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A MATHEMATICAL MODEL OF INDUCED CANCER-ADAPTIVE IMMUNE SYSTEM COMPETITION

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We present a model of competition between an artificially induced tumor and the adaptive immune system based on the use of an autonomous system of ordinary differential equations (ODE). The aim of this work is to reproduce experimental results which find two possible outcomes depending on the initial quantities of the tumor and the adaptive immune cells. The ODE system is positively invariant and its solutions are bounded. The linear stability analysis of the fixed points of the model yields two groups of solutions depending on the initial conditions. In the first one, the immune system wins against the tumor cells, so the cancer disappears (elimination). In the second one, the cancer keeps on growing (escape). These results are coherent with experimental results which show these two possibilities, so the model reproduces the macroscopic behavior of the experiments. From the model some conclusions on the underlying competitive behavior can be derived.

Keywords: Biological Modelling; Ordinary Differential Equations; Least Squares Fit.

1. Introduction

Among all the challenges which the immune system faces, cancer is one of the most complicated ones on account of the character of this illness, because tumor cells are not foreign to the body of an organism. The exact dynamics of the immune reaction to the presence of a tumor *in vivo* is very complicated and not well understood. In general, it is similar to the response to any kind of inflammation. The main problem in the case of a tumor is to start the immune cascade so to recognize cancer cells as non-self. This is the role of resident macrophages, a type of white blood cell which are present in most body organs. They recognize pathogens through toll-like receptors (TLRs) and they approach the hypoxic regions of the tumor via chemotaxis (reaction to a chemical stimulus which cause either approach to it or escape from it). There they catch the tumor's cells, secrete a cytotoxic substance into them, and finally engulf them. Simultaneously macrophages release cytokines which activate T-helper cells which multiply and send signals to different kind of immune cells: natural killer cells, B-cells and more T-cells, which migrate to the place of the problem from neighboring tissues. As the number of B-cells increases,

T-helper cells send a signal to start the process of the production of antibodies which later can be attached to tumor's cells. This in turn accelerates the occurence of engulfment by macrophages or killing by natural killers, see Ref. 1.

Unfortunately, the immune response may also have a negative effect. Macrophages secrete some substances which encourage angiogenesis, and hence the creation of new blood vessels by tumor, see Refs. 2 and 3. The role of adaptive immunity in the fight against cancer is studied in Ref. 4. There, two groups of wild-type mice were injected with a single low dose of the chemical carcinogen 3-methylcholanthrene (MCA) and monitored for the next 200–230 days. The ones which developed progressively growing sarcomas were removed from the experiments (because for those mice to neutralize the immune system has no longer effect), meanwhile the remaining ones, which often displayed small stable masses, were placed on weekly injections of either control immunoglobulin or monoclonal antibodies that deplete or block specific immunological components and were monitored for the appearance of tumors. Mice treated with control immunoglobulin that deplete the non-adaptive immune system did not develop additional neoplasms. Mice in which some elements of the adaptive immune system were blocked or depleted, i.e. treated with a mixture of monoclonal antibodies that deplete $CD4^+$ and $CD8^+$ cells and neutralize interferon-gamma (IFNγ) developed progressively growing sarcomas. These results suggest that adaptive immunity has an important role in preventing MCA-induced sarcoma outgrowth. Only those mice with strong initial immunoresponse are the subject of the study. For this reason in the model the mice with low initial immunoresponse evolve towards growing sarcoma and the ones with strong initial immunoresponse evolve towards disappearing sarcoma.

We tried to reproduce these experimental results using a model of a system of ordinary differential equations (ODE) of induced tumor-adaptive immune system competition. Our aim was to obtain a model with the two possibilities reported in the experiments, elimination and escape depending only on the initial conditions. In Ref. 4, they report a possible equilibrium, that in fact corresponds to a small solution that tends to zero. This model would correspond to the macroscopic behavior and it could give an insight on the underlying competitive behavior.

There are some ODE models of tumor-immune system competition in Refs. 5–8. In these models the different possibilities depend on the values of the parameters. In our model the two types of solutions are attained for one set of parameters, and hence the behavior of the solution depends only on the initial condition, meanwhile in the other models in order to change the character of a solution it is necessary to change the values of the parameters.

