

Referring to equation (2.2), we consider in the model a term describing the tendency of the immune system to relax to a given healthy state, represented by some constant value  $A_2^*$ . Similarly to the case studied in [9], 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. Moreover, a source term due to the presence of the tumor cells is taken into account as it is shown by the last term of the equation.

In the evolution equation for the tumor cells (2.3), we assume that no proliferation occurs due to interactions with other cells of the same type but we include in the equation a proliferation term with a coefficient  $r(u)$ , depending on the activity of the cells. On the other hand, interactions with immune cells generate a destruction linearly depending on their activation state  $A_2$ .

The evolution equations (2.1)-(2.3) are linked to the following initial conditions

$$A_1(0) = A_1^0, \quad A_2(0) = A_2^0, \quad f_3(t=0, u) = f_3^0(u), \quad (2.4)$$

and to the only boundary condition needed, that is the one for  $f_3$ ,

$$f_3(t, 0) = \beta A_1(t), \quad (2.5)$$

where  $\beta$  is a positive constant. The boundary condition (2.5) represents an inlet flow for the tumor cells due to the environmental cells and it states that the tumor cells are originated by mutated endothelial (tissues) cells. Several gene mutations are needed to turn a normal cell into a tumor cell and when this situation takes place then the normal mechanisms controlling growth, proliferation and death of the cell are disrupted. We decide to fix at  $u = 0$  the beginning of the mutation process, but any other initial value can be chosen without altering the meaning of condition (2.5).

Six parameters should be included in the problem (2.1)-(2.5), but a rescaling of the three depending variables  $A_1, A_2, f_3$  and of the two independent variables  $t, u$  enables

us to reduce the system to one parameter only. We chose to place such parameter in the boundary condition (2.5).

Problem (2.1)-(2.5) represents one example of modelling the competition among multicellular systems constituted by several, say  $n$ , components, in the framework of the kinetic theory for active particles. The general principles followed toward modeling are precisely the same we have already described in [7], [8], [9] and we refer to [4] and [6] for a complete review of the general modelling procedure. We just mention here that the main idea consists in considering each population characterized by a peculiar way of expressing both its self-organizing ability and its capability to interact with the entities of the other populations. Each component, i.e. each cell population in this case, is able to express a biological function different from those expressed from the other components.

From a mathematical point of view, this characterization is described by a scalar variable  $u \in I = [0, +\infty)$ , called the *activity variable*. The meaning of such variable has to be specified for each population playing the game. As an example, if we consider the three populations as it is in our model: endothelial (or environmental) cells, immune cells and tumor cells, labelled respectively by the indexes  $i = 1, 2, 3$ , then the activity variable can assume the meaning of feeding ability for the environmental cells, activation for the immune cells and progression for the tumor cells.

The description of the overall state of the system at time  $t \in [0, T]$  is defined by the *generalized one-particle distribution function* for each population

$$f_i = f_i(t, u),$$

for  $i = 1, \dots, n$ , generally depending on time  $t$  and activity  $u$ .

Using  $f_i$  we can compute macroscopic quantities characterizing the behaviour of the system. Let us just recall here the definition of the *number density* of active particles at time  $t$  for the  $i$ -th population

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

the total density, or *local size*

$$n(t) = \sum_{i=1}^n n_i(t),$$

and the activity of each population

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

We don't report here all the modelling principles, but we address the reader to [7], [8], [9] for more details. One important aspect consists in taking into account that interactions with cells of the other populations modify the biological state and may also generate proliferation and/or destruction phenomena. Let us just mention that, as it was already pointed out in [8], also in the case of our model (2.1)-(2.5), the equations

for the distribution functions  $f_1$  and  $f_2$  of the endothelial cells and the immune system are not really necessary. As already explained in the first part of this Section, the only interesting quantities are  $A_1$  and  $A_2$  as well as their relative equations.

### 3 Analytic Results and their Biological Interpretation

As already mentioned this paper deals with the qualitative analysis of the following problem

$$\begin{cases} \frac{d}{dt}A_1 = -A_1A_3 + \alpha(A_1)A_1 \\ \frac{d}{dt}A_2 = A_2^* - A_2 + A_3 \\ \partial_t f_3 + \partial_u f_3 = r(u)f_3 - A_2f_3 \end{cases} \quad (3.1)$$

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

$$A_1(0) = A_1^0, \quad A_2(0) = A_2^0, \quad f_3(t=0, u) = f_3^0(u). \quad (3.2)$$

and boundary condition

$$f_3(t, 0) = \beta A_1(t), \quad (3.3)$$

where  $\beta$  is a positive constant.

The main goal of this paper is to carry out the analysis of the asymptotic behaviour in time of this new system, that requires new ideas and new proofs which are presented in details.

**Assumption 3.1** *From now on, we assume that  $\alpha(\xi)$  and  $r(u)$ , the coefficients of the proliferation terms respectively in (2.1) and (2.3), satisfy the following conditions:*

i)  $\alpha(\xi) \in L^\infty[0, +\infty)$ , and  $\alpha$  vanishes on  $[A_1^*, +\infty)$ , with  $A_1^* > 0$ ;

ii)  $r(u) \in L^\infty[0, +\infty)$ , and  $r(0) = 0$ ;

iii)  $r(u) = R^* - \frac{A}{u} + O\left(\frac{1}{u^2}\right)$ , as  $u \rightarrow +\infty$ .

Parts i) and ii) of Assumption (3.1) express the boundedness of the coefficient of the two source terms respectively in Equations (2.1) and (2.3), as it is reasonable from a biological point of view. Moreover, the function  $\alpha$  is assumed to have a logistic type form. We assume that there exists a threshold value  $A_1^*$  for  $A_1$  above which the activity of the endothelial cells can only decrease in time, due to the presence of tumor cells.

Parts iii) of Assumption (3.1) refers to the asymptotic behaviour of  $r = r(u)$  and it will be shown how this is related to the asymptotic behaviour of  $f_3$ , the distribution function of the tumor cells.

In the first part of this section we present the analytical results related to the qualitative analysis of the solution to the initial-boundary value problem (3.1) - (3.3) and we postpone to the next Section the technical proofs.

The following theorem states the existence of solutions to the initial-boundary value problem (3.1) - (3.3)

**Theorem 3.1** *Assume that the initial condition  $f_3^0(u)$  satisfies the following assumption*

$$f_3^0(u) \geq 0 \quad \text{and} \quad \int_0^{+\infty} (1+u) f_3^0(u) du < +\infty, \quad (3.4)$$

*Then there exists at least one solution  $(A_1, A_2, f_3)$  to the initial-boundary value problem (3.1) - (3.3) (in the distributional sense), such that  $(A_1, A_2) \in C([0, \infty))$ , and  $f_3 \in L^1((1+u)du)$ .*

The proof of this theorem is a direct consequence of the equations and we omit the details.

Concerning the asymptotic behaviour in time of the solutions, we have investigated the system in the case when the only equilibrium solution of the system (3.1) is the trivial one. The following proposition states a sufficient condition to assure this situation. In this case we will see how the asymptotic behaviour in time of the solutions will be not given by the equilibrium solution.

