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Citation: AIP Conference Proceedings **1124**, 79 (2009); doi: 10.1063/1.3142956
View online: http://dx.doi.org/10.1063/1.3142956
View Table of Contents:
http://scitation.aip.org/content/aip/proceeding/aipcp/1124?ver=pdfcov
Published by the AIP Publishing

Mathematical model of cancer with competition

Joanna M. Chrobak[*,†] and Henar Herrero[*,**]

[*]*Universidad de Castilla La Mancha,*
Departamento de Matemáticas,
Avda. Camilo José Cela 3,
13071 Ciudad Real, Spain
[†]*Joanna.Chrobak@uclm.es*
[**]*Henar.Herrero@uclm.es*

Abstract. In this paper we present a model of tumor based on the use of an autonomous system of ordinary differential equations (ODE). The model assumes that normal cells and cancer cells coexist in an environment as two different species which compete for nutrients and space. The immune system and the tumor cells fight against each other. The analysis of the linear stability of the fixed points of the model yields to two groups of solutions. In the first one, the immune system wins against the tumor cells, so the cancer disappears. In the second one, the cancer grows until some fixed level and then stabilizes.

Keywords: <Cancer, mathematical model autonomous ODE.>
PACS: 87.10.Ed, 87.19.xj

1. INTRODUCTION

Cancer is a broad term that encompasses more than 200 types of malignancies. Each of them has some special features, with its causes, its evolution and its specific treatment. The number of deaths caused by different kinds of malignant tumors increases every year all over the world. We have to deal with a big variety of tumors, but they have one thing in common: their cells reproduce in an uncontrolled way. The mechanism of apoptosis (programmed cell death - a genetically directed process of cell self-destruction) is unsettled, and a cancer cell does not react to its stimulus. This is the onset of the formation of a malignant tumor.

In general the problem of tumor can be treated from three scale levels [2]:

1. Subcelular or biochemical scale. One can include here all phenomena which occurs inside the cell and in its membrane like for example DNA mutations, perturbations of celular cicle, emission and interpretation of signals between cells, response of cells to these signals or absorption of nutrients.
2. Celular scale. This scale refers to relations between a cell and its surroundings, i.e. the proliferation of tumor's cells and their competition with immune system and healthy tissue.
3. Macroscopic scale. In this approach the phenomena typical for a continuous system are taken into account: migration of cells, convection, diffusion of nutrients and chemical substances, transition of dispersed cells into connected ones (solid tumor), dispersion of cells and metastasis.

CP1124, *Mathematical Models in Engineering, Biology, and Medicine, Proceedings of the International Conference on Boundary Value Problems,* edited by A. Cabada, E. Liz, and J. J. Nieto

The first two points refer to a phenomenon of the celular scale, the latter two to a macroscopic occurrence.

Mathematical models which attempt at describing a cancer from a celular point of view are based on the use of ordinary differential equations (ODEs), see [15, 12, 7], while macroscopic approaches require the use of nonlinear partial differential equations (nonlinear PDEs), see [9, 16, 5, 6, 8] . A good review of models that address evolutionary questions about cancer can be found in [14] and in [1].

Our model approaches the problem of cancer at the celular scale and, consequently, it uses ordinary differential equations. We consider populations of cancer cells and their competition with the immune system as an attempt to model the experimental results presented in Ref. [13]. We also take into account the interaction between tumor and healthy tissues. Although the model itself and its analysis is very basic, it provides a description which could match reality.

In section 2 of this paper the model is introduced. Section 3 is devoted to the linear stability of the fixed points. In section 4 interpretation of the results is presented. The conclusions are listed in section 5.