Cancer is a very complex system that can be modeled at different levels of detail. From macroscopic to microscopic, the complexity increases. In Ref. 9, a microscopic molecular–cellular level is considered, at this level a complex network is necessary for the description of the system. The model we consider is thought-out at a highly macroscopic level, and at this level what is observed is either a continuous growing or a disappearance, depending on the adaptive immune system, and this is what is modeled and what occurs in the model. This model, fitted with the

experiments, can be useful, it is simple and we are able to give some information to the experimentalists, as can be seen in the next sections, i.e. an equilibrium state is not possible as they claim.

In Sec. 2 of this paper the model is introduced and some of its characteristics are discussed. In Sec. 3, the interpretation of the results is presented. The conclusions are listed in Sec. 4.

2. The Model

The model is an autonomous system of ODE which describes competition between an induced cancer and the adaptive immune system. We consider a well known model of two species competition with finite carrying capacities.[10–12] In the most general way it can be written as

$$\frac{dx}{dt} = ax - bxy - cx^2, \tag{2.1}$$

$$\frac{dy}{dt} = dy - exy - fy^2, \tag{2.2}$$

where t is the time, measured in days, $x(t)$ is the density of cancer cells measured in area in cm^2 because area is proportional to the number of cells and it is the measure reported in Ref. 4, $y(t)$ is the density of immune cells whose measure cannot be specified from Ref. 4. a–f are positive coefficients.

In the first equation of the system (2.1), ax is the rate of the cancer's growth. The part $-bxy$ describes the loss of tumor cells due to the interaction between cancer and the immune system. The term $-cx^2$ means a competition of cancer cells with themselves which results in the creation of a necrotic core. At the beginning, malignant cells create a small spheroid of a few millimeters of diameter which grows until the level of nutrients concentration (mainly oxygen and glucose) falls below the critical level. The cells in the centre of the spheroid cannot survive, so they undergo necrosis. In consequence, the inner region of the tumor is formed by dead cells, and is called the necrotic core, which hinders its growing.

The dynamics of the immune system is unknown, i.e. the production rates, division rates and distribution of lifespans of mouse or human lymphocyte populations,[13] so we simply assume a logistic model as a possible one. Then in the second equation of the system (2.2), the term dy is the rate of the immune system's growth. The term $-exy$ describes the loss of immune system cells due to the competition between cancer and immune cells. The term $-dy^2$ represents the internal control of growth for immune system cells.

There is evidence of immune cells penetrating the solid tumor in Refs. 14 and 15, then collision type interaction assumed in the model makes sense.

Following the experiment presented in Ref. 4, the injection of sarcoma in several mice suggests an initial amount of induced cancer, the same for every mouse, and an initial state of adaptive immune system, different for different groups of mice; after waiting 200 days of evolution, some of the mice possess a growing sarcoma and

others possess a smaller tumor. The mice with growing sarcoma (first group of mice) were removed from the experiment, some of the remaining (second group of mice) were treated with antibodies that deplete the non-adaptive immune system (control immunoglobulin) and the remaining (third group of mice) were injected with antibodies that deplete or neutralize the adaptive immune system (anti-CD4/CD8, anti-IFNγ, or anti-IL-12p40 which is critical for IFNγ production). Then after these 200 days the adaptive immune system was kept in the first and the second group, and it was changed in the third group of mice. Hence, new initial conditions are considered after 200 days. In the second group cancer disappears, and in the third group cancer keeps on growing. These facts suggest that the adaptive immune system plays an important role in the fight against induced tumours. The removed mice tend to develop the maximum possible amount of sarcoma and death, the second group of mice tends to beat cancer and in the third type the cancer keeps on growing, eventually leading to death. Hence, only two states are possible as the final or asymptotic states: disappearance of cancer with constant level of immune system or maximum growth of cancer with vanished immune system. What is changed in the experiment is the amount of the variables, cancer or adaptive immune system, i.e. the resulting asymptotic state depends only on the initial conditions. The initially induced sarcoma and the treatment that depletes the adaptive immune system refer to conditions for the competing species, and not the parameters, then a bifurcation does not occur. In order to reproduce the results presented in Ref. 4, we look for a model which would have two types of solutions, elimination and escape, such that the behavior of a solution would depend only on the initial condition, not on the values of the parameters. To obtain agreement with reality we also need the solutions to be bounded and positively invariant. We assume that the immune and cancer cells coexist in an environment as two different competing species which fight against each other.