**Proposition 3.1** *If*

$$\sup_{\xi \in \mathbb{R}^+} \alpha(\xi) + A_2^* < R^*, \quad (3.5)$$

*where*

$$R^* = \sup_{u \in \mathbb{R}^+} r(u),$$

*then the only equilibrium solution of (3.1) is the trivial solution, i.e.  $A_1 = 0, A_2 = A_2^*, f_3 = 0$ . Such equilibrium is unstable.*

Our main result is described by the following Theorem related to the asymptotic behaviour in time of the system (3.1) - (3.3)

**Theorem 3.2** *Assume that the initial condition  $f_3^0(u)$  satisfies assumption (3.4). Then as  $t \rightarrow \infty$  we have*

*i)  $A_1(t) \rightarrow 0$ ;*

*ii)  $n_3(t) \rightarrow 0$ ;*

*iii)  $A_2(t) \rightarrow R^*$  and  $A_3(t) \rightarrow R^* - A_2^*$ ;*

*iv)  $\exists L(u) \in L^1(du, \mathbb{R})$  and  $\exists \Phi(t)$  such that  $f_3$ , with the right normalization, converges to  $L(u)$ :*

$$\int_{-\infty}^{+\infty} \left| f_3(t, u+t) \frac{e^{A \log(u+t)}}{\Phi(t)} - L(u) \right| du \leq \frac{c}{t}$$

*where  $c$  is constant and  $A$  is defined in Assumption (3.1).*

*In other words, the behavior of  $f_3(t, u)$  is the behavior of  $\Phi(t) L(u-t) e^{-A \log u}$ .*

Some interesting biological implication can be gathered from the main results described in this section. First of all we recall that, as already pointed out, Assumption (3.1) expresses the reasonable condition that there is a bound for the reproduction capability both of the endothelial cells and the tumor cells. We also observe that condition (3.4) is consistent with the biological requirements of cell populations.

The main result is stated in Theorem (3.2) and concerns the asymptotic behaviour of the system. Comparing this model to other models developed in the same mathematical framework, as for example the ones analyzed in [7], [8] and in the references therein, we are now able to capture some new features of the system. We just recall briefly that in the previous papers the asymptotic analysis indicated two possible behaviours as the result of the competition: regression of progressed cells due to an effective action of the immune system and the opposite one, with the blow up of progressed cells and the progressive inhibition of the immune system. This analysis corresponds to the medical motivation related to investigate whether a suitable action on the immune system may make it able to recognize and possibly destroy the tumor cells.

What we get now is a different *scenario*: we observe the evolution of the progression of the tumor cells in such a way that their number decreases and their activity can be kept under control, even if it is not decreasing to zero. In other words, what we have is a situation characterized by a few number of tumor cells with high progression values. At the same time, the activity of the immune system, after being activated, is able to come back to a situation very close to the physiological one, while the activity of the endothelial cells decrease to zero.

The asymptotic behaviour described by our model is very close to the one related to the immunosurveillance: the proliferating tumor cells are kept at low numbers and in a controlled situation in terms of progression values. The analytic result shows an evolution of the tumour cells as a sort of “travelling waves” through the function  $L(u)$  and in Section 5 we will see some numerical examples of possible shapes of these waves. Of course, from a biological point of view this situation cannot be really “stable” for a long time, as it is from a mathematical point of view. Even if the latency periods may range from years even to decades, what we aspect is that at a certain point a real system should evolve towards behaviours characterized, for example, either by the total destruction of the tumor cells or by the reactivation of the few tumor cells with very high progression values and the outcome of the disease, [13]. Our model and the macroscopic quantities here described are not still able to describe such behaviors and this represents a limit of the model itself.

## 4 Estimates and proofs

In this section we prove the theorems and the related qualitative properties of the solutions of (3.1) - (3.3).

Let us consider the Equations in (3.1), namely

$$\frac{d}{dt}A_1 = -A_1A_3 + \alpha(A_1)A_1 \quad (4.1)$$



$$\frac{d}{dt}A_2 = A_2^* - A_2 + A_3 \quad (4.2)$$

$$\partial_t f_3 + \partial_u f_3 = r(u)f_3 - A_2 f_3 \quad (4.3)$$

for all  $t, u \in \mathbb{R}^+$  and assume Hypothesis (3.4).

#### 4.1 Proof of Proposition 3.1

Let  $\bar{A}_1, \bar{A}_2$  and  $\bar{f}_3$  be a nontrivial equilibrium solution of (4.1)-(4.3). From (4.1) we see that

$$\bar{A}_3 := \int_0^{+\infty} u \bar{f}_3(u) du = \alpha(\bar{A}_1),$$

while from (4.3) we obtain

$$\bar{f}_3(u) = \bar{A}_1 e^{R(u) - \bar{A}_2 u}, \quad \text{where} \quad R(u) = \int_0^u r(s) ds,$$

and this implies

$$\bar{A}_3 = \bar{A}_1 \int_0^{+\infty} u e^{R(u) - \bar{A}_2 u} du =: \bar{A}_1 G(\bar{A}_2).$$

Comparing the two expression obtained for  $\bar{A}_3$ , we have

$$\alpha(\bar{A}_1) = \bar{A}_1 G(\bar{A}_2)$$

and this yields

$$\bar{A}_2 = G^{-1}\left(\frac{\alpha(\bar{A}_1)}{\bar{A}_1}\right) =: H(\bar{A}_1).$$

Finally, from (4.2), we obtain the following equation for  $\bar{A}_1$ :

$$A_2^* - H(\bar{A}_1) + \alpha(\bar{A}_1) = 0. \quad (4.4)$$

Let us now define the function

$$g(\xi) = A_2^* - H(\xi) + \alpha(\xi).$$

For  $\xi = 0$  we have  $g(0) = A_2^* - R^* + \alpha(0)$ , moreover for  $\xi \rightarrow +\infty$  we have  $g(\xi) \rightarrow -\infty$ , and this implies that if  $\varepsilon \in \mathbb{R}^+$  is such that

$$R^* - \varepsilon > \max_{\xi \in \mathbb{R}^+} \alpha(\xi) + \varepsilon + A_2^*,$$

then equation (4.4) cannot be satisfied and this proves Proposition (3.1).

## 4.2 Proof of some useful Lemmas

**Lemma 4.1** *For the solution of the initial-boundary value problem (3.1) - (3.3) given by Theorem 3.1,  $A_2$  and  $A_3$  are bounded.*

**Proof.** It is sufficient to prove the boundedness of  $A_3$ . In fact, if there exists  $k > 0$  such that  $A_3(t) \leq k$ , for all  $t > 0$ , then from Eq. (4.2) we get  $A_2(t) \leq k + A_2^*$ , for all  $t > 0$ .

Let us assume, by contradiction, that for all  $k > 0$ , there exists an interval  $[s, t]$  such that

$$A_3(r) \geq k, \quad \forall r \in [s, t], \quad A_3(s) = k, \quad A_3(t) = 2k.$$

From (4.3), it is easy to see that, formally,

$$\frac{d}{dt}A_3 \leq R^*A_3 + n_3 - A_2A_3$$

and

$$n_3 \leq A_3 + \int_0^1 u f_3(t, u) du.$$

To prove these estimates rigorously, we refer to Lemma 5.5 in [7]. Moreover, we have

$$\partial_t f_3 + \partial_u f_3 \leq R^* f_3$$

and this implies that  $f_3(t, u) \leq f_3(t - u, 0) e^{R^* u}$ .

