Second order models of tumor-immune system competition

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Dedicated to the 70-th anniversary of Professor Constantin Udriste

Abstract. This paper deals with the qualitative analysis, existence of equilibria and asymptotic behavior of a second order model of the competition between tumor and immune cells. The background model belongs to D'Onofrio [1,2] various developments are proposed in this paper focussed to the hiding learning dynamics, followed by the qualitative analysis.

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1 Introduction

The competitition between tumor and immune cells can be modeled, in the more general approach, by a nonlinear dynamical system which identifies the evolution of the number of cells belonging to different interacting populations, tumor cells and immune-system cells, at different scales: molecular, cellular and macroscopic [3]-[15]. As immune-system cells we shortly refer to the generic immunostimulations e.g. by cytokines. The general framework is the dynamical system, proposed by d'Onofrio [1,2], which is mainly based on the following assumptions

i) is a Lotka-Volterra like model,

ii) there exist a tumor free equilibrium,

iii) the number of tumor cells may tend asymptotically to either infinity or to a finite value,

iv) there exist an equilibrium state compatible with a finite small value of the tumor cells,

v) for any time t, there not exist negative values of the variables,

vi) the influx of lymphocytes is a function of the tumor cells.

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It has been shown, by d'Onofrio [1,2], that this model generalizes some well-known competition models such as the exponential [7], logistic, Gompertz [7,13], Hart-Schochat-Agur [5], von Bertanlaffy [13], Stepanova [8], etc.. (see also references in [1,2]). We propose a generalization of the d'Onofrio approach [1,2], in order to take into account some delay in the immune system reaction. This can be realized either by using some delay models (see e.g. [17]-[21]) or by assuming a time dependence of the parameters. This time dependence summarizes, at the microscopic scale, the evolution of the dynamical system due to the hiding-learning process of cells [13]-[16].

In fact, during their interactions, the cells exchange also information and, after processing the information, they choose a suitable strategy, such as hiding, competing, etc., which can be modified in time (due to the learning process). These features, which are typical of biological units, belong to the cells activity (which is usually neglected in classical competition models). In general, the mathematical definition of the cells activity is a complex task which implies at least three different approaches: microscopic, macroscopic, hybrid. Active particles show the existence of a biological function (or better a mathematical function of a biological parameter which is the activity). Active particles belong to the same population of cells if they have the same biological function. If all particles of a single population express the biological function in the same way then we have the microscopic approach, in other words the biological function (as a function of the activity) is constant [1,2,5,7,8,9,11]. If the biological function is statistically distributed on the population then we have the macroscopic model of the kinetic theory [3],[16],[23]-[26]. In the hybrid model, instead, the biological function is constant (with respect to activity) but at least one coefficient of the modelling equations is time dependent thus showing an interaction statistically distributed [22]. Thus, as a first approach, it seems reasonable to take into account of the cells activity by assuming the time dependence of at least one parameter of the dynamical system. This functional dependence can be seen and justified in the more general framework of the kinetic equations model [22], where the two scales microscopic-macroscopic join together. Indeed only at the macroscopic level the cells distribution function is time dependent. Thus, in order to enable the competition to take into account the hiding-learning strategy of cells [22], as a part of the cells activity, the basic structure of the dynamical system has to change time to time. In [22] it was shown that this time dependence of the essential parameters might be referred to the hybrid model interaction: microscopic-macroscopic (coupled equations). In other words, if we count on the microscopic interaction of cells, in the framework of the kinetic approach [23,25], while additional bibliography is reported in [24]-[26], some parameters must be specified by a distribution function which comes as the solution of some kinetic-like equations. In the following, we will choose a suitable distribution function (normal) and show that the asymptotic analysis is in accordance with a realistic model of cancer evolution.

