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Citation for published version (APA):
Doban, A. I., & Lazar, M. (2015). An evolutionary-type model for tumor immunotherapy. IFAC-PapersOnLine, 48(20), 575-580. DOI: 10.1016/j.ifacol.2015.10.203

DOI:
10.1016/j.ifacol.2015.10.203

Document status and date:
Published: 01/01/2015

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:
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An evolutionary–type model for tumor immunotherapy

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Abstract: In this paper we propose a new dynamical model for describing the interactions between immune and tumor cells. This model captures the effects of the tumor cells on the immune system and vice versa, through predator–prey competition terms. Additionally, it incorporates the immune system’s mechanism to produce hunting immune cells, which makes the model suitable for immunotherapy strategies analysis and design. Consequently, we propose an approach based on Lyapunov functions in order to compute domains of attraction of equilibria of interest.

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Keywords: Mathematical biology, nonlinear systems, stability domains, Lyapunov methods, bilinear systems.

1. INTRODUCTION

Developing dynamical models which can be employed to describe and predict tumor evolution has been the focus of a considerable amount of research work in the past decades. The majority of this work is based on capturing the competition interaction between the immune cells and cancer cells, which turns out to be dynamical and nonlinear. See Adam and Bellomo (1996) for a collection of such models, or the more recent Enderling et al. (2013) for a more specific survey focused on tumor dormancy. This interaction is best understood if seen from an evolutionary perspective, as the competition of two populations for space in the tissue. Such models have been developed and studied in Gatenby (1995) and Gatenby and Vincent (2003). Although the model proposed therein is a two states Lotka–Volterra model, it is able to effectively capture certain phases in tumor development and growth. Some other type of models take into account also the immune system’s mechanism of producing hunting immune cells (killer T–cells) by conversion from resting immune cells (helper T–cells). See for example the model proposed in Sarkar and Banerjee (2005). This type of models is particularly interesting for immunotherapy.

Immunotherapy is a type of treatment which uses certain parts of the immune system to fight tumor growth and can act towards boosting the immune system in a general way or by helping it to attack cancer cells specifically. If the mechanism which produces hunting immune cells acts optimally, this has great influence on helping eradicating cancer or at least on driving it to dormancy. The usefulness of a dynamical model which incorporates this mechanism comes from the fact that such a model allows for assessment of immunotherapy effectiveness and for designing new strategies.

In this work we propose a new model for describing the tumor–immune system predator–prey interaction, which also incorporates the dynamics driving the immune system itself, i.e. the conversion of resting cells to hunting ones. The proposed model is polynomial of order two and has three states, which represent the tumor population, the hunting immune cells population and the resting immune cells population. We consider analyzing the equilibria of this system, which are of interest for treatment by means of their corresponding domains of attraction (DOAs). It is not sufficient to assess whether a certain equilibrium becomes stable or unstable under treatment, for predicting for example, a certain type of treatment outcome. It is also necessary to be able to say from which set of initial conditions the system will converge to that certain equilibrium, i.e. by computing the domain of attraction. Furthermore, as we focus our attention on immunotherapy, the analysis will be carried out with respect to a subset of the model parameters which has the most influence in the immune system response to cancer.

The idea that maintaining a stable dormant tumor might actually increase a patient’s survival chances more than by trying to completely eradicate the tumor was proposed, for example, in Gatenby (2009). In terms of tumor dynamical models, this implies that the optimal treatment tactic would be to try to maintain the stable tumor dormancy equilibrium. Therefore, in our analysis we will focus on determining the effect of immunotherapy driven parameters on the tumor dormancy equilibrium of the proposed model.

The paper is organized as follows. In Section 2, the proposed model is described together with its equilibria and their stability properties and biological interpretations. In Section 3, the model parameter analysis is carried out along with a comparison with previous models and conclusions are drawn in Section 4.
2. TUMOR MODEL

We propose the following model:
\[
\begin{align*}
T &= R_T T - \frac{R_T T^2}{K_T} - \frac{R_T}{K_T} N T N T \\
N &= -\alpha_{NT} N T + \beta N Z \\
Z &= R_Z Z - \frac{R_Z}{K_Z} Z^2 - \frac{R_Z}{K_Z} \beta N Z.
\end{align*}
\]

(1)

The states in this model represent cell densities. The tumor cells also have a mechanism to fight back, which is resisting the treatment. This is due to the fact that the tumor cells on the immune cells is not illustrated in the differential equations. This effect is particularly important, since it can be related to treatment resistance. In many cases, whether the treatment is specifically targeted to destroy the cancer cells or whether it is aimed at stimulating the immune cells to either multiply faster or to strengthen the immune response, the tumor is resisting the treatment. This is due to the fact that the tumor cells also have a mechanism to fight back, which is illustrated in the model (1) by the term \(-\alpha_{NT} N T\). The above mentioned models will be recalled in Section 3.1.