Since  $\alpha(\xi) = 0$  for  $\xi \in [A_1^*, +\infty)$ , we have that  $\frac{d}{dt}A_1 \leq 0$  and we deduce that  $A_1 \leq A_1^*$ .

Consequently,  $f_3(t, u) \leq f_3(t - u, 0) e^{R^* u} \leq A_1^* e^{R^* u}$  which implies

$$n_3 \leq A_3 + A_1^* e^{R^*}.$$

On the other hand, if  $k$  is such that  $k > A_1^* e^{R^*}$ , we obtain

$$\frac{d}{dt}A_3 \leq (R^* + 2 - A_2)A_3, \quad (4.5)$$

so that  $A_3(t) \leq A_3(s)e^{(R^*+2)(t-s)}$  and  $e^{(R^*+2)(t-s)} \geq 2$ .

Let us now consider Eq. (4.2), from which we have  $\frac{d}{dt}A_2 \geq A_2^* + k - A_2$ ; this implies that

$$A_2(r) \geq (A_2(s) - A_2^* - k) e^{-(r-s)} + A_2^* + k \geq k(1 - e^{-(r-s)})$$

and hence

$$\int_s^t A_2(r) dr \geq k(t - s - 1 + e^{-(t-s)}) \geq k\varepsilon(t - s) \quad (4.6)$$

where we have used the elementary inequality

$$\xi - 1 + e^{-\xi} \geq \varepsilon \xi$$

for  $\xi > c$  and  $\varepsilon = \varepsilon(c)$ , in the case  $c = \frac{\log 2}{R^* + 2}$ .

Using (4.6) in (4.5), we arrive at

$$2k = A_3(t) \leq A_3(s) e^{(R^*+2)(t-s) - \int_s^t A_2(r) dr} \leq k e^{(R^*+2-k\varepsilon)(t-s)}$$

and this is impossible if we take  $k > \frac{R^* + 2}{\varepsilon}$ . Thus Lemma 4.1 is proved.  $\square$

**Lemma 4.2** *For the solution of the initial-boundary value problem (3.1) - (3.3) given by Theorem 3.1, we have the following estimates:*

$$i) \int_0^t A_2(s) ds \geq -k' + (R^* - \varepsilon)t;$$

$$ii) \int_0^t A_3(s) ds \geq -k'' + (R^* - \varepsilon - A_2^*)t;$$

where  $k', k''$  are positive constants and  $\varepsilon$  is such that (by (3.5))

$$\max_{\xi \in \mathbb{R}^+} \alpha(\xi) + A_2^* - R^* < -2\varepsilon.$$

**Proof.** From (3.5), we can take  $\varepsilon$  such that

$$R^* - A_2^* - \varepsilon > \max_{\xi \in \mathbb{R}^+} \alpha(\xi) + \varepsilon.$$

We take  $u^*$  such that  $r(u) > R^* - \varepsilon$ , for all  $u \geq u^*$  and we define

$$I(t) = \int_{u^*}^{+\infty} u f_3(t, u) du.$$

From (4.3), we have

$$\frac{d}{dt} I \geq (R^* - \varepsilon)I - A_2 I. \quad (4.7)$$

Because of Lemma 4.1, there exists  $k > 0$  such that  $A_2, A_3 \leq k$  and this immediately implies, from (4.3), that

$$\partial_t f_3 + \partial_u f_3 \geq -k f_3.$$

As a consequence,

$$\partial_t f_3(t, u+t) \geq -k f_3(t, u+t),$$

so that

$$f_3(t, u+t) \geq f_3^0(u) e^{-ku^*}, \quad \forall u \geq 0.$$

Now

$$\begin{aligned} I(u^*) &= \int_{u^*}^{+\infty} u f_3(u^*, u) du = \int_0^{+\infty} (u + u^*) f_3(u^*, u + u^*) du \\ &\geq e^{-ku^*} \int_0^{+\infty} (u + u^*) f_3^0(u) du \geq e^{-ku^*} \int_0^{+\infty} u f_3^0(u) du = A_3^0 e^{-ku^*}. \end{aligned} \quad (4.8)$$

From (4.7) we also have

$$\begin{aligned} k &\geq I(t) \geq I(u^*) \exp\left((R^* - \varepsilon)(t - u^*) - \int_{u^*}^t A_2(s) ds\right) \\ &\geq A_3^0 e^{-ku^*} \exp\left((R^* - \varepsilon)(t - u^*) - \int_{u^*}^t A_2(s) ds\right) \end{aligned}$$

where the last inequality has been obtained using estimate (4.8). Taking the logarithm, we obtain

$$(R^* - \varepsilon)(t - u^*) - \int_{u^*}^t A_2(s) ds \leq C \quad (4.9)$$

where  $C = ku^* + \log \frac{k}{A_3^0}$ .

As a final step, consider the following estimates

$$\begin{aligned} \int_0^t A_2(s) ds &\geq \int_{u^*}^t A_2(s) ds \geq -C - (R^* - \varepsilon)u^* \\ &+ (R^* - \varepsilon)t = -k' + (R^* - \varepsilon)t \end{aligned} \quad (4.10)$$

obtained using (4.9) and where  $k' = (R^* - \varepsilon)u^* + C$ .

This proves part (i) of Lemma (4.2).

Now let us first consider that due to the fact that  $f_3$  is positive, also  $A_3$  is positive and this implies  $A_2 > A_2^*$ .

From Eq. (4.2), we get

$$A_2(t) - A_2^0 = - \int_0^t A_2(s) ds + \int_0^t A_3(s) ds + A_2^* t$$

and using (4.10) we have

$$\int_0^t A_3(s) ds \geq (R^* - \varepsilon - A_2^*)t - k' - A_2^0 = -k'' + (R^* - \varepsilon - A_2^*)t \quad (4.11)$$

where  $k'' = k' + A_2^0$ , and this proves part ii) of Lemma (4.2).  $\square$

### 4.3 Proof of Theorem 3.2

Part i):

From Eq.(4.1) we have

$$A_1(t) \leq A_1^0 \exp\left(\left(\max_{\xi \in \mathbb{R}^+} \alpha(\xi)\right) t - \int_0^t A_3(s) ds\right) \leq A_1^0 e^{-\varepsilon t} e^{k''} \quad (4.12)$$

where the last inequality is obtained through (4.11) and (3.5); so part i) of Theorem (3.2) is proved.

Part ii):

Let us define  $l(t, u) = f_3(t, t + u)$  so that, from (4.3),  $l$  is the solution of the equation

$$\partial_t l = (r(t + u) - A_2)l$$

and  $l(t, -t) = \beta A_1(t)$ .