2.1. *Linear stability*

The system (2.1)–(2.2) is positively invariant. The proof can be found in the Appendix.

We calculated the fixed points of the system (2.1)–(2.2), obtaining:

$$P_1 = (0,0),\ P_2 = \left(0, \frac{d}{f}\right),\ P_3 = \left(\frac{a}{c}, 0\right),\ P_4 = \left(\frac{bd - fa}{be - fc}, \frac{cd - ea}{cf - eb}\right).$$

The character of the fixed points was checked by calculating the Jacobian matrix and eigenvalues for each point $P_i,\ i = 1, 2, 3, 4$.

$$D\overrightarrow{G}(\overrightarrow{x}) = \begin{pmatrix} a - by - 2cx & -bx \\ -by & d - ex - 2fy \end{pmatrix}. \tag{2.3}$$

From the calculation of the eigenvalues we deduce that P_1 is an unstable node, P_2 is a stable node if $a > bd/f$, P_3 is a stable node if $d > ea/c$, P_4 is a saddle point if both conditions are fulfilled. The condition $fc > be$ must be verified. A phase

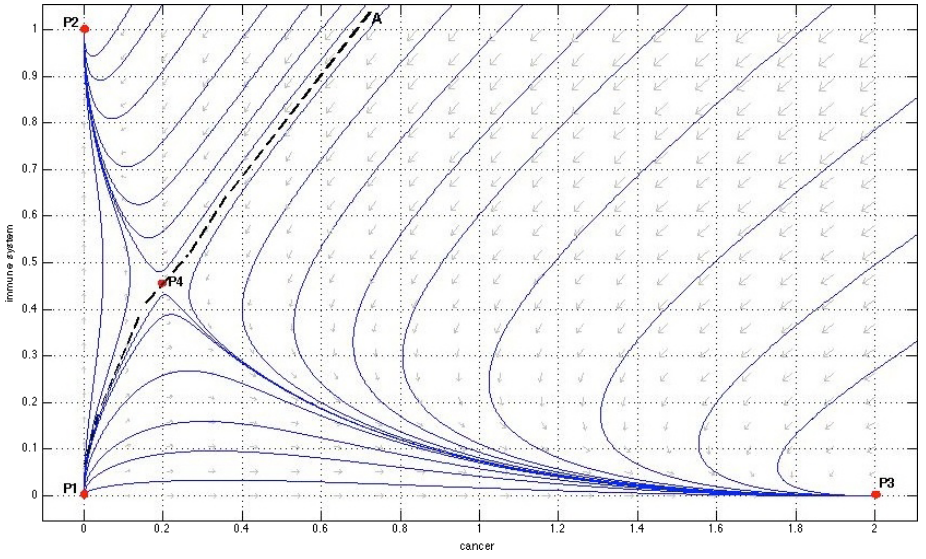

Fig. 1. (Color online). Phase diagram obtained for the values of the parameters $a = 1/16$, $b = 1/8$, $c = 1/32$, $d = 1/32$, $e = 275/3200$ and $f = 1/32$. The fixed points are marked as P_i for $i = 1, 2, 3, 4$ and the curve marked A separates the basins of attraction of P_2 and P_3.

diagram is presented in Fig. 1. The fixed points are marked with red dots and the curve A separates the basins of attraction of the stable fixed points P_2 and P_3.

Curve A can be calculated as an invariant manifold of P_4, it is the solution to the ODE

$$\frac{dz}{dt} = \frac{z(d - fz - et)}{t(a - ct - bz)}, \tag{2.4}$$

with initial conditions near P_4 in the directions of the eigenvalues.

2.2. *Impossibility of sarcoma equilibrium state*

In Ref. 4, an equilibrium state with an area of sarcoma below the value of area of a solution that tends to zero is suggested. For these models this case is not possible because an equilibrium state with a value smaller than a solution that tends to zero is dynamically inconsistent. The main reason for this is the fact that two attractors need to be separated by a saddle point.[12] In a system with three asymptotic states, elimination, escape and equilibrium different from zero, necessarily the value of the equilibrium has to be larger than the maximum value of the solutions that tend to zero, but this is not the case in Ref. 4.

In the experiment they suggest that the equilibrium is smaller than solutions which tend to zero. What happens in this case is that they obtain a solution which tends to zero, but it has not disappeared yet, the treatment translates it towards the region below the curve A and this solution tends to sarcoma outgrowth, and hence to an escape case.