The parameters in (1) have the following interpretations. \(R_T\) and \(R_Z\), represent, respectively, the growth rate of the tumor cells and the resting immune cells, while \(K_T\) and \(K_Z\) are their respective carrying capacities. The parameter \(\alpha_{TN}\) illustrates the effect of the immune cells on the tumor cells, while \(\alpha_{NT}\) represents the effect of the tumor cells on the immune cells. Finally, \(\beta\) represents the conversion rate of the resting immune cells to hunting immune cells. This parameter is of interest, particularly for treatment evaluation and treatment design, since on one hand, it controls the immune system dynamics and on the other hand, along with \(\alpha_{TN}\) it defines the aggressiveness of the immune response against the invader cells, which in this case are the cancer cells.

The system (1) has multiple equilibrium points, including the one in the origin which is irrelevant from a biological perspective. The other equilibria are given by:

1. \(E_1 = (0 \ p \ 0)\), \(p \in \mathbb{R} \setminus \{0\}\)
2. \(E_2 = (E_2^1 \ \ E_2^2 \ \ E_2^3)\)
3. \(E_3 = (0 \ 0 \ K_Z)\)
4. \(E_4 = (K_T \ 0 \ K_Z)\)
5. \(E_5 = (K_T \ 0 \ 0)\).

In all the computations in the remainder of this paper, we will denote \(T\) by \(x_1\), \(N\) by \(x_2\) and \(Z\) by \(x_3\).

The Jacobian matrix for the system (1) is given by
\[
A = \begin{pmatrix}
a_{11} & -\alpha_{TN} R_Z x_1 \beta K & 0 \\
-\alpha_{NT} x_2 & -\alpha_{NT} x_1 + \beta x_3 \beta Z & 0 \\
0 & -\beta R_Z x_2 - \frac{\alpha_{TN} R_T x_2}{K_T} & a_{33}
\end{pmatrix},
\]

where \(a_{11} = R_T - 2 R_Z x_2 - \frac{\alpha_{TN} R_T x_2}{K_T}\), and \(a_{33} = R_Z - \frac{\beta R_Z x_2 - 2 R_Z x_2}{K_Z}\).

2.1 Stability of equilibria

Since in the remainder of this paper we will study stability of equilibria of (1) and other related properties, we refer to Hahn (1967) and Rouche et al. (1977) for the classical stability (in the sense of Lyapunov) definitions. When dealing with nonlinear systems, stability is studied as a local property of the origin of a system. According to Lyapunov’s first method for stability analysis, local asymptotic stability can be verified by looking at the eigenvalues of the (Jacobian) matrix corresponding to the linearization of the dynamics around the equilibrium. Specifically, if all the eigenvalues of the Jacobian are strictly negative, then the equilibrium is locally asymptotically stable. For more details see (Rouche et al., 1977, Chapter I).

\[\text{Stability of the equilibria of (1)}:\]

Based on the Jacobian matrix, we can directly assess the stability properties of some of the equilibria, as follows.

- \(E_1\) corresponds to a healthy equilibrium situation, however it doesn’t make sense from a biological point of view, since it contains nonzero hunting cells populations, whereas the tumor and resting cells populations are zero. For this reason, it will be discarded from the analysis.
- \(E_3\) is always unstable since \(R_T > 0\),
- \(E_4\) is always unstable. If \(\beta > \frac{\alpha_{TN} x_1}{K_Z}\), then \(E_4\) is unstable.
- \(E_5\) is always unstable since \(R_Z > 0\),
- \(E_6\) is always unstable. If \(\beta > \frac{\alpha_{TN} x_1}{K_Z}\)

As for what concerns the stability of the equilibrium \(E_2\), since the corresponding Jacobian expression becomes too complex to analyze symbolically, the analysis will be carried for particular parameter values of interest in Section 3.
2.2 Clinical interpretations

After discarding $E_1$, the other five equilibria of the tumor dynamics model (1) correspond to the following real-life situations.