Consequently

$$l(t, u) = l\left(\frac{t}{2}, u\right) \exp\left(\int_{\frac{t}{2}}^t (r(s + u) - A_2(s)) ds\right).$$

Let us take  $u < \frac{t}{2}$ ; then

$$f_3(t, u) \leq f_3(t - u, 0) \exp\left(\int_{t-u}^t (r(u + s - t) - A_2(s)) ds\right)$$

from (4.3). Considering that

$$f_3(t - u, 0) = \beta A_1(t - u) \leq k e^{-\varepsilon(t-u)} \leq k e^{-\varepsilon \frac{t}{2}},$$

where we have used (4.12), we have

$$f_3(t, u) \leq k e^{-\varepsilon' t} \exp\left(\int_{t-u}^t (r(s - \frac{t}{2}) - A_2(s)) ds\right). \quad (4.13)$$

Now if  $\underline{t} < t$  and  $v > t - \underline{t}$ , we have

$$f_3(t, u) = f_3(t, v - t - \underline{t}) \exp\left(\int_{\underline{t}}^t (r(v + s - t) - A_2(s)) ds\right),$$

so that if  $u < \frac{t}{2}$ ,  $\underline{t} = t - u$ , and  $v > u$  we deduce that

$$\begin{aligned} f_3(t, v) &= f_3(t - u, v - u) \exp\left(\int_{t-u}^t (r(v + s - t) - A_2(s)) ds\right) \\ &\geq f_3(t - u, v - u) \exp\left(\int_{t-u}^t (r(u + s - t) - A_2(s)) ds\right). \end{aligned}$$

By definition of  $A_3$ , using the last inequality above and (4.13), we obtain the following estimates

$$\begin{aligned} A_3(t) &\geq \int_u^{+\infty} v f_3(t, u) dv \\ &\geq \exp\left(\int_{t-u}^t (r(u + s - t) - A_2(s)) ds\right) \int_u^{+\infty} v f_3(t - u, v - u) dv \\ &\geq \exp\left(\int_{t-u}^t (r(u + s - t) - A_2(s)) ds\right) \int_u^{+\infty} (v - u) f_3(t - u, v - u) dv \\ &\geq \frac{e^{\varepsilon \frac{t}{2}}}{k} f_3(t, u) A_3(t - u) \end{aligned}$$

and we can deduce that

$$f_3(t, u) \leq k e^{-\varepsilon \frac{t}{2}} \frac{A_3(t)}{A_3(t-u)} \leq k' e^{-\varepsilon \frac{t}{2}}, \quad \forall u \leq \frac{t}{2}. \quad (4.14)$$

Recalling the definition of  $n_3$ , we have

$$\begin{aligned} n_3(t) &= \int_0^{\frac{t}{2}} f_3(t, u) du + \int_{\frac{t}{2}}^{+\infty} f_3(t, u) du \\ &\leq \frac{t}{2} k' e^{-\varepsilon \frac{t}{2}} + \frac{2}{t} \int_0^{+\infty} u f_3(t, u) du \\ &\leq k' e^{-\varepsilon' t} + \frac{k'}{t} A_3(t), \end{aligned} \quad (4.15)$$

and this concludes the proof of Part ii) of Theorem 3.2.

Part iii):

From Equation (4.3) we have

$$\begin{aligned} \frac{d}{dt} A_3(t) &= \int_0^{+\infty} u r(u) f_3(t, u) du - A_2(t) A_3(t) + n_3(t) \\ &= R^* A_3(t) - A_2(t) A_3(t) + \varepsilon(t), \end{aligned}$$

where we have defined  $\varepsilon(t)$  as follows:

$$\varepsilon(t) = n_3(t) + \int_0^{+\infty} u(r(u) - R^*) f_3(t, u) du.$$

Now, from part *iii*) of Assumption (3.1), we have

$$\varepsilon(t) \leq n_3 + c \int_0^{+\infty} f_3(t, u) du \leq c n_3(t) \leq \frac{c}{t}$$

where the last estimate can be obtained using (4.15).

For the asymptotic behaviour of  $A_2$  and  $A_3$ , we use a *dissipation* argument, introducing the following Liapunov functional

$$\begin{aligned} F(t) &= \frac{1}{2} (R^* - A_2)^2 + \eta (A_2 - A_3 - A_2^*)^2 \\ &\quad + (R^* - A_2^*) \log \frac{R^* - A_2^*}{A_3} + A_3 - (R^* - A_2^*) \end{aligned}$$

with  $\eta$  small enough. By definition, we have

$$\begin{aligned} \frac{d}{dt} F(t) &\leq (R^* - A_2)^2 (1 - \eta A_3)^2 - \eta (A_2 - A_3 - A_2^*)^2 \\ &\quad + \varepsilon(t) \left[ \frac{1}{A_3} (A_3 - A_2 - A_2^*) + \frac{1}{A_3} (A_2 - R^*) + 2\eta (A_3 - A_2 - A_2^*) \right] \\ &\leq -(R^* - A_2)^2 (1 - \eta A_3^2 - \frac{1}{2}) + \varepsilon^2(t) \left[ \frac{1}{2A_3^2} + \frac{3}{A_2^2} + 12 \right] \\ &\quad - \eta (A_2 - A_3 - A_2^*)^2 (1 - \frac{\eta}{3} - \frac{\eta}{3}). \end{aligned}$$

Summarizing, we have proved that

$$\frac{d}{dt}F(t) \leq -cF + c'(\varepsilon^2(t))$$

with  $c$  and  $c'$  suitable constants, and consequently  $F(t) \rightarrow 0$  as  $t \rightarrow +\infty$ . This concludes the proof of part iii) of Theorem 3.2. Note moreover that as  $|\varepsilon(t)| \leq \frac{c}{t}$ , we have

$$F(t) \leq \frac{c}{t^2}. \quad (4.16)$$

Part iv):

Let us define

$$g(t, u) = \begin{cases} f_3(t, u+t) e^{A \log(u+t)} & \text{if } u \geq -t \\ 0 & \text{if } u < -t \end{cases}$$

From Equation (4.3) we have

$$\begin{aligned} \partial_t g &= (r(u+t) + \frac{A}{u+t} - A_2)g \\ &= (r(u+t) + \frac{A}{u+t} - R^*)g + (R^* - A_2)g \\ &=: a(u+t)g + b(t)g \\ &= O\left(\frac{1}{(u+t)^2}\right) + b(t)g, \end{aligned}$$

where in the last estimate we have applied part *iii*) of Assumption (3.1).

Let now  $\Phi(t)$  be the solution of the following Cauchy Problem

$$\begin{cases} \Phi'(t) = b(t) \Phi(t) \\ \Phi(0) = 1 \end{cases}$$

From (4.16) we know that  $|b(t)| \leq \frac{c}{t}$ , so that

$$\int_0^t |b(s)| ds \leq c \log t$$

and

$$e^{-c \log t} \leq \Phi(t) \leq e^{c \log t}.$$

Now taking  $h(t, u) = \frac{1}{\Phi(t)} g(t, u)$ , so that  $\partial_t h = a(u+t)h$ , we can prove the following lemma:

**Lemma 4.3** *The function  $h = h(\cdot, u)$  verifies the Cauchy condition in  $L^1(du, \mathbb{R})$ , for  $t \rightarrow +\infty$ .*

**Proof.** Because of the definition of  $h$  we have

$$\begin{aligned}
\frac{d}{dt} \int_{-\infty}^{+\infty} h(t, u) du &= \frac{d}{dt} \int_{-t}^{+\infty} h(t, u) du = h(t, -t) + \int_{-t}^{+\infty} \partial_t h du \\
&= \frac{A_1}{\Phi} + \int_{-t}^{+\infty} a(u+t)h(t, u) du \\
&= \frac{A_1}{\Phi} + \int_{-t}^{-\frac{t}{2}} a(u+t)h(t, u) du + \int_{-\frac{t}{2}}^{+\infty} a(u+t)h(t, u) du \\
&\leq e^{-\varepsilon t + c \log t} + c \int_0^{\frac{t}{2}} f_3(t, u) du + \frac{c}{1+t^2} \int_{-t}^{+\infty} h(t, u) du,
\end{aligned}$$

and this implies

$$\frac{d}{dt} \int_{-\infty}^{+\infty} h(t, u) du \leq e^{-\varepsilon' t} + \frac{c}{1+t^2} \int_{-\infty}^{+\infty} h(t, u) du,$$

so what we get is the following estimate for  $h$ :

$$\begin{aligned}
\int_{-\infty}^{+\infty} h(t, u) du &\leq \exp\left(\int_0^t \frac{c}{1+s^2} ds\right) \left(\int_{-\infty}^{+\infty} h(0, u) du\right) \\
&+ \int_0^t e^{-\varepsilon' s} \exp\left(-\int_0^s \frac{c}{1+x^2} dx\right) ds \leq e^c (n_3(0) + \frac{1}{\varepsilon'}),
\end{aligned}$$

which proves that  $h(t, u) \in L^1(du, \mathbb{R})$ .