2.3. *Least squares fits*

As there is no information about the values of the immune system variable y and there are three degrees of freedom in the coefficients of the system, some of the coefficients can be fixed, $a = 1/16$, $c = 1/32$, $d = 1/32$ and $f = 1/32$. The maximum value of x in the cases where cancer is eliminated has a mean value 0.2 cm^2, then the first component of P_4 can be assumed to take this value,

$$\frac{bd - fa}{be - fc} = \frac{b/32 - 1/(16 \times 32)}{be - 1/32^2} = 0.2, \tag{2.5}$$

from this expression we deduce $e = (160b - 9)/(32^2 b)$. Then there is only one parameter to fit the model with the experimental data.

We look for the value of b that minimizes the mean quadratic error F in least squares procedure

$$F(b) = \frac{1}{N} \sum_{i=1}^{N} (X(t_i) - x(t_i, b))^2, \tag{2.6}$$

where $X(t_i)$ is the experimental value of the area of the tumor at time t_i, $x(t_i, b)$ is the solution of the system (2.1)–(2.2) at time t_i and N is the number of data, $N = 31$. The function $F(b)$ can be seen in Fig. 2. The minimum of this

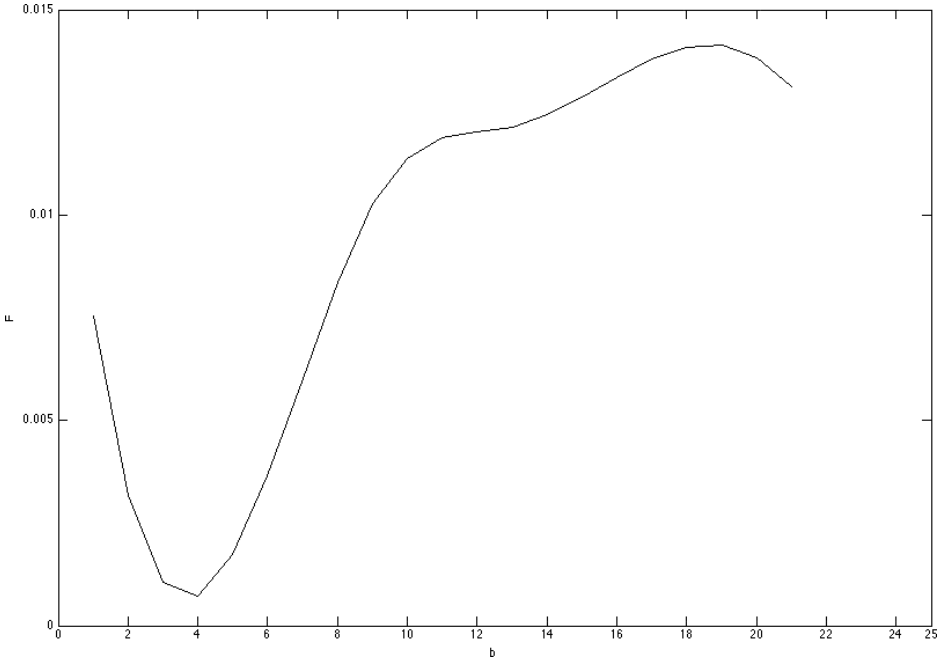

Fig. 2. Mean quadratic error depending on the parameter b. The values of the parameters are $a = 1/16$, $c = 1/32$, $d = 1/32$, $e = 275/3200$ and $f = 1/32$.

Table 1. ANOVA test.

	Sum of squares M	D.F.	Mean squares	$F_{1,29}$
Regression	$\sum(x(t_i, b_o) - \bar{X})^2 = 0.1436$	1	0.1436	65.27
Residual	$\sum(x(t_i, b_o) - X(t_i))^2 = 0.0643$	29	0.0643/29=0.0022	

function corresponds to the optimal value of b to fit the data. The obtained value is $b_o = 4$.

To know the goodness of the fit the determination coefficient can be calculated

$$R^2 = \frac{\sum_{i=1}^{N}(x(t_i, b_o) - \bar{X})^2}{\sum_{i=1}^{N}(X(t_i) - \bar{X})^2} = 0.94, \tag{2.7}$$

this coefficient is high. In order to decide if the fit is acceptable an ANOVA test has been performed and the data can be seen in Table 1.

