Third order model for tumor-immune system competition

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Abstract. In this paper we give a theorem of existence of critical points for a third order competition model. This dynamical system is an approximation of a general model considered for the analysis of cells competition during the tumor-growth.

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1 Introduction

In recent years many different dynamical system were proposed to investigate the evolution of large systems of particles undergoing classical or quantum interactions (see e.g. [1],[2],[3]).

The system is assumed to be constituted by a large number of interacting entities (not classical particles) called active particles [4]. The microscopic state of active particle may include not only geometrical and mechanical variables, but also an additional variable, called activity suitable to describe their physical-chemical (shortly biological) state additional to position and momentum (see e.g. [5],[6]). In particular, this approach has been very useful in mathematical immunology [7], [8].

Recently has been proposed also some hybrid models [9],[10] in which the macroscopic evolution is influenced by the microscopic evolution, in other words the ordinar differential equations, which describe the competing populations, contain a functional solution of a partial differential system for some kind of distribution functions. Thus the macroscopic evolution depends on the influence of the microscopic distribution.

In a recent paper [11] it has been proposed a dynamical system, for the tumor-immune system competition, which can be considered a generalization of the mostly known competition models and moreover it does not contain (biological) contradictions. This model, however is too general and does not enable us to give an explicit computation of the evoluion. Therefore in the following we will consider the third order approximation (for the second approximation see [10]) and we will give a theorem of existence for the critical points.

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2 Dynamical system for the Immune Competition of cells

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 lost of energy or to a random process.

In active particle competitions the simplest model of binary interaction is based on proliferation-destructive competition. That is when, one of the population get aware of the presence of the other competing population start to proliferate and destroy the competing cells. However, in this process an important step is the ability of cells to hide them selves and to learn about the activity of the competing population.

In details consider a physical system is constituted by two interacting populations each constituted by a large number of ***active particles*** with sizes:

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

for $i = 1, 2$. Particles are homogeneously distributed in space, while each population is characterized by a microscopic state, called ***activity***, denoted by the variable u. The physical meaning of the microscopic state may differ for each population.

Let us now restrict ourselves to the analysis of the macroscopic system only. The modelling of the immune competition can be approached, at the 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 [11], which generalizes most of the know competition models, such as Gompertz, Hart-Schochat-Agur, von Bertanlaffy, Nani and Freedmn etc..(see references there)

$$\begin{cases} \dfrac{dn_1}{dt} &=& c_1 n_1 f(n_1) - c_2\phi(n_1)n_1 n_2, \\[2ex] \dfrac{dn_2}{dt} &=& -c_3\psi(n_1)n_2 + c_4 q(n_1) \quad . \end{cases} \tag{2.2}$$

n_1 is the numerical density of tumor cells, n_2, the numerical density of lymphocyte population, under conditions $n_1 \geq 0,\ n_2 \geq 0$, while α's and β's are deterministic parameters.

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

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

System (2.2) is more suitable for the description of tumor-immune cells competition since is mainly based on the following hypotheses [11]

1. There not exist negative solutions of the numerical densities for non small n_1, which would be physically unacceptable.

2. The death of lymphocytes depend on the function $\psi(n_1)$ which describe the stimulatory effect 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 seems to be 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.

3. Tumor growth rate $f(n_1)$ is a positive function which summarizes the carrying capacity (or malignancy) such that [11]
$$f(0) > 0 \ , \ \frac{\mathrm{d}}{\mathrm{d}n_1} f(n_1) \leq 0 \ , \ \lim_{n_1 \to 0} n_1 f(n_1) = 0 \ .$$
With this general assumption on $f(n_1)$ we can summarize many different models: exponential, logistic, etc. We will assume that initially it is
$$f'(0) = 0.$$

4. The loss of tumor cells depending on the competition with lymphocytes is represented by the function $\phi(n_1)$ characterized by [11]
$$\phi(n_1) > 0 \ , \ \phi(0) = 1 \ , \ \frac{\mathrm{d}}{\mathrm{d}n_1} \phi(n_1) \leq 0 \ , \ \lim_{n_1 \to \infty} n_1 \phi(n_1) = \ell < \infty \ .$$
In other words, if the tumor growth tends to infinity the loss of tumor cells would tend to a constant rate. It can be assumed that
$$\phi'(0) = 0 \ .$$

5. Regarding the influx of immune cells $q(x)$ we assume that $q(0) = 1$, as well as
$$|q'(0)| \leq 1$$
so that, at least initially, the inlux of effector cells is not greater than in the linear model.