2. THE MODEL

We construct a model of an ecosystem based on the use of an autonomous system of ordinary differential equations. In the most general way it can be written as

$$\begin{cases} \dfrac{dx_1^*}{dt} = -\gamma^* x_1^* x_2^*, \\ \dfrac{dx_2^*}{dt} = \alpha^* x_2^* - c_1 x_1^* x_2^* - c_2 x_2^* x_3^* - c_3 (x_2^*)^2, \\ \dfrac{dx_3^*}{dt} = \beta^* x_3^* - f^* x_2^* x_3^*. \end{cases}$$

where:
x_1^* – normal cells,
x_2^* – cancer cells,
x_3^* – the response of the immune system,
$\gamma, \alpha, c_1, c_2, c_3, \beta, f$ – positive coefficients.
where to reduce the number of the coefficients we rescale the equations, and in this way we obtain our preliminary model of cancer:

$$\begin{aligned} \frac{dx_1}{dt} &= -\gamma x_1 x_2, \\ \frac{dx_2}{dt} &= \alpha x_2 - x_1 x_2 - x_2 x_3 - x_2^2, \\ \frac{dx_3}{dt} &= \beta x_3 - f x_2 x_3, \end{aligned} \tag{2.1}$$

where:
$x_1 = x_1^* c_1$, $x_2 = x_2^* c_3$, $x_3 = x_3^* c_2$, $\gamma = \dfrac{\gamma^*}{c_3}$, $\alpha = \alpha^*$, $\beta = \beta^*$, $f = \dfrac{f^*}{c_3}$.

We assume that normal and cancer cells coexist in an environment as two different species which compete for nutrients and space. We do not consider any spatial limitation. The immune system and the tumor cells fight against each other. The variables x_1, x_2, representing normal and cancerous cells, are proportional to the volume occupied by healthy tissue and by the tumorous zone, respectively. The variable x_3, representing the response of the immune system, is proportional to the density of the immune cells per unit of the body volume. The cell cycle of tumorous cells is unsettled (see, for example, [10]). As a direct consequence of that, if we consider short periods of time, we obtain enormous number of malignant cells beside the number of the healthy ones almost does not change. To reflect this phenomenon in our model we assume that healthy cells do not reproduce. Part $-\gamma x_1 x_2$ describes competition between normal cells and cancer ones. The term αx_2 corresponds to the reproduction of the tumor cells, $-x_2 x_3$ refers to the fight between immune system and cancer, $-x_2^2$ is a competition within the tumor for space and nutrients (some of its cells die and form necrotic core, see [2]), and βx_3 is the response of immune system, which results in an increase of the immune cell concentration. The origin of equations is related to predator-prey models (see [11]). With regard to the different parameters, α and β represent the linear part of the growth rate of tumor cells and immune system, respectively; γ and f are the rates of competition between x_1 and x_2 and x_2 and x_3, respectively. The different parameters should be adjusted according to medical experiences.

The set $\{(x_1, x_2, x_3) \in R^3 : x_1 \geq 0, x_2 \geq 0, x_3 \geq 0\}$ is positively invariant. Because the planes $x_1 = 0$, $x_2 = 0$ and $x_3 = 0$ are invariant manifolds, i.e., $(x_1(t) \equiv 0, x_2(t), x_3(t))$, is a solution of system (2.1) if $(x_2(t), x_3(t))$ are solution of

$$\begin{aligned} \frac{dx_2}{dt} &= \alpha x_2 - x_2 x_3 - x_2^2, \\ \frac{dx_3}{dt} &= \beta x_3 - f x_2 x_3, \end{aligned} \tag{2.2}$$

$(x_1(t), x_2(t) \equiv 0, x_3(t))$, is a solution of system (2.1) if $(x_1(t), x_3(t))$ are solution of

$$\begin{aligned} \frac{dx_1}{dt} &= 0, \\ \frac{dx_3}{dt} &= \beta x_3, \end{aligned} \tag{2.3}$$

in this case the solution can be displayed: $x_1(t) = C_1, x_3(t) = C_2 e^{\beta t}$, $C_1, C_2 \in R$. $(x_1(t), x_2(t), x_3(t) \equiv 0)$, is a solution of system (2.1) if $(x_1(t), x_2(t))$ are solution of

$$\begin{aligned} \frac{dx_1}{dt} &= -\gamma x_1 x_2, \\ \frac{dx_2}{dt} &= \alpha x_2 - x_2 x_1 - x_2^2. \end{aligned} \tag{2.4}$$

As the planes $x_1 = 0$, $x_2 = 0$ and $x_3 = 0$ are invariant, the flow can not cross that planes and if $x_1(t_0) \geq 0$, $x_2(t_0) \geq 0$ and $x_3(t_0) \geq 0$ the solution for these initial conditions satisfies $x_1(t) \geq 0$, $x_2(t) \geq 0$ and $x_3(t) \geq 0$ $\forall t > 0$.