In the equilibrium $E_2$, all the cell populations are present, thus this equilibrium corresponds to the tumor dormancy situation. The stability of $E_2$ implies a stable, contained tumor volume.

The $E_3$ equilibrium corresponds to another healthy equilibrium situation, but when both tumor and hunting cells are zero. This equilibrium is realistic and it is always unstable.

The $E_4$ equilibrium is one of the undesired equilibria, since no hunting predator cells are present. If we want to look at $E_4$'s stability with respect to the conversion rate $\beta$ of resting predator cells to hunting predator cells, then we observe that a lower limit for $\beta$ for instability is depending on the effect of the tumor on the hunting cells ($\alpha NT$) the carrying capacity of the tumor cells ($K_T$) and the carrying capacity of the resting cells ($K_Z$). So if the conversion rate of resting cells to hunting cells is high enough, then the undesired equilibrium $E_4$ is destabilized. Similarly, $E_4$ becomes unstable if the effect of the tumor cells on the hunting cells is smaller than a bound which depends on the carrying capacity of the normal cells and carrying capacity of the tumor cells.

The $E_5$ equilibrium is the other undesired equilibrium. In this case, none of the predator cells populations are present. This equilibrium is always unstable.

From a strictly biological perspective, it is disputable if the numbers in these equilibria can ever be equal to zero. Most likely, in reality they are very close to zero. In that sense, the most sensible choice is to focus our analysis on the $E_2$ and $E_4$ equilibrium.

2.3 Problem formulation

Immunotherapy acts mainly towards boosting the body’s immune response to fight diseases such as cancer. Specific immunotherapy targets certain proteins in cells which are stimulated so that the immune response against cancer is stronger. If we consider the model (1), the key parameters in boosting the response of the immune cells against cancer are $\alpha_{TN}$, $\alpha_{NT}$ and $\beta$. Therefore, one strategy for immunotherapy is to target the above mentioned parameters. How these parameters influence the immune response, and therefore the dynamical behavior of the tumor–immune cells interaction, can be determined by looking into stability of equilibria of interest. Moreover, for treatment purposes it is not sufficient to have only information on the equilibria of the tumor dynamics and their respective stability. It is of crucial importance to be able to assess whether from a certain initial condition, the trajectory of the tumor dynamics will converge to a specific equilibrium. This can help making the distinction from a patient which is on the path of being cured, or who is converging towards a stable, noninvasive tumor, or one which has a tumor that will malignantly grow. This distinction can be done or estimated, by computing the DOA of an equilibrium of interest.

In this work, we consider the analysis of the tumor dormancy equilibrium ($E_2$) and the invasive tumor equilibrium ($E_4$) of the proposed model (1). More specifically, we focus on how their properties are influenced by the relevant parameters which can be driven through immunotherapy. This will be addressed by means of computing the DOAs of these equilibria.

3. PARAMETER ANALYSIS FOR IMMUNOTHERAPY

In what follows we will make use of the tools in (Doban and Lazar, 2015, Section II) for computing rational Lyapunov functions (RLFs) and corresponding DOA estimates. Due to space limitations we refer the interested reader for a detailed account of the procedure for computing RLFs to Doban and Lazar (2014). Further, we will focus on analyzing the properties of the tumor dormancy and invasive tumor equilibria of the system (1). For this, we look into three possible cases with respect to the effects that the immune cells and the tumor cells have on each other, and analyze the influence of the rate of conversion of hunting immune cells from resting ones on the overall dynamics. More specifically, we consider $\beta$ as the parameter which can be driven by immunotherapy and we look into how $\beta$ influences the two equilibria of interest. As such, in what follows we will consider three situations with respect to the $\alpha_{NT}$ and $\alpha_{TN}$ parameters.

In all three cases, we consider the fixed parameter values $R_T = R_Z = 2.9$, $K_Z = K_T = 10$ and we look into the stability properties of $E_2$ and $E_4$. These specific parameter values have been chosen as indicated in Gatenby and Vincent (2003). Note that by keeping $K_T$ and $K_Z$ fixed, $E_4$ stays the same in all three cases, unless specified otherwise.