On applying an ANOVA test to the data we can compare the data parameter $F_{(1,29)} = 65.27$, with the corresponding value of F for the Fisher–Snedecor distribution with (1,29) degrees of freedom at the 0.01 level of confidence, $F_{(0.01,1,29)} = 7.5976$. $F_{(1,29)} > F_{(0.01,1,29)}$, then the relation found is significant and the fit assumption is correct.

The data and the numerical solution obtained for the best coefficient are shown in Fig. 3. The results are quite satisfactory.

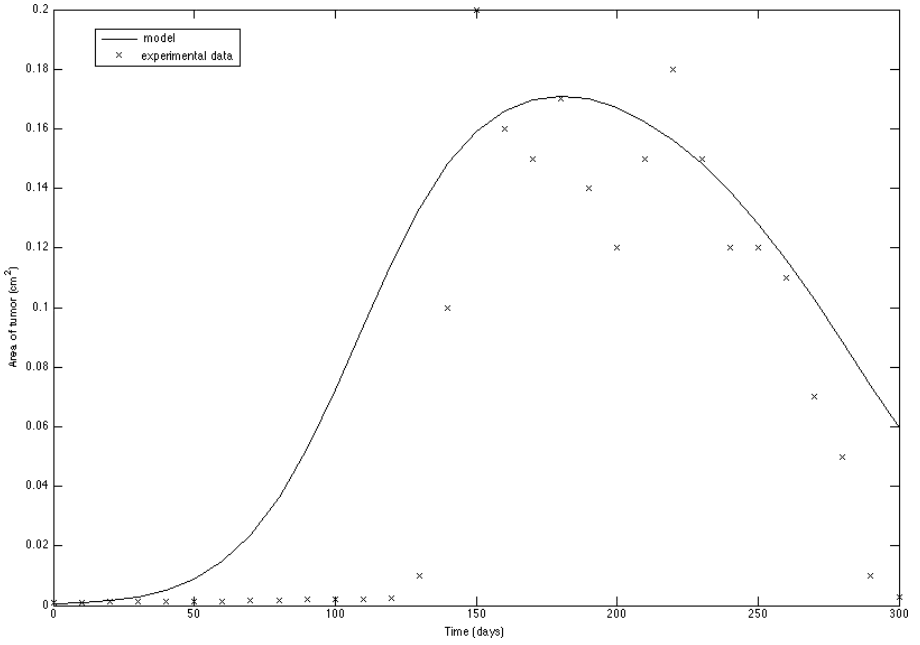

Fig. 3. Data of the area of sarcoma and the fitted model solution. The values of the parameters are $a = 1/16$, $b = 1/8$, $c = 1/32$, $d = 1/32$, $e = 275/3200$ and $f = 1/32$.

3. Discussion and Conclusion

Comparing the results with Ref. 4, as initial conditions the same amount of induced cancer for all mice is taken, but there are differences in adaptive immune system. Some of the mice, which we call the first group M_1, would have adaptive immune system below curve A and some others, that we call the second group M_2 and the third group M_3, respectively, would have immune systems above curve A. This initial situation can be seen in Fig. 4.

Mice M_1 will evolve towards a continual outgrowth of the tumor and they will be removed from the experiment, see Fig. 5. In this case cancer escapes from the control of the immune system and keeps on growing. This escape occurs when cancer cells evade the immune system's defenses and often become more malignant. Also this case can be associated with a negative influence of the immune response, so the situation that it encourages angiogenesis by secreting some substances which facilitate creation of new blood vessels.

Mice M_2 were treated with control immunoglobulin, in this case cancer disappears. These mice have an adaptive immune system above curve A and the adaptive immune system is not changed, then elimination is observed, see Fig. 6. The cancer disappears due to its destruction by adaptive immune system and the adaptive immune system tends to a constant positive value.