This paper proposes a generalization of d'Onofrio model [1,2] where one parameter is assumed to be time dependent. The qualitative-asymptotic analysis is done, in particular, for the second order approximation of the dynamical system. After having qualitatively studied and characterized the critical points in the autonomous system we have analyzed the asymptotic behaviour of the non autonomous system, when a time dependent coefficients representing the hiding-learning dynamics (due to a microscopic-stochastic interaction) is introduced. This time dependence of one

parameter might explain some time delay in the reaction of biological system. In fact, in most of all biological system, when we analyze cells competition, there is always a time delay before one population starts to organize a macroscopic reaction to the competing population. The initial stage of the competition is at the microscopic level, where we must take into consideration the density distribution of the cells activity. A stochastic parameter is defined by the density distribution of the two populations. This parameter, which describe the mechanism of the learning-hiding dynamics, included into the deterministic macroscopic equations gives rise to different evolutionary models. We have choose as a distribution function a function (sigmoid) which can explain a simple delay process in learning the facing population.

2 A nonlinear model for the immune competition of complex systems

Let us consider a system of two interacting and competing populations. Each population is constituted by a large number of individuals called *active particles*, their microscopic state is called (biological) *activity*. This activity enable the particle to organize a suitable response with respect to any information process. In absence of prior informations, the activity reduces either to a minimal loss of energy or to a random process.

In active particle competitions the simplest model of binary interaction is based on proliferation destructive competition, so that when one population gets aware of the other competing population then it starts to proliferate and/or to destroy the competing cells. However, in this process an important step is the ability of cells to hide themselves and to learn about the activity of the competing population [22]. In details, consider the relatively simpler case, when all particles are the same in each population. Then the state of the system is identified by the sizes:

$$n_i = n_i(t), \quad [0,T] \to \mathbb{R}_+ \tag{2.1}$$

for $i = 1, 2$, with particles homogeneously distributed in space. The modelling of the immune competition can be approached, at the super-macroscopic level, by a system of ordinary differential equations describing the evolution of the number of cells belonging to the two competing populations. Specifically we consider the following model proposed by D'Onofrio [1],[2]

$$\begin{cases} \dfrac{dn_1}{dt} = c_1 n_1 F(n_1) - c_2 \alpha(t) \phi(n_1)\, n_1\, n_2\,, \\ \dfrac{dn_2}{dt} = -c_3 \psi(n_1) n_2 + c_4 \beta(t) q(n_1) + \Omega(t)\,, \end{cases} \tag{2.2}$$

where n_1 is the numerical density of tumor cells, n_2 the numerical density of lymphocyte population, under conditions $n_1 \geq 0$ and $n_2 \geq 0$, while $F(n_1), \phi(n_1), \psi(n_1)$ and $q(n_1)$ are deterministic functions of n_1.

2.1 Hiding-learning parameters

We suppose that the learning-hiding actions is expressed by two time-dependent parameters $\alpha(t)$, $\beta(t)$ that we shall call the learning-hiding parameters. They are qualitatively similar: since they encode both the initial phase of learning by the immune system and the following phase of immunoevasion. Indeed in a more complete approach we should assume that

$$\alpha = \alpha(n_1\ , n_2\ , t; \sigma) \quad , \quad \beta = \beta(n_1\ , n_2\ , t; \sigma)\ ,$$

being σ a stochastic coefficient. About these functions, we assume that it exists a finite time $\widehat{t}_p$ such that:

$$0 < t < \widehat{t}_p \Rightarrow p'(t) > 0, \quad p = \alpha, \beta$$

and

$$t > \widehat{t}_p \Rightarrow p'(t) < 0, \quad p = \alpha, \beta\ .$$

Moreover, under the hypothesis that the initial time is the onset time of tumor, it is important to remark that the process of increase of the parameters is far faster than the process of decrease, since they mirror similar phenomena having two very different time scales:

- The learning of immune system of the presence of tumor cells, which is a fast process;
- The learning of tumor cells in evading from the immune control which is very slow.

In particular, the initial phase of immuno-learning may be decomposed in a first phase of - relatively - slow increase of parameters, followed by a rapid increase.