Using the estimates above, we see that for  $t \geq s$ :

$$\begin{aligned}
\int_{-\infty}^{+\infty} |h(t, u) - h(s, u)| du &= \int_{-s}^{+\infty} |h(t, u) - h(s, u)| du + \int_{-t}^{-s} |h(t, u)| du \\
&\leq \int_{-s}^{+\infty} \int_s^t |\partial_t h(x, u)| dx + \int_{-u}^{-s} |h(-u, u)| du + \int_{-u}^t \partial_t h(x, u) du \\
&\leq \int_s^t \int_{-s}^{+\infty} \frac{c}{(1+x+u)^2} h(x, u) du dx + \int_s^t \frac{A_1(x)}{\Phi(x)} dx \\
&+ \int_{-t}^{-s} \int_{-u}^t \frac{c}{(1+x+u)^2} h(x, u) du dx \\
&\leq \int_s^t e^{-\varepsilon x + c \log x} dx + \int_s^t \int_{-\infty}^{+\infty} \frac{c}{(1+x+u)^2} h(x, u) du dx \\
&\leq c e^{-\varepsilon' s} + c \int_s^t \int_{-x}^{-\frac{x}{2}} h(x, u) dx du + \int_s^t \frac{c}{(1+\frac{x}{2})^2} \int_{-\infty}^{+\infty} h(x, u) du dx \\
&\leq c e^{-\varepsilon' s} + c \int_s^t \frac{1}{\Phi(x)} e^{A \log \frac{x}{2}} + \int_{-x}^{-\frac{x}{2}} e^{-\varepsilon x} du dx + \int_s^t \frac{c'}{(1+\frac{x}{2})^2} dx \\
&\leq c e^{-\varepsilon' s} + c e^{-\varepsilon'' s} + \frac{c'}{(1+s)} \longrightarrow 0, \quad \text{for } s, t \rightarrow +\infty,
\end{aligned}$$



and this proves the Lemma.  $\square$

Because of Lemma (4.3), there exists  $L(u) \in L^1(du, \mathbb{R})$  such that  $h(t, u) \rightarrow L(u)$  in  $L^1(du, \mathbb{R})$ , as  $t \rightarrow +\infty$ . Moreover, we know that

$$\int_{-\infty}^{+\infty} |h(t, u) - L(u)| du \leq \frac{c}{t},$$

and this concludes the proof of Theorem (3.2).

We now prove the following Proposition related to the convergence of  $A_3(t) = A_3[f_3](t)$  and to the convergence of the corresponding ‘‘activity functional’’ defined using the limit function  $L$ , as  $t \rightarrow +\infty$ :

**Proposition 4.1**

$$\lim_{t \rightarrow +\infty} \int_{\frac{t}{2}}^{+\infty} u \Phi(t) L(u-t) e^{-A \log u} du = \lim_{t \rightarrow +\infty} A_3(t). \quad (4.17)$$

**Proof.** Recalling the estimate (4.14), we have that

$$\int_{\frac{t}{2}}^{+\infty} u f_3(t, u) du = A_3(t) - \int_0^{\frac{t}{2}} u f_3(t, u) du = A_3(t) + O(e^{-\varepsilon t})$$

and this implies that

$$\lim_{t \rightarrow +\infty} \int_{\frac{t}{2}}^{+\infty} u f_3(t, u) du = \lim_{t \rightarrow +\infty} A_3(t).$$

From this last inequality, we deduce that we can prove (4.17) showing that

$$\int_{\frac{t}{2}}^{+\infty} u f_3(t, u) du - \int_{\frac{t}{2}}^{+\infty} u \Phi(t) L(u-t) e^{-A \log u} du \rightarrow 0 \quad \text{for } t \rightarrow +\infty.$$

By definition of  $h$ , we have

$$\frac{d}{dt} \int_{-\frac{t}{2}}^{c(t+1)} h(t, u) du \geq \int_{-\frac{t}{2}}^{c(t+1)} \alpha(u+t) h(t, u) du \geq -\frac{c}{(1+t)^2} \int_{-\frac{t}{2}}^{c(t+1)} h(t, u) du,$$

from which we deduce

$$\int_{-\frac{t}{2}}^{c(t+1)} h(t, u) du \geq \exp\left(-\int_0^t \frac{c}{(1+s)^2} ds\right) \int_0^c f_3^0(u) du \geq c',$$

where the last inequality is true if  $c$  is such that  $\int_0^c f_3^0(u) du > 0$ .

Applying the estimate obtained in Part ii) for  $n_3$ , we have:

$$\begin{aligned} \frac{c}{1+t} &\geq n_3(t) \geq \int_{\frac{t}{2}}^{c(t+1)} f_3(t, u) du \\ &= \int_{\frac{t}{2}}^{c(t+1)} \Phi(t) h(t, u) e^{-A \log(u+t)} du \geq c' \Phi(t) e^{-A \log t}, \end{aligned}$$

and this implies

$$\Phi(t)e^{-A \log t} \leq \frac{c}{1+t}.$$

We will also use the following estimate:

$$\begin{aligned} \frac{d}{dt} \int_{-\infty}^{+\infty} h(t, u) u_+ du &= \int_0^{+\infty} \partial_t h(t, u) u_+ du \\ &= \int_0^{+\infty} a(u+t) h(t, u) u_+ du \leq \frac{c}{(1+t)^2} \int_{-\infty}^{+\infty} h(t, u) u_+ du \end{aligned}$$

which yields

$$\int_{-\infty}^{+\infty} h(t, u) u_+ du \leq c.$$

We are now ready for the last step of the proof:

$$\begin{aligned} &\int_{\frac{t}{2}}^{+\infty} u (f_3(t, u) - \Phi(t)L(u-t)e^{-A \log u}) du \\ &= \int_{-\frac{t}{2}}^{+\infty} (u+t) (f_3(t, u+t) - \Phi(t)L(u)e^{-A \log(u+t)}) du \\ &\leq \Phi(t) \int_{-\frac{t}{2}}^{+\infty} (u+t) e^{-A \log(u+t)} (h(t, u) - L(u)) du \\ &= \Phi(t) \int_{-\frac{t}{2}}^{+\infty} (u+t) e^{-A \log(u+t)} \int_t^{+\infty} \partial_t h(x, u) dx du \\ &\leq \Phi(t) \int_t^{+\infty} \int_{-\frac{t}{2}}^{+\infty} (u+t) e^{-A \log(u+t)} |a(u+x)| h(x, u) dx du \\ &\leq c \Phi(t) e^{-A \log(t)} \int_t^{+\infty} \int_{-\frac{t}{2}}^{+\infty} \frac{|u+t|}{(1+u+x)^2} h(x, u) dx du \\ &\leq \frac{c}{1+t} \int_t^{+\infty} \int_{-\frac{t}{2}}^{+\infty} \frac{t}{(1+x)^2} h(x, u) du dx \\ &\quad + \frac{c}{1+t} \int_t^{+\infty} \int_t^{+\infty} \frac{u}{(1+x)^2} h(x, u) du dx \\ &\leq c \int_t^{+\infty} \frac{1}{(1+x)^2} dx + \frac{c}{1+t} \int_t^{+\infty} \frac{1}{(1+x)^2} dx \\ &\leq \frac{c}{1+t} + \frac{c}{(1+t)^2} \rightarrow 0, \quad \text{for } t \rightarrow +\infty, \end{aligned}$$

and this concludes the proof of the Proposition.  $\square$

## 5 Numerical Simulations

This Section is devoted to some numerical simulations with the main aim to give an idea of which kind of shapes the function  $L(u)$  may assume. We do not claim a detailed

numerical precision or completeness in performing these simulations, but we would just like to give some information on  $L(u)$  that we have not got theoretically. We remember that  $L = L(u)$  is linked to the asymptotic behaviour of  $f_3$ , as it is expressed in Theorem (3.2).

We also compare the solutions of problem (3.1)-(3.3) corresponding to different sets of initial and boundary conditions.

A finite difference scheme has been applied to solve numerically problem (3.1)-(3.3). Following Assumption 3.1, we fix a parabola as function  $\alpha = \alpha(u)$  and the following form for  $r$ :

$$r(u) = \frac{1}{1 + \frac{1}{u}},$$

so that we have  $R^* = 1$  and  $A = 1$ .

We always fix the threshold value  $A_2^*$  of the immune system equal to the initial value  $A_2^0$ .

The routine we applied is defined by the following steps:

1. we fix a set of initial and boundary conditions;
2. we solve problem (3.1)-(3.3);
3. we compute  $\Phi = \Phi(t)$ , that is, up to a normalization constant, equal to

$$\int_0^{+\infty} f_3(t, u+t) e^{A \log(u+t)} du;$$

4. we compute

$$h(t, u) = \frac{1}{\Phi(t)} f_3(t, u+t) e^{A \log(u+t)},$$

that is such that  $h(t, u) \rightarrow L(u)$  in  $L^1(du, \mathbb{R})$ , as  $t \rightarrow +\infty$ .

We fix the value of the parameter  $\beta$  in the boundary condition for  $f_3$  as well as the values of the initial conditions for  $A_1$  and  $A_2$  in the range  $[0, 1]$ .

Concerning the initial condition for  $f_3$ , that is  $f_3^0(u) = f_3(0, u)$ , we have analyzed two different cases:

**Case 1:**  $f_3^0(u) = 0$ , for all  $u \in \mathbb{R}$ ;

**Case 2:**  $f_3^0(u)$  is a Gaussian type function;

and we describe the corresponding numerical results in the following two subsections.

## 5.1 Numerical Results for Case 1

This is the case of initial condition for  $f_3$  identically equal to zero.

Let us consider a first example of numerical simulations obtained with the following set of initial data respectively for  $A_1$  and  $A_2$  and for the parameter  $\beta$  in the boundary condition for  $f_3$ :

$$\text{Set 1 : } A_1^0 = 0.5, \quad A_2^0 = 0.2, \quad \beta = 1.$$

reported in Figure 1-3. The graphs of  $A_1$ ,  $A_2$ ,  $A_3$  show how the asymptotic behaviour described in Theorem (3.2) is reached. The 2-D and the 3-D graphs of  $f_3(t, u)$  show how the tumour cells evolve as a sort of travelling waves moving from lower values of progression toward higher values. The graphs represented on the right in Figure 3 show a first example of the evolution of function  $h(t, u)$  as time increases, from which we can conjecture the possible shape of  $L(u)$ .

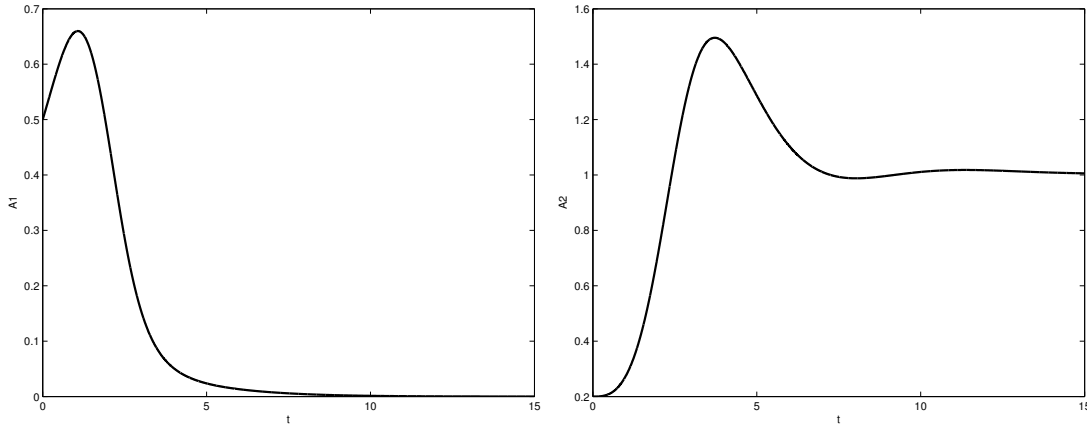


Figure 1:  $A_1(t)$  and  $A_2(t)$  in the case of Set 1.

Other simulations have been obtained varying the values of the parameters to respect the ones fixed in Set 1. The corresponding graphs do not show significant qualitative variations, but just quantitative ones. One example is reported in Figure 4, where we report the graphs of  $A_1$  and  $f_3$  corresponding to the set of parameters:

$$\text{Set 2 : } A_1^0 = 0.05, \quad A_2^0 = 0.2, \quad \beta = 1.$$

The last graphs of this subsection have been obtained with the aim of showing once again and hopefully more clearly the trend of the system, as time increases. Due to computational time, we force the parameter  $\beta$  to assume an higher value with respect to the previous ones, that is  $\beta = 10$ , while the values of  $A_1^0$  and  $A_2^0$  are fixed as in Set 1. The results are in Figure 5: on the left we have the 2-D graphs of  $f_3(t, u)$  as function of the progression  $u$ , for  $t = 10, 20, 30, 40$ , moving from the left to the right. The graph on the right of Figure 5 shows a 2-D representation of  $h(t, u)$  as function of the progression  $u$ , for  $t = 10, 20, 40$ , moving from the right to the left.