The remaining mice M_3 were treated with a mixture of monoclonal antibodies that deplete the adaptive immune system. In this case the starting condition is

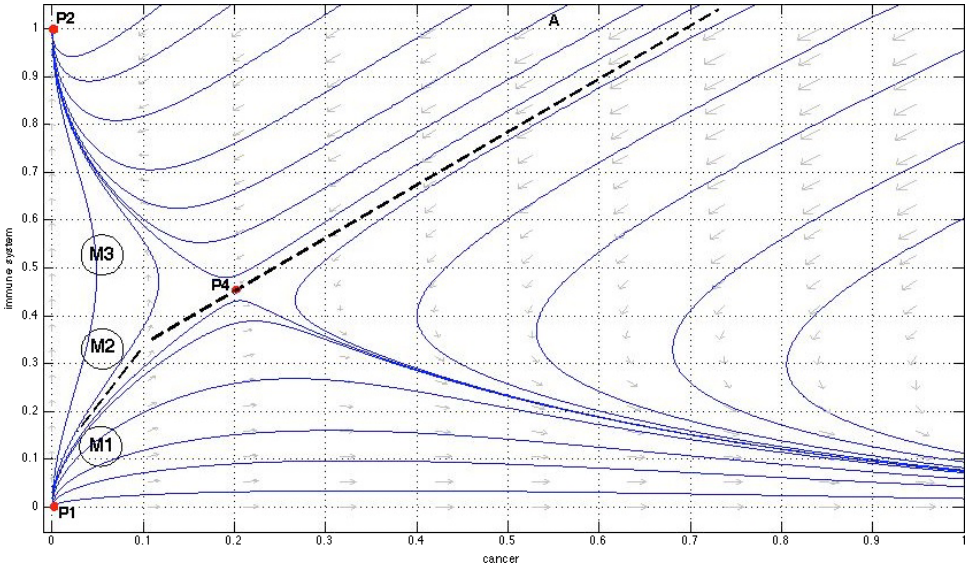

Fig. 4. Phase diagram obtained for the values of the parameters $a = 1/16$, $b = 1/8$, $c = 1/32$, $d = 1/32$, $e = 275/3200$ and $f = 1/32$. The fixed points are marked as P_i for $i = 1, 2, 3, 4$ and the curve marked A separates the basins of attraction of P_2 and P_3.

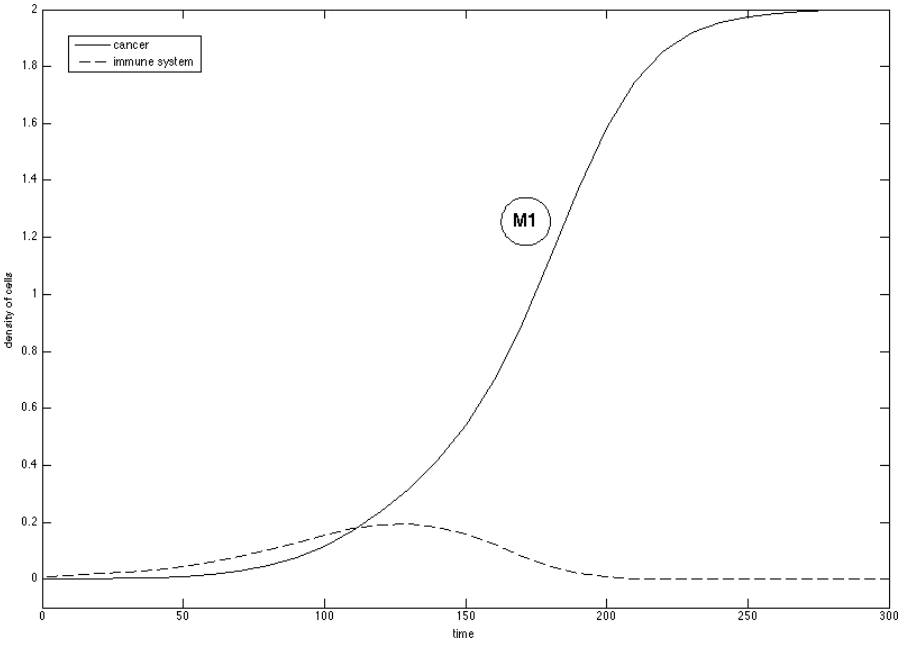

Fig. 5. Escape. Evolution of the area of the sarcoma for mice M_1. Solution for the initial condition $x_0 = 0.0005, y_0 = 0.01$. The values of the parameters are $a = 1/16$, $b = 1/8$, $c = 1/32$, $d = 1/32$, $e = 275/3200$ and $f = 1/32$.