Thus, the generic learning parameters are characterized by three characteristic times: τ_1, τ_2, which characterize the learning phase, and τ_3 of the hiding phase that are such that:

$$\tau_1 > \tau_2$$

and

$$\tau_1 << \tau_3\ .$$

We propose as a function replying this qualitative behavior the following:

$$p(t) = \left[P_1 + P_2\,\mathrm{erf}\left(\frac{t-\tau_1}{\tau_2}\right)\right]\exp\left(-\frac{t}{\tau_3}\right) \tag{2.3}$$

being $P_1\ , P_2$ some positive constant ($P_2 \geq 0$) values and

$$p(0) = \left[P_1 + P_2\mathrm{erf}\left(\frac{-\tau_1}{\tau_2}\right)\right] \quad , \quad \lim_{t\to\infty} p(t) = 0\ .$$

Indeed in the hiding-learning process one should take into account also some small oscillations (as shown in [14]) or random noise so that (2.3) should be modified as (see Fig. 1)

$$p(t) = \left\{\left[P_1 + P_2\mathrm{erf}\left(\frac{t-\tau_1}{\tau_2}\right)\right] + \epsilon\sin\frac{\pi t}{2\epsilon}\right\}\exp\left(-\frac{t}{\tau_3}\right). \tag{2.4}$$

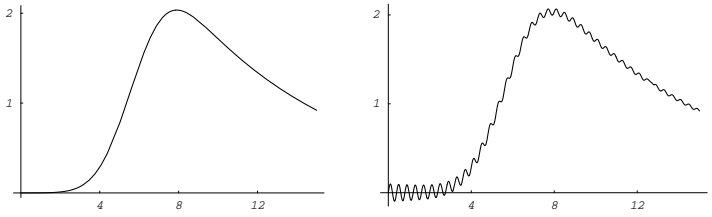

Figure 1: *Hiding learning process explained by the time dependent parameters smooth as eq. (2.3) (on the left) and with periodic small amplitude oscillations (on the right) as represented by eq.2.4*

In other words, a more reasonable interpretation of the hiding-learning dynamics should reflect the small amplitude oscillation in the learning assessment due to some uncertainty and improvements. In any definitions (2.3),(2.4) we assume that the learning process is an increasing function with an absolute peak.

In the simplest case of eq.(2.3), if we expand the error function up to a first order Taylor approximation it is

$$p(t) = \left[P_1 - P_2 \mathrm{erf}\left(\frac{\tau_1}{\tau_2}\right) + 2\,P_2 \left(\frac{e^{-\tau_1^2/\tau_2^2}}{\sqrt{\pi}\tau_2}\right) t \right] \exp\left(-\frac{t}{\tau_3}\right) ,$$

with

$$p(0) = \left[P_1 - P_2 \mathrm{erf}\left(\frac{-\tau_1}{\tau_2}\right) \right] \quad , \quad \lim_{t\to\infty} p(t) = 0\,,$$

$$p'(t)|_{t=t_e} = 0 \ , \qquad t_e = \tau_3 + \frac{1}{2} e^{\tau_1^2/\tau_2^2} \sqrt{\pi}\tau_2 \left(-\frac{P_1}{P_2} + \mathrm{erf}\left(\frac{\tau_1}{\tau_2}\right)\right) \ .$$

The absolute peak is reached in a time t_e which is

$$t_e < \tau_3 \ , \ \frac{P_1}{P_2} > \mathrm{erf}\left(\frac{\tau_1}{\tau_2}\right),$$

$$t_e = \tau_3 \ , \ \frac{P_1}{P_2} = \mathrm{erf}\left(\frac{\tau_1}{\tau_2}\right),$$

$$t_e > \tau_3 \ , \ \frac{P_1}{P_2} < \mathrm{erf}\left(\frac{\tau_1}{\tau_2}\right) \ .$$

This model, might be considered as the generalization of the Lotka-Volterra model, which is obtained from (2.2) by choosing

$$F(n_1) = Cnst. = 1 \ , \ \ \phi(n_1) = Cnst. = 1 \ , \ \ \psi(n_1) = -n_1 \ , \ \ q(n_1) = -n_1 \ .$$