1. Influence of tumor cells on immune cells is equal to the influence of immune cells on tumor cells: $\alpha_{NT} = \alpha_{TN} = 0.5$.

For the known parameter values the eigenvalues of $E_4$ become $\lambda_1 = (-0.9, -0.9, -5 + 10i)$, therefore for values of $\beta < 0.5$, $E_2$ will be stable. If we evaluate the eigenvalues of the Jacobian for $\beta < 0.5$ and $E_2$, it results that $E_2$ will be unstable. For $\beta > 0.5$, $E_4$ becomes stable, and the corresponding Jacobian will have complex eigenvalues. Therefore, if the conversion rate from resting predators to hunting predators is high enough, this will lead a stable confined tumor.

Let $\beta$ be equal to 0.9. Then the equilibria will be $E_2 = (6.42857 \ 7.14286 \ 3.57143)$, stable and $E_4 = (10 \ 0 \ 10)$, unstable. For $E_2$ a RLF of order 4 was computed and an approximation of the DOA of $E_2$ defined by the level set value $C^* = 83.102$ of $V_4$ is shown in Figure 1 together with a left-angle view of the set and a vector field plot of (1). The value of $C^*$ was computed via the optimization problem (15) in Doban and Lazar (2014). Let now $\beta = 0.2$. Then the dormancy equilibrium becomes $E_2 = (2.85714 \ 14.2857 \ 7.14286)$, unstable while $E_4 = (10 \ 0 \ 10)$ will be stable. By a similar procedure, an approximation of the DOA of $E_4$ was computed for the level set value $C^* = 36$. This is shown in Figure 2 together with a left-angle view of the set and a vector field plot of (1). Note that for
this case the realistic DOA approximation is a subset of the set displayed in Figure 2 which results from its intersection with the positive axes. This is allowed by Fact II.9 in Doban and Lazar (2015), since the tumor system (1) is positive and the positive axes are an invariant set for this system.

![Fig. 1. Case I: Level set plot $V_4(x) = 83.102$ for $\beta = 0.9$, i.e. stable tumor dormancy–(a) and with vector fields–(b).](image1)

![Fig. 2. Case I: Level set plot $V_4(x) = 36$ for $\beta = 0.2$, i.e. stable invasive tumor–(a) and with vector fields–(b).](image2)

**II. Influence of tumor cells on immune cells is stronger than the influence of immune cells on tumor cells:**

Similarly as in the previous case, we get $\lambda_4 = (-0.9, -0.9, -9 + 10\beta)$, therefore for $\beta < 0.9$, $E_4$ will be stable and $E_2$ unstable.

For $\beta = 0.91$, the Jacobian corresponding to $E_2$ has stable, real eigenvalues and complex for $\beta > 0.91$, thus we pick $\beta = 1.2$ to illustrate the complex eigenvalues case as well. The DOA of the stable equilibrium $E_2 = (9.52381, 2.38095, 7.14286)$ is shown in both plots from Figure 3. In Figure 3(b) a left angle view of the set is shown together with the corresponding vector field plots. For $\beta = 0.2$, the stable equilibrium is $E_4$, while $E_2 = (0, 50, 0)$–unstable can be discarded since it is not realistic. The corresponding DOA is displayed in Figure 4. The same set is plotted from a left angle view together with the system’s vector fields in Figure 4(b).

![Fig. 3. Case II: Level set plot $V_4(x) = 5.2$ for $\beta = 1.2$, i.e. stable tumor dormancy–(a) and with vector fields–(b).](image3)

![Fig. 4. Case II: Level set plot $V_4(x) = 40$ for $\beta = 0.2$, i.e. stable invasive tumor–(a) and with vector fields–(b).](image4)

**III. Influence of tumor cells on immune cells is weaker than the influence of immune cells on tumor cells:**

By the same reasoning as in the previous two cases, it can be concluded that for $\beta < 0.2$, $E_4$ is stable. However, in this case, $E_2$ will remain unstable, irrespective of the value of $\beta$. For $\beta = 0.05$, $E_2 = (2.39437, 8.45075, 9.55746)$. We exclude here the cases which generate stable $E_2$, but with negative equilibrium values, which are not biologically admissible. As such, an estimation of the DOA of $E_4$ was computed for $\beta = 0.05$. The computed set is shown in Figure 5(a) and in Figure 5(b) together with vector field plots.