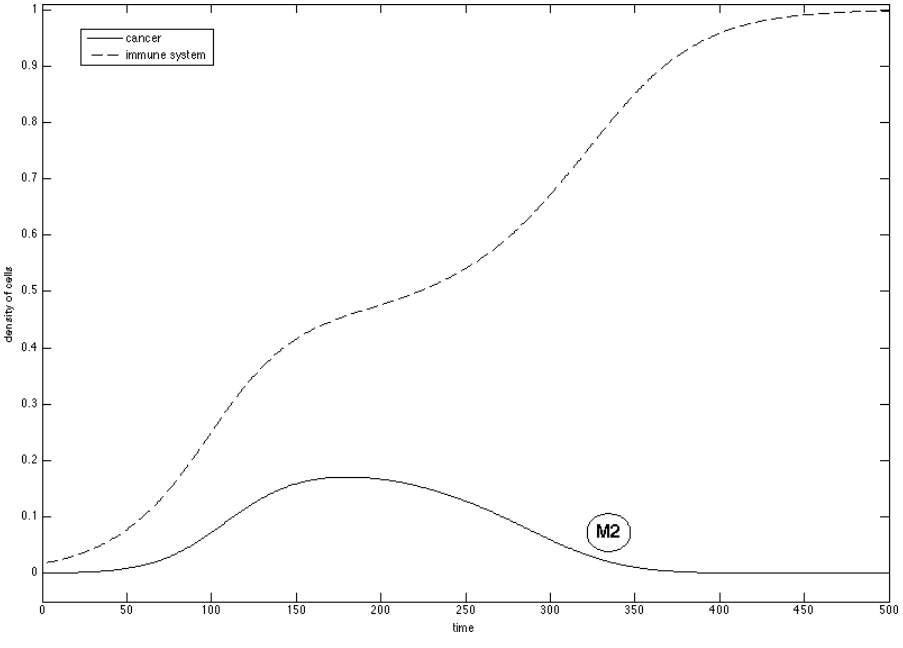

Fig. 6. Elimination. Evolution of the area of the sarcoma for mice M_2. Solution for the initial condition $x_0 = 0.0005, y_0 = 0.0175$. The values of the parameters are $a = 1/16$, $b = 1/8$, $c = 1/32$, $d = 1/32$, $e = 275/3200$ and $f = 1/32$.

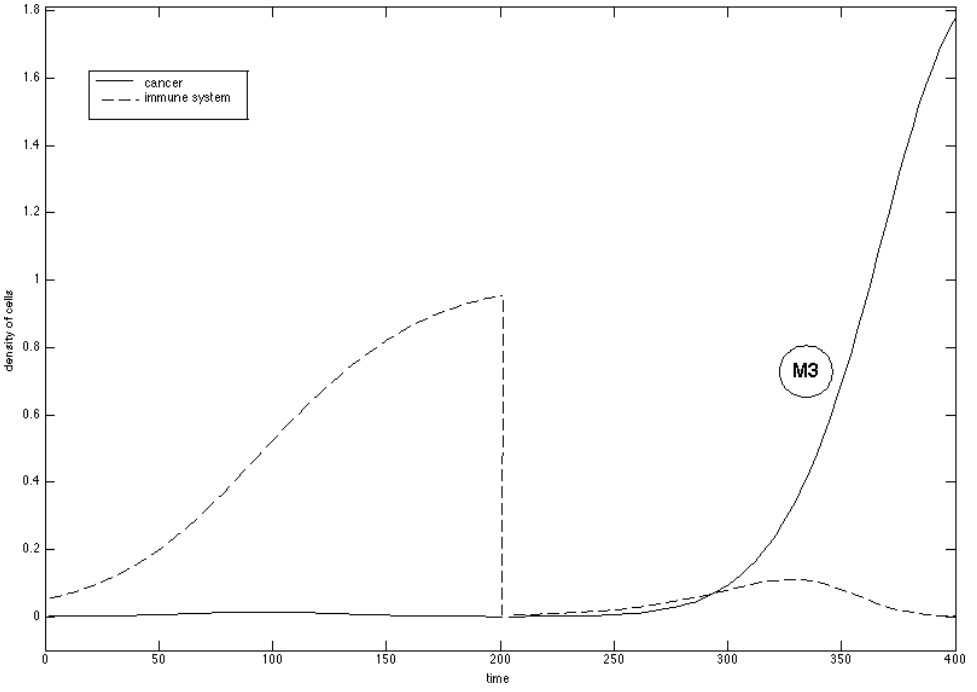

Fig. 7. At the beginning, elimination, after the treatment, escape. Evolution of the area of the sarcoma for mice M_3. Solution for the initial condition $x_0 = 0.0005, y_0 = 0.05$ and after the treatment the initial data becomes $x_0 = 0.00034275, y_0 = 0.005$. The values of the parameters are $a = 1/16$, $b = 1/8$, $c = 1/32$, $d = 1/32$, $e = 275/3200$ and $f = 1/32$.