3. STABILITY ANALYSIS

Using matrix notation we can rewrite our system of equations in the following general form

$$\overrightarrow{x}' = \overrightarrow{F}(\overrightarrow{x}),$$

and calculate the Jacobian matrix:

$$D\overrightarrow{F}(\overrightarrow{x}) = \begin{pmatrix} -\gamma x_2 & -\gamma x_1 & 0 \\ -x_2 & \alpha - x_1 - x_3 - 2x_2 & -x_2 \\ 0 & -fx_3 & \beta - fx_2 \end{pmatrix}$$

We also calculate the fixed points by solving the system of equations:

$$\begin{cases} -\gamma x_1 x_2 = 0, \\ \alpha x_2 - x_1 x_2 - x_2 x_3 - x_2^2 = 0, \\ \beta x_3 - f x_2 x_3 = 0. \end{cases}$$

In this way the following fixed points are obtained:

$$P_1 = (a;0;0), \text{where } a = const. \neq 0,$$

$$P_2 = (0;0;0),$$

$$P_3 = (0;\alpha;0),$$

$$P_4 = (0;\frac{\beta}{f};\alpha - \frac{\beta}{f}).$$

The third coordinate of the point P_4 implies the condition:

$$\alpha - \frac{\beta}{f} > 0 \Longrightarrow \alpha f > \beta. \tag{3.1}$$

since this coordinate represents the concentration of immune cells, which must be positive. It cannot even be zero because in every part of healthy tissue there are some immune cells called resident macrophages which are watching the situation and in case of a problem they send signals to neighboring tissues.
To check the stability of the fixed points it is necessary to calculate their eigenvalues. In order to do that we need to solve for each point the following equation:

$$det(D\overrightarrow{F}(P_i) - \lambda I) = 0, \text{ for } i = 1,2,3,4, \tag{3.2}$$

where I is an identity matrix and λ is an eigenvalue.
For the first point we have:

$$D\overrightarrow{F}(P_1) = \begin{pmatrix} 0 & -\gamma a & 0 \\ 0 & \alpha - a & 0 \\ 0 & 0 & \beta \end{pmatrix}$$

and solving the equation (3.2) we obtain the following eigenvalues:

$$\lambda_1 = 0,\ \lambda_2 = \beta > 0,\ \lambda_3 = \alpha - a,$$

in this case λ_3 can be positive or negative, depending on the value of a. So, each of points P_1 can be a source (if $a \leq \alpha$) or a saddle point (if $a > \alpha$).
For the second point we have:

$$D\overrightarrow{F}(P_2) = \begin{pmatrix} 0 & 0 & 0 \\ 0 & \alpha & 0 \\ 0 & 0 & \beta \end{pmatrix}$$

and solving the equation (3.2) we obtain the following eigenvalues:

$$\lambda_1 = 0,\ \lambda_2 = \alpha > 0,\ \lambda_3 = \beta > 0,$$

so the point P_2 is a source.
For the third point we have:

$$D\overrightarrow{F}(P_3) = \begin{pmatrix} -\gamma\alpha & 0 & 0 \\ -\alpha & -\alpha & -\alpha \\ 0 & 0 & \beta - f\alpha \end{pmatrix}$$

and solving the equation (3.2) we obtain the following eigenvalues:

$$\lambda_1 = -\gamma\alpha < 0,\ \lambda_2 = -\alpha < 0,\ \lambda_3 = \beta - f\alpha < 0.$$