By assuming
$$x = n_1 \ , \ y = \frac{n_2}{\beta_2} \ , \ \tau = \beta_1 t$$
and
$$a = \frac{c_1}{c_3} \ , \ b = \frac{1}{c_3} \ , \ \mu = \frac{c_2 c_4}{c_3}$$
we get the non dimensional model

$$\boxed{\left\{ \begin{array}{rcl} \dfrac{dx}{d\tau} & = & a x f(x) - \mu \phi(x) x y \ , \\ \\ \dfrac{dy}{d\tau} & = & -y \psi(x) + b q(x) \ . \end{array} \right.} \tag{2.3}$$

3 First order approximation of D'Onofrio model [11]

The equilibrium points of (2.3), given by

$$\begin{cases} x\,(af(x) - \mu\phi(x)y) &= 0 \,, \\ \\ -y\psi(x) + bq(x) &= 0 \,, \end{cases}$$

are $P_0 \equiv (x_0, y_0)$ and eventually $\overline{P} \equiv (\overline{x}, \overline{y})$ with

$$x_0 = 0 \ , \ y_0 = \frac{b}{\psi(0)}$$

$$af(\overline{x})\psi(\overline{x}) - \mu b\phi(\overline{x})q(\overline{x}) = 0 \ , \ \overline{y} = b\frac{q(\overline{x})}{\psi(\overline{x})} \ .$$

The Jacobian is

$$\begin{pmatrix} af(x) + axf'(x) - \mu\phi'(x)xy - \mu\phi(x)y & -\mu\phi(x)x \\ -y\psi'(x) + bq'(x) & -\psi(x) \end{pmatrix}$$

which, taking into account the hypotheses on the functions, in P_0 is

$$\begin{pmatrix} af(0) - \mu b\dfrac{\phi(0)}{\psi(0)} & 0 \\ -b\dfrac{\psi'(0)}{\psi(0)} + bq'(0) & -\psi(0) \end{pmatrix}$$

The eigenvalues in P_0 are

$$\lambda_1 = -\psi(0) \ , \ \lambda_2 = af(0) - \mu b\frac{\phi(0)}{\psi(0)} \ .$$

Since $\psi(0) > 0$, we have that

1. P_0 is a stable node if $af(0) < \mu b\dfrac{\phi(0)}{\psi(0)}$
2. P_0 is an unstable saddle point if $af(0) > \mu b\dfrac{\phi(0)}{\psi(0)}$
3. P_0 is a node (type II) point (stable or unstable) if $\lambda_1 = \lambda_2$ i.e. $f(0) = \dfrac{1}{a}\left(\mu b\dfrac{\phi(0)}{\psi(0)} - \psi(0)\right)$, with, according to the hypotheses, $\mu b\dfrac{\phi(0)}{\psi(0)} > \psi(0)$, i.e. $\psi(0)^2 < \mu b\phi(0)$.

The linearization in P_0 gives the system

$$\boxed{\begin{cases} \dfrac{dx}{d\tau} &= \left[af(0) - \mu b\dfrac{\phi(0)}{\psi(0)}\right] x \\ \\ \dfrac{dy}{d\tau} &= b\left[-\dfrac{\psi'(0)}{\psi(0)} + q'(0)\right] x - \psi(0)y + b \end{cases}} \tag{3.1}$$

4 Third order approximation of D'Onofrio model [11]

In this section we consider the third order Taylor expansion of system (2.3) around the initial (equilibrium) state $x_0 = 0, y_0 = b/\psi(0)$ (for the second order approximation see [10]). From (2.3) it is

$$\boxed{\left\{\begin{array}{rcl} \dfrac{dx}{d\tau} &=& af(0)x + af'(0)x^2 - \mu\left[x + \phi'(0)x^2\right]y + \dfrac{1}{2}\left[af''(0) - \mu\phi''(0)y\right]x^3, \\ \\ \dfrac{dy}{d\tau} &=& bq'(0)x - \psi(0)y + b + \dfrac{1}{2}bq''(0)x^2 - \left[\psi'(0)x + \dfrac{1}{2}\psi''(0)x^2\right]y- \\ \\ && -\dfrac{1}{6}\left[\psi'''(0)y - bq'''(0)\right]x^3 \ . \end{array}\right.} \tag{4.1}$$

We assume

$$f'(0) = 0 \ , \ \phi'(0) = 0 \ , \ \phi''(0) = 0 \ , \ q''(0) = 0 \ , \ q'''(0) = 0$$

so that by defining,
(4.2)

$$\boxed{\begin{array}{l} \alpha_1 = af(0) \ , \ \alpha_2 = \dfrac{1}{2}af''(0) \ , \\ \\ \beta_1 = \psi'(0) \ , \ \beta_2 = \psi(0) \ , \ \beta_3 = bq'(0) \ , \ \beta_4 = b \ , \ \beta_5 = \dfrac{1}{2}\psi''(0) \ , \ \beta_6 = \dfrac{1}{6}\psi'''(0) \end{array}}$$

we have

$$\left\{\begin{array}{rcl} \dfrac{dx}{d\tau} &=& \alpha_1 x - \mu xy + \alpha_2 x^3 \ , \\ \\ \dfrac{dy}{d\tau} &=& -\beta_1 xy - \beta_2 y + \beta_3 x + \beta_4 - \beta_5 yx^2 - \beta_6 yx^3 \ . \end{array}\right. \tag{4.3}$$