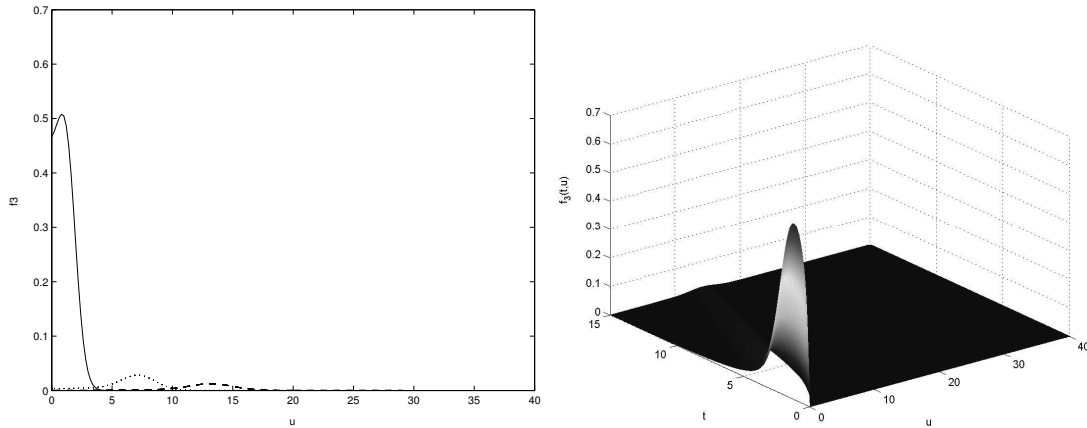


Figure 2: 2-D and 3-D representation of  $f_3(t, u)$  in the case of Set 1. In the 2D graph, the continuous line corresponds to  $t = 2$ , the dotted line to  $t = 8$  and the dashed line to  $t = 14$ .

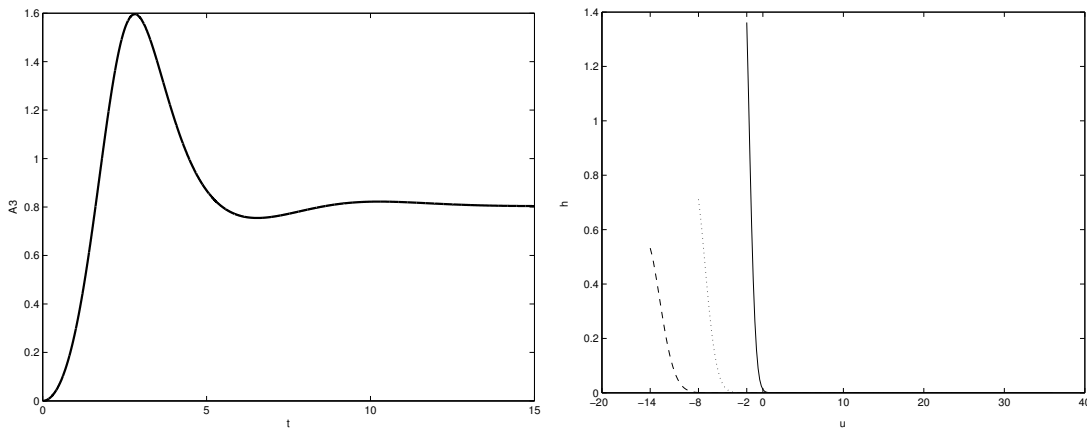


Figure 3: Case of Set 1: on the left we have  $A_3(t)$  and on the right we have  $h(t, u)$ . Here the continuous line corresponds to  $t = 2$ , the dotted line to  $t = 8$  and the dashed line to  $t = 14$ .

## 5.2 Numerical Results for Case 2

This is the case with  $f_3^0(u)$  as a Gaussian type function. As in the previous subsection, we first report the results corresponding to the value of parameters as in Set 1 and what we obtained is showed in Figures 6-8.

Also in this case, a variation of the values of the parameters corresponds to a quantitative but not qualitative modification of the graphs and we omit to show the results. The trend of the system is one more time showed in the last figure, Figure 9, where, as for Figure 5,  $\beta = 10$  and the values of  $A_1^0$  and  $A_2^0$  are fixed as in Set 1. On the right we have the 2-D graphs of  $f_3(t, u)$  as function of the progression  $u$ , for  $t = 10, 20, 30, 40$ ,

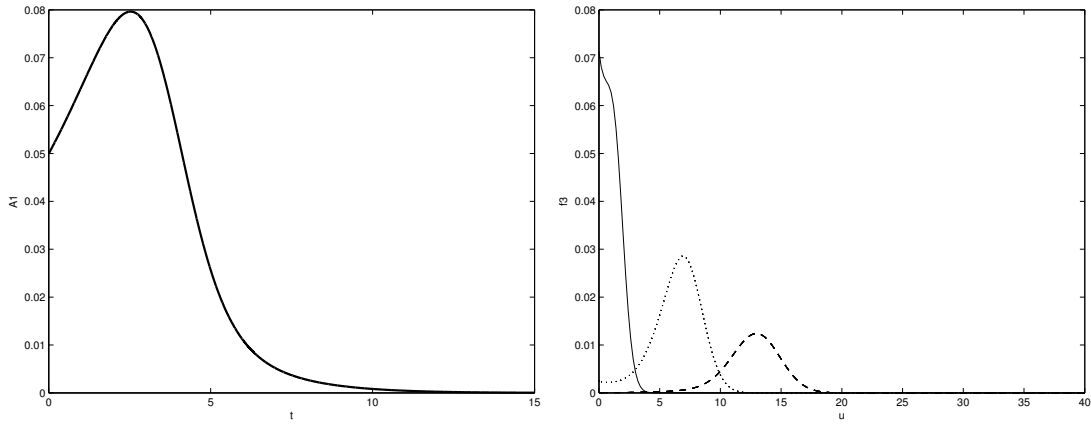


Figure 4: Case of Set 2: on the left we have  $A_1(t)$  and on the right we have  $f_3(t, u)$ . Here the continuous line corresponds to  $t = 2$ , the dotted line to  $t = 8$  and the dashed line to  $t = 14$ .

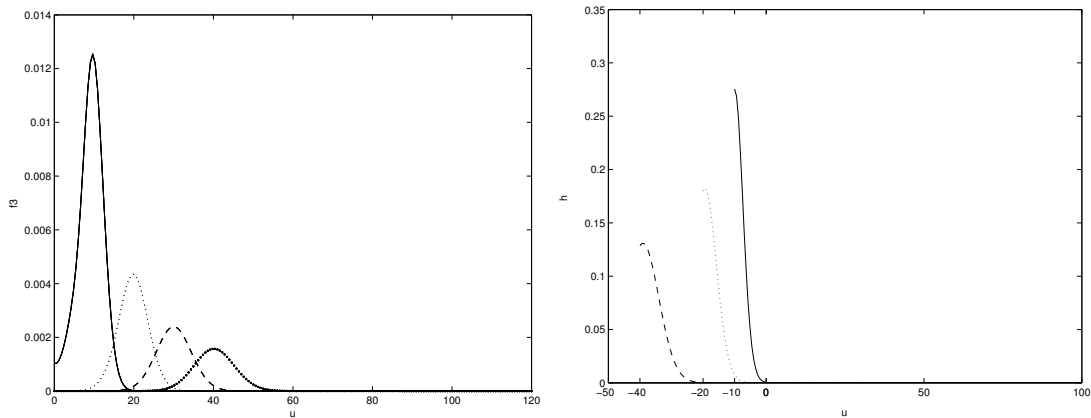


Figure 5: On the left we have  $f_3(t, u)$  and on the right we have  $h(t, u)$ .

moving from the left to the right. The graph on the left of Figure 9 shows a 2-D representation of  $h(t, u)$  as function of the progression  $u$ , for  $t = 10, 20, 40$ , moving from the right to the left.