above curve A, the mice evolve towards elimination, but before the cancer is totally eliminated, the treatment of the mice moves them below curve A and then they evolve towards a continual increase of cancer. The cancer escapes from the control of the immune system and keeps on growing. This situation can be seen in Fig. 7. In Ref. 4, the hypothesis of an equilibrium state before the treatment is suggested, but this case is not possible because an equilibrium state with a value smaller than a solution that tends to zero seems to be dynamically inconsistent.[16] What happens in this case is a small solution that tends to zero, but it has not disappeared yet. The treatment translates it towards the region below curve A and this solution tends to sarcoma outgrowth.

These results are in agreement with the experimental data in Ref. 4. We observed that the final scenario depends on the level of adaptive immune response: if it is high enough it is possible to eliminate the cancer, in the contrary case, the tumor will grow to the maximum possible level. Furthermore, the solutions fit some patterns which happens in oncology, like the stimulating role of the immune system in angiogenesis, see Refs. 2 and 3. As in Bru's model,[17, 18] a sufficiently intense response of the immune system could eliminate a cancer. In our model, two types of solutions exist for one set of parameters, so the behavior of the solution depends

only on the initial condition, meanwhile in the other models,[5–7] in order to change the character of a solution it is necessary to change the value of the parameters.

This model reproduces the macroscopic behavior in induced tumor experiments, where the evolution result depends more on the initial conditions of the adaptive immune cells and cancer cells than on the values of the parameters.

Acknowledgments

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Appendix

Positive Invariance

Using matrix notation we can rewrite (2.1)–(2.2) in the following general form:

$$\vec{x}' = \vec{G}(\vec{x}),\ \vec{G}(\vec{x}) : \Re^2 \longmapsto \Re^2. \tag{A.1}$$

The right-hand side $\overrightarrow{G}(\overrightarrow{x})$ is a polynomial vector field, so a Cauchy problem with an initial condition $(x_0(t_0), y_0(t_0)) \in \Re^2$ has a local solution, based on the Peano existence theorem. Also as $\overrightarrow{G}(\overrightarrow{x})$ has continuous partial derivatives it is a Lipschitz function, so the solution of the system is unique, based on the Picard-Lindelöf theorem.

Theorem. *The system* (2.1–2.2) *is positively invariant, i.e. for any non-negative initial condition* $(x_0(t_0), y_0(t_0))$ *such that* $x_0(t_0) \geq 0, y_0(t_0) \geq 0$ *the unique solution* $(x(t), y(t))$ *is non-negative, so* $x(t) \geq 0, y(t) \geq 0, \forall t > 0$.

Proof. The line $x = 0$ is an invariant manifold, i.e. $(0, y(t))$ is a solution of (2.1)–(2.2) if $y(t)$ is a solution of the equation:

$$\frac{dy}{dt} = dy - fy^2. \tag{A.2}$$

The right-hand side of (A.2) is a polynomial, so for any initial condition there exists a unique solution of (A.2), so $(0, y(t))$ is a solution of (2.1)–(2.2).

Analogically, the line $y = 0$ is an invariant manifold, so $(x(t), 0)$ is a solution of (2.1)–(2.2) if $x(t)$ is a solution of:

$$\frac{dx}{dt} = ax - cx^2. \tag{A.3}$$

The right-hand side of (A.3) is a polynomial, so for any initial condition there exists a unique solution of (A.3), so $(x(t), 0)$ is a solution of (2.1)–(2.2).

As the lines $x = 0$ and $y = 0$ are invariant manifolds, the flow can not cross them, so for any non-negative initial condition $(x_0(t_0), y_0(t_0))$ such that $x_0(t_0) \geq 0$, $y_0(t_0) \geq 0$ the unique solution $(x(t), y(t))$ of (2.1)–(2.2) is non-negative, $x(t) \geq 0$, $y(t) \geq 0, \forall t > 0$. □