The parameters (4.2) according to the hypotheses on functions, are such that,

$$\boxed{\alpha_1 > 0 \ , \ |\beta_1| \leq 1 \ , \ \beta_2 > 0 \ , \ |\beta_3| < 1 \ , \ 0 \leq \beta_4 \leq 1} \tag{4.4}$$

A critical point is

$$P_1 = \left(0, \frac{\beta_4}{\beta_2}\right)$$

which, according to (4.2) is

$$P_1 = \left(0, \frac{b}{\psi'(0)}\right)$$

the other points are given by the intersection of the null clines. Assuming $\mu \neq 0$, we define

$$A = \frac{\alpha_2}{\mu} \ , \ B = \frac{\alpha_1}{\mu}$$

Figure 1: *Null clines of the system* (4.3)*, intersection of* (4.5) *with* $y'(0) < 0$*.*

so that the critical points of the system (4.3) are given by the intersection of

$$\left\{ \begin{array}{lcl} y & = & A\,x^2 + B \\ \\ y & = & \dfrac{\beta_4 + \beta_3 x}{\beta_6 x^3 + \beta_5 x^2 + \beta_1 x + \beta_2} \end{array} \right. \tag{4.5}$$

Thus the critical points are on the intersection of the family (depending on μ) of parables (parallel to the y-axis) and the fixed curve

$$y = \frac{\beta_4 + \beta_3 x}{\beta_6 x^3 + \beta_5 x^2 + \beta_1 x + \beta_2} \ .$$

It can be easily seen that, for $x > 0$,

$$\lim_{x \to 0^+} \frac{\beta_4 + \beta_3 x}{\beta_6 x^3 + \beta_5 x^2 + \beta_1 x + \beta_2} = \frac{\beta_4}{\beta_2} \geq 0 \qquad , \qquad \lim_{x \to +\infty} \frac{\beta_4 + \beta_3 x}{\beta_6 x^3 + \beta_5 x^2 + \beta_1 x + \beta_2} = 0 \ .$$

The intersection with the x-axis is the point

$$P_2(-\frac{\beta_4}{\beta_3} \ , \ 0)$$

We are interested mainly on the number of critical points which belongs to the positive sector of x , y. Thus we should first analize the function $(4.5)_2$ in order to focus on the singular points. It can be easily shown that

Theorem 1 *When*

$$-\frac{\beta_4}{\beta_3} > 0$$

for $x > 0$*, and*

Figure 2: *Null clines of the system* (4.3), *intersection of* (4.5) *with* $y'(0) > 0$.

1. $\beta_3\beta_2 \leq \beta_4\beta_1$, *there exists only one critical point of* $(4.5)_2$, *for (Fig. 1)*

$$0 \leq \frac{\alpha_1}{\mu} \leq \frac{\beta_4}{\beta_2}$$

2. $\beta_3\beta_2 > \beta_4\beta_1$, *there exists only one critical point of* $(4.5)_2$, *for (Fig. 2)*

$$0 \leq \frac{\alpha_1}{\mu} \leq \frac{\beta_4}{\beta_2}$$

and two critical points for

$$\frac{\beta_4}{\beta_2} \leq \frac{\alpha_1}{\mu} < y_* - \frac{\alpha_2}{\mu} x_*^2$$

being (x_*, y_*) *the tangent point of the two null clines, given as solution of the system*

$$\left\{ \begin{array}{lcl} y & = & Ax^2 + B \\ & & \\ 2Ax & = & \dfrac{\beta_2\beta_3 - \beta_1\beta_4 - x\left[\beta_3 x\left(\beta_5 + 2\beta_6 x\right) + \beta_4\left(2\beta_5 + 3\beta_6 x\right)\right]}{\left[\beta_2 + x\left(\beta_5 + \beta_6 x\right)\right]^2} \end{array} \right. .$$

Proof. The existence of one critical point immediately follows by observing that the intersection of parable family with y-axis is $B = \dfrac{\alpha_1}{\mu}$ (see Figg. 1,2). We have, instead two intersection only when B ranges from β_4/β_2 and the value of B which corresponds to the common tangent line. Thus by equating the first derivatives of the null clines there follows tha last part of theorem. ■

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