The fact that λ_3 is negative results from the condition (3.1). Summarizing, the point P_3 is a sink.
For the fourth point we have:

$$D\overrightarrow{F}(P_4) = \begin{pmatrix} -\gamma\dfrac{\beta}{f} & 0 & 0 \\ -\dfrac{\beta}{f} & -\dfrac{\beta}{f} & -\dfrac{\beta}{f} \\ 0 & -f\alpha + \beta & 0 \end{pmatrix}$$

and the solution of equation (3.2) yields

$$\lambda_1 = -\gamma\frac{\beta}{f} < 0$$

and the quadratic equation:

$$\lambda^2 + \frac{\beta}{f}\lambda - \beta\alpha + \frac{\beta^2}{f} = 0,$$

which describes the relation between λ_2 and λ_3. As we are interested only in the sign of eigenvalues, instead of solving this equation we can apply Viète's formulas, which for a general cuadratic equation $a\lambda^2 + b\lambda + c = 0$ can be written as following:

$$\begin{cases} \lambda_2 + \lambda_3 = -\dfrac{b}{a} \\ \lambda_2 \cdot \lambda_3 = \dfrac{c}{a}, \end{cases}$$

where λ_2, λ_3 are the roots of the general cuadratic equation. In this case we obtain:

$$\lambda_2 + \lambda_3 = -\frac{\beta}{f} < 0,$$

$$\lambda_2 \cdot \lambda_3 = -\beta\alpha + \frac{\beta^2}{f} = \beta\left(\frac{-\alpha f + \beta}{f}\right) = \frac{\beta}{f}(-\alpha f + \beta) < 0,$$

because $-\alpha f + \beta < 0$ (see condition (3.1)). Therefore, each of the eigenvalues has a different sign. So, for the point P_4 there are two possible situations: $\lambda_1 < 0,\ \lambda_2 > 0,\ \lambda_3 < 0$ or $\lambda_1 < 0,\ \lambda_2 < 0,\ \lambda_3 > 0$. In any of these cases P_4 is a saddle point.

The phase diagram obtained by using the standard MatLab function "ode45" for different initial conditions is presented in Figure 1. Fixed points are marked with red circles and the green curve is a stable manifold.

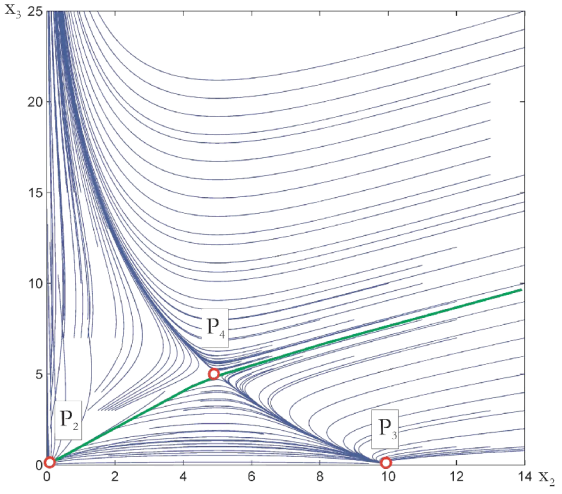

FIGURE 1. Phase diagram. The fixed points are the red points and the stable manifold is the green curve.

4. INTERPRETATION OF THE RESULTS

We obtained two types of solutions of the problem. The first group are those solutions for which the immune system wins and the cancer disappears. The initial condition for these solutions is situated over the stable manifold, which is marked as a green curve in the Figure 1. The second group of solutions corresponds to the case in which the cancer grows until it achieves some maximum size. On the phase diagram (see Figure 1) they have initial values situated under the stable manifold. In general we observe that the worst result occurs when the response of the immune system, so the value of x_3, is below the level of the stable manifold. In this case cancer stabilizes at some level of growth. If the immune response is over the stable manifold then the cancer disappears. These results are in coincidence with experimental data in Ref. [13]. Following that reference the competition between the immune system and cancer can lead to three possible outcomes that compared with our solutions are:

1. Elimination: immune system destroys the cancer. In our model this situation is described by the first group of solutions.
2. Equilibrium: immune system monitors the cancer's growth but it is unable to eradicate it. These are the solutions which lie on the stable manifold and tend to equilibrium P_4.
3. Escape: cancer cells evade the immune system's defenses and often become more malignant. In the model this is the second group of solutions, where the cancer grows until some level.