![Fig. 5. Case III: Level set plot $V_4(x) = 60$ for $\beta = 0.05$, i.e. stable invasive tumor–(a) and with vector fields–(b).](image5)

As for what concerns $E_2$, if we allow for the parameters $K_T$ and $K_Z$ to be different, we can achieve stability. For example for $K_T = 10$ and $K_Z = 5$, then $E_4 = (10, 0, 5)$ will be stable for $\beta < 0.4$ and $E_2$ will be stable for $\beta > 0.4$. If $\beta = 1.2$, then
If we consider the case when $\beta$ is such that $E_2$ is stable, we see that the first case allows for high ranges for all the cell populations. In the second case, when the tumor is stronger than the hunting cells, due to the fact that $\beta$ is large enough a high number of hunting cells is not necessary. In the third case, since the immune system is strong enough ($\alpha_{TN}$ big enough), when $\beta$ is high enough, a smaller amount of resting cells is sufficient to produce enough hunting cells that would maintain a dormant tumor.

3.1 Compare with other models

Let us consider the model proposed in Gatemanby (1995):

$\dot{N}_N = R_N N_N - \frac{R_N}{K_N} N_N^2 - \frac{R_N \alpha_{NT}}{K_N} N_T N_N$

$\dot{N}_T = R_T N_T - \frac{R_T}{K_T} N_T^2 - \frac{R_T \alpha_{TN}}{K_T} N_T N_N,$

where $N_N$ represents the normal cells and $N_T$ the tumor cells, and the model proposed in Sarkar and Banerjee (2005):

$\dot{M} = q + rM (1 - \frac{M}{K_1}) - \alpha MN$

$\dot{N} = \beta NZ - d_1 N$

$\dot{Z} = sZ (1 - \frac{Z}{K_2}) - \beta NZ - d_2 Z,$

where $M$ denotes the tumor cells and $N$ and $Z$ have the same meaning as in (1). Consider in Figure 7(a) the vector fields of the system (2) together with a level set of a RLF corresponding to the tumor dormancy equilibrium of that system which was computed in Doban and Lazar (2015). For a valid comparison to the model proposed in this paper, we projected the vector field and the corresponding level set of $V_0$ computed in Case I for the stable tumor dormancy equilibrium and we have plotted it in the $(x_1, x_3)$ ($\{T, Z\}$) plane in Figure 8. We can observe that although the vector fields of the two models are comparable, the level set of the RLF in the latter case delimits a smaller subset of the DOA of $E_2$. This is due to the fact that the presence of the third state in the model (the resting cells populations) adds additional restrictions in terms of the zero level set of the derivative of the RLF. Now, consider a similar projection of the vector fields of the model proposed in Sarkar and Banerjee (2005) together with the corresponding projection of a level set of a RLF computed in Doban and Lazar (2014), which are shown in Figure 7(b). By comparison with the behavior of (1) shown in Figure 8 we can observe an unsimilar behavior of the vector fields, which is mostly due to the fact that in (3) the influence of the tumor cells $M$ on the immune cells $N$ and $Z$ is neglected. We can conclude that the proposed model (1) is closer to tumor behavior observed in real-life while (2) is too idealistic and (3) is the least realistic.

3.2 Discussion and future work

The computed estimations of DOAs of equilibria of interest admit sets in the cell state space from which the interaction dynamics between the immune system and cancer cells autonomously converges either to immune cells extinction or to a stable co-existence of immune cells and cancer cells, depending on the considered case. Naturally, of main interest is the situation in which convergence to a stable co-existence of populations is possible. This allows...
each patient, the parameters influencing this dynamics are different, while the competing mechanisms between immune and cancer cells is the same. Note that the model discussed in this paper is not specific to a type of cancer, nevertheless the employed analysis tools can be enhanced if specific cancer information is available through the model parameters. An example of such a model, whose parameters are clinical data validated, was derived in Liu et al. (2015) for prostate cancer.

4. CONCLUSIONS

A new model for describing the tumor-immune system predator–prey interaction, which also incorporates the conversion of resting immune cells to hunting ones was proposed. For this model, we considered the analysis of the tumor dormancy equilibrium and the invasive tumor equilibrium. More specifically, we focused on how their properties are influenced by the relevant parameters which can be driven through immunotherapy and have the most influence in the immune system response to cancer. This was addressed by means of computing the DOAs of these equilibria.

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