According to [1,2], system (2.2) is the more appropriate model for the description of tumor-immune cells competition, because:

i) There not exist negative solutions of the numerical densities n_1 , n_2, for non small t, since they are physically unacceptable, so that

$$n_1(t) \geq 0 \quad , \quad n_2(t) \geq 0 \qquad \forall t \ .$$

ii) The function $\psi(n_1)$ describes the stimulatory effect of the tumor cells on the immune cells. We can assume that this function is positive (at least initially)

$$\psi(0) > 0 \ ,$$

and might be negative only in a finite interval. It is reasonable to assume

$$|\psi'(0)| \leq 1 \ ,$$

so that, at least initially, the death rate of lymphocytes is not greater than in the linear model.

iii) Tumor growth rate $F(n_1)$ is a positive function which summarizes the carrying capacity (or malignancy) such that [6]

$$F(0) > 0 \ , \quad \frac{d}{dn_1}F(n_1) \leq 0 \ , \quad \lim_{n_1 \to 0} n_1 F(n_1) = 0 \ ,$$

with the additional assumption that initially it is $F'(0) = 0$, where primes denote derivation with respect to n.

iv) The loss of tumor cells, which depends on the competition with lymphocytes, is represented by the function $\phi(n_1)$ characterized by [1,2]

$$\phi(n_1) > 0 \ , \quad \frac{d}{dn_1}\phi(n_1) \leq 0 \ , \quad \lim_{n_1 \to \infty} n_1 \phi(n_1) = \ell < \infty \ .$$

In other words, if the tumor growth tends to infinity the loss of tumor cells would tend to a constant rate. It can be also assumed that

$$\phi'(0) = 0 \ .$$

v) Regarding the influx of immune cells $q(n_1)$ we take

$$q(0) = 1 \quad , \quad |q'(0)| \leq 1 \ ,$$

so that, at least initially, the influx of effector cells is not greater than in the linear model.

vi) The source term $\Omega(t)$ plays the time dependent effects of a therapy on the immune system. This function can be considered as a positive rapidly decay function, localized nearby the initial time, i.e.

$$\Omega(t) > 0 \ , \quad \lim_{t \to \infty} \Omega(t) = 0 \ , \quad \exists \max_{t < \varepsilon} \Omega(t) \ .$$

According to the experimental results it should be also expected that $\Omega(t)$ is an oscillating function, likewise

$$\Omega(t) = \frac{\sin^2 \pi t}{\pi t} \ . \tag{2.5}$$

By assuming

$$x = n_1 \ , \ y = \frac{n_2}{c_4} \ , \ \tau = c_3 t$$

and

$$a = \frac{c_1}{c_3} \ , \ b = \frac{1}{c_3} \ , \ \mu = \frac{c_2 c_4}{c_3} \tag{2.6}$$

we get the non dimensional model [6]

$$\boxed{\begin{cases} \dfrac{dx}{d\tau} = axF(x) - \mu\alpha(t)\phi(x)xy \, , \\ \\ \dfrac{dy}{d\tau} = -y\psi(x) + b\beta(t)q(x) + \Omega(t) \ . \end{cases}} \tag{2.7}$$

with $\Omega(t)$ given by (2.5).

Time dependence The parameter μ in (2.6): $0 \leq \mu \leq 1$, plays an important role for modelling the cells competition. When $\mu = 0$, tumor cells grows according to the law

$$\int_{x_0}^{x(\tau)} \frac{dx}{axF(x)} = \tau \, ,$$

which represents the evolution of tumor cells in absence of competition with the immune system. This could be either the initial evolution of the tumor cells when they are not yet recognized by the immune system, or the final stage of the evolution when the immune system is unable to compete with tumor cells.

When $\mu = 1$, we take this value in correspondence to the maximum strenght of the immune system when facing the tumor cells generation. This happens when tumor cells are recognized by the immune system and the competition initiates. In a more realistic case this parameter may be considered as a function of τ:

$$0 \leq \mu(\tau) \leq 1 \ ,$$

such that

$$\lim_{\tau \to 0} \mu(\tau) = 0 \quad , \quad \lim_{\tau \to \infty} \mu(\tau) = 1 \ .$$

In other words, initially the immune system shows some (time) delay before recognizing the tumor cells but in long range the immune is always able to fully recognize the cancer growth.

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