To have a closer look at the solutions we fixed three different initial conditions, which are marked as IC1, IC2 and IC3 in Figure 2.

The first initial condition is equal to IC1$= (1, 11, 8)$. The solution for it is shown as Figure 3. In this case the immune system overcomes the cancer, so we can observe a decrease of x_2 and increase of x_3.

The second initial condition is equal to IC2$= (1, 6, 5.01)$. The solution is presented in Figure 4. In this situation cancer grows until some maximum size and immune response does not fight the cancer but contrarily, it encourages its angiogenesis. This behaviour coincides with the macroscopic interpretation: first immune system is activated through the recognition of the cancer cell by immune cells. Macrophages from neighboring tissues migrate into the hypoxic regions of the tumor (regions with low level of oxygen) through the external layer of well nourished cells of the tumor. Macrophages move by chemotaxis (reaction to a chemical stimulus which cause either the approaching to or the escaping from it), attracted by macrophage chemoattractants which is secreted by the tumor. A cytotoxic substance is secreted into the tumor's cells which kills it. But at the same time macrophages secrete other chemical substances which help the tumor to create microvessels and to start process of angiogenesis.

Third initial condition is equal to IC3$= (0.5, 11, 0)$. The numerical solution in this case is shown in Figure 5. There is no immune response, but the cancer decreases in size until it stabilizes on some level (this level depends on the value of parameter α). This kind of phenomenon was described by Nagy [15], who referred to it as a hypertumor - a focus

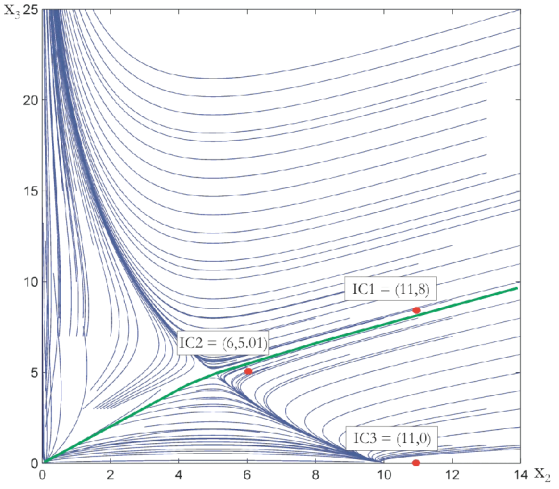

FIGURE 2. Phase diagram with the three different initial conditions IC1, IC2 and IC3 developed in figures 3, 4 and 5.

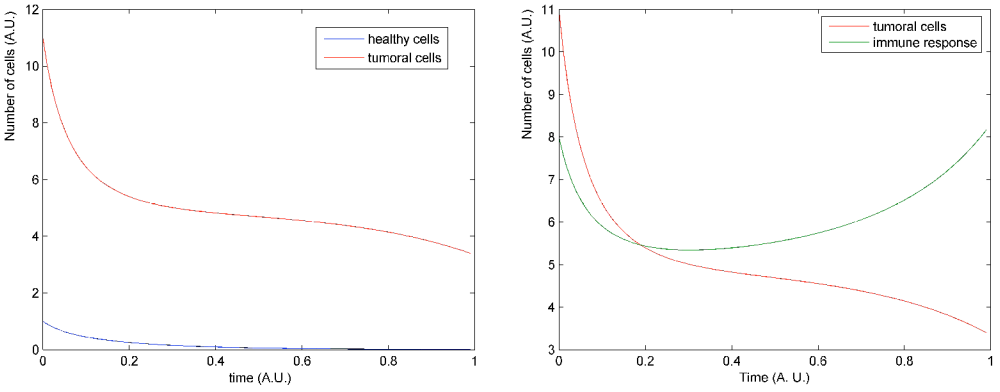

FIGURE 3. Solution for the initial condition (1,11,8): immune system wins the cancer.

of aggressively reproducing parenchyma cells that invade and destroy part or the whole tumor. This kind of tumors develop an aggressive histology but are paradoxically prone to extinction in some cases. An example can be neuroblastoma, a common childhood cancer, which sometimes fit this pattern.