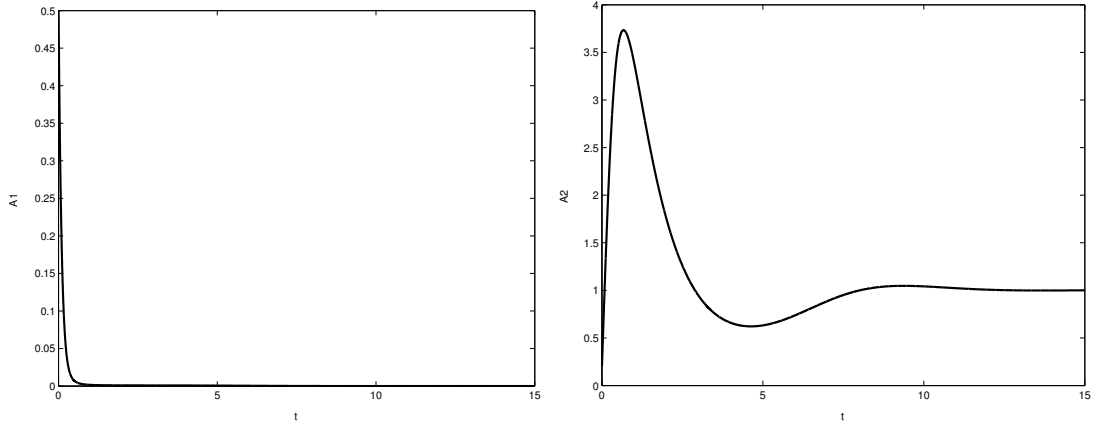


Figure 6:  $A_1(t)$  and  $A_2(t)$  in the case of Set 1.

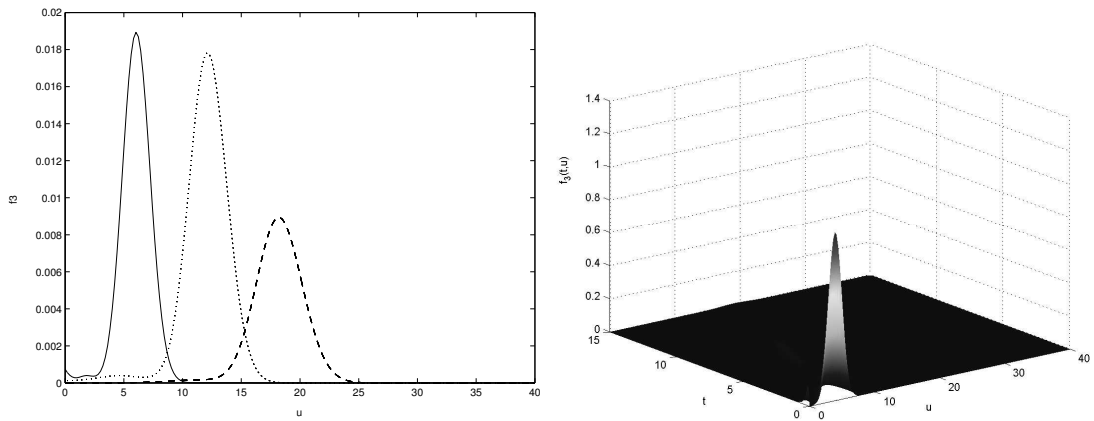


Figure 7: 2-D and 3-D representation of  $f_3(t, u)$  in the case of Set 1. In the 2D graph, the continuous line corresponds to  $t = 2$ , the dotted line to  $t = 8$  and the dashed line to  $t = 14$ .

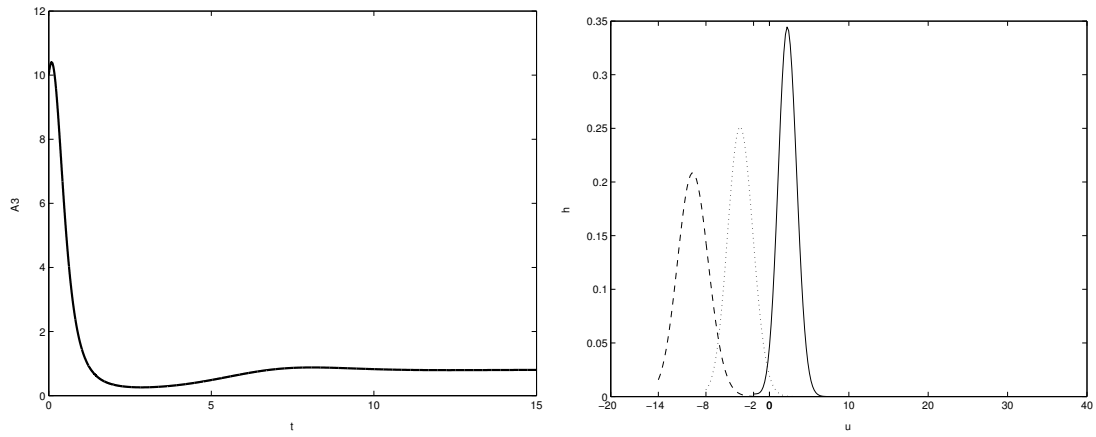


Figure 8: Case of Set 1: on the left we have  $A_3(t)$  and on the right we have  $h(t, u)$ . Here the continuous line corresponds to  $t = 2$ , the dotted line to  $t = 8$  and the dashed line to  $t = 14$ .

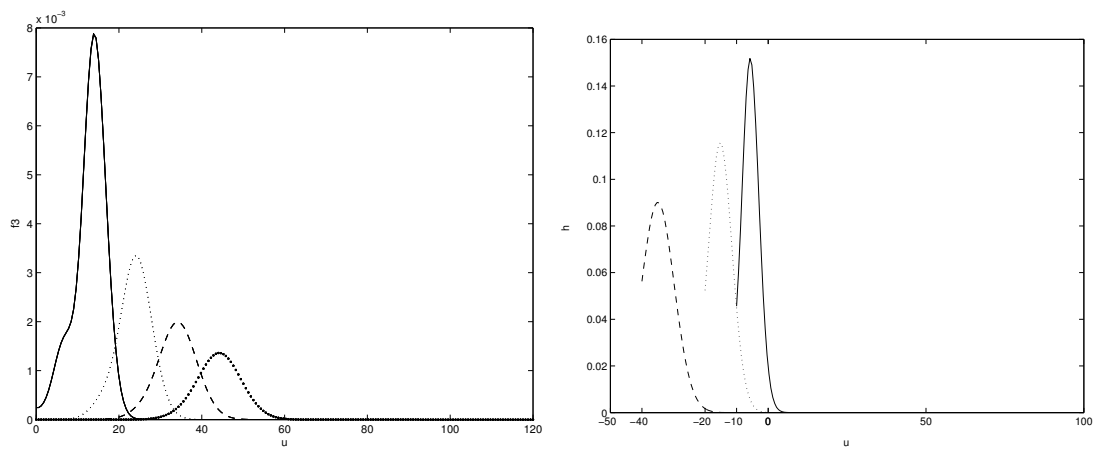


Figure 9: On the left we have  $f_3(t, u)$  and on the right we have  $h(t, u)$ .



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