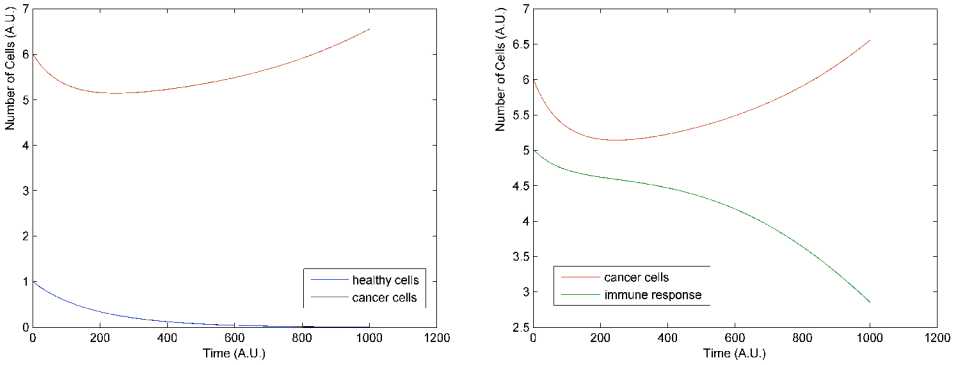

FIGURE 4. Solution for the initial condition (1,6,5.01): immune system helps the cancer angiogenesis.

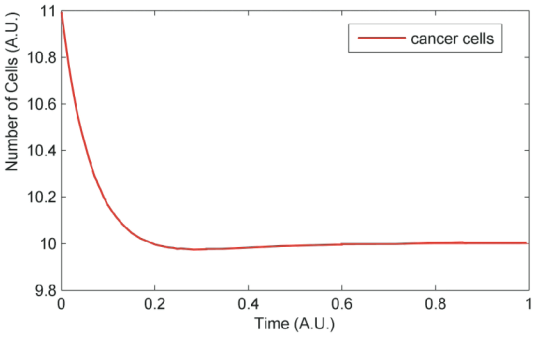

FIGURE 5. Solution for the initial condition (0.5,11,0): cancer decreases its size and stabilize.

5. CONCLUSIONS

In this paper we introduced a model of tumor based on the use of an autonomous system of ordinary differential equations. The model assumes that normal cells and cancer cells coexist in an environment as two different species which compete for nutrients and space. The immune system and the tumor cells fight against each other. The solution of the model is bounded, so only limited growth is possible. The analysis of the linear stability of the fixed points of the model yields to two groups of solutions. In the first one, the immune system wins against the tumor cells, so the cancer disappears. In the second one, the cancer grows until some fixed level and then stabilizes. A phase diagram has been derived, which presents a stable manifold associated with the response of the immune system. Thus, the fate of the tumor is determined by whether the action of the immune system falls above (cancer disappears) or below (cancer grows until some level) this stable manifold. These results reflect well the biological reality in Ref.

[13]. Furthermore the solutions fit some patterns which happens in oncology, like for example the existence of "hypertumor" or the stimulating role of the immune system in angiogenesis [15]. As in Bru's model [3, 4], a sufficiently intense response of the immune system could eliminate a cancer.

ACKNOWLEDGMENTS

This work was partially supported by the Research Grant MEC (Spanish Government) MTM2006-14843-C02-01 and CCYT (Junta de Comunidades de Castilla-La Mancha) PAI08-0269-1261, which include RDEF funds.
The authors want to thank their collaborators: Gloria Bueno from ETSI Industriales (UCLM) and oncologists from Hospital General de Ciudad Real and Hospital Virgen de la Salud de Toledo.

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