Tumors under periodic therapy – Role of the immune response time delay

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Abstract

We model the interaction between the immune system and tumor cells including a time delay to simulate the time needed by the latter to develop a chemical and cell mediated response to the presence of the tumor. The results are compared with those of a previous paper, concluding that the delay introduces new instabilities in the system leading to an uncontrolable growth of the tumour. Then a cytokine based periodic immunotherapy treatment is included in the model and the effects of its dosage are studied for the case of a weak immune system and a growing tumour. We find the existence of metastable states (that may last for tens of years) induced by the treatment, and also of potentially adverse effects of the dosage frequency on the stabilization of the tumour. These two effects depend on the delay, the cytokine dose burden and other parameters considered in the model.

Keywords: tumor growth, delay differential equations, immunotherapy, immunodepression

1 Introduction

Immunotherapy is defined as the use of the immune system and its products to prevent, treat and control some illness. Immunotherapy may act stimulating the immune system of a patient with some kind of melanoma, kidney cancer, etc. in order to eliminate or control the population of tumoral cells.

The development of a cancer tumor under the influence of the immune system deploys a very rich dynamics with some aspects that must be highlighted:

1. T-lymphocytes are the cells that perform the tumor elimination, but to do that, another cells, the B-lymphocytes, must activate them with the help of cytokines [1, 2, 3]

2. When the tumor size increases, it induces a deactivation of lymphocytes that enter the tumor region. This phenomenon is known as immunodepression

3. Obviously, in the whole process of interaction between the immune system and the tumor, a delay between the detection of the “strange cells” (antigen) and the attack of the T-lymphocytes is present. This delay will be considered as the control parameter in
the system under study [4, 5]. As we shall see, it is important since it produces changes in the stability of the solutions of the set of equations describing the system.

In this paper, the model proposed in [6] is modified with the inclusion of a “memory effect” in the term describing the interaction between the immune system and the tumor. This leads to formulate the problem in terms of a set of delay differential equations [7, 8, 9]. The influence of this memory effect is studied both with and without therapy. Besides, the range of variation of the biologic parameters is estimated, so that the numeric simulations were performed inside the range.

As far as we know, the existence of a delay between the stimulus (antigen) and the triggering of the defenses of the immune system has not been considered enough in the literature, despite the excellent reports in [10, 11], where the effect of time delay in the dynamics of tumor-immune system is included in the model proposed in [12]. There, it is shown that time delay is a very important factor to take into account in the modelling of the immune system and the reaction of living organisms to diseases. Another delay times have been shown to be of importance. For example, in [13] this characteristic time is introduced in a cycle, leading to a linear delayed term in the equations.

In this way, the study presented in this paper is based on the model introduced by some of the authors in [6] to describe the effects of tumor immunodepression, now including a time characterising the immune system delayed response to the tumor.

2 The model

2.1 Construction of the model

In [5], a Lotka-Volterra model with the inclusion of some additional terms was proposed as:

\[ \frac{dX}{dt} = aX - bXY \]
\[ \frac{dY}{dt} = dXY - fY - kX + u + F \cos^2 \omega t \]  

(1)

where \( X(t) \) and \( Y(t) \) are the populations of tumor cells and T-lymphocytes, respectively. The growing rate of tumor cells is proportional to \( X \) and the mortality rate is proportional to the frequency of interaction with the lymphocytes. The growing rate of lymphocytes is proportional to the interaction with the tumor cells and to the flux rate \( u \) of lymphocytes to the region where the tumor is localized. Their death rate is linked in this model to two terms: natural death \(( -fY )\) and the increase of the tumor mass, which may induce a depression of the immunity system \(( -kX )\). A characteristic of this system is that the immunodepression has been taken into account. Immunodepression may lead to fatal consequences since it may annihilate the whole immune system, mathematically expressed as \( Y(t) = 0 \). (In this model, the population of lymphocytes may even become negative after being null, so that in that case it makes no sense to follow the integration).

To introduce the effects produced by the periodic therapy with cytokines we choose, as in [6], the term \( F \cos^2 \omega t \), as a first model of a periodic positive function, being \( w \) the frequency of the therapy and \( F \) the peak value of the dose.

The term \( dX \) is specially important for this study. It mimics the interaction between the two populations, \( X \) and \( Y \), with a frequency \( d \) of recognition of malignant cells by the immune system. We consider the effect of time delay for this chemical signal mediated interaction which, according to [10], introduces here the values \( X(t - T) \) and \( Y(t - T) \). The evolution equations (1) become now:

\[ \frac{dX}{dt} = aX - bXY \]
\[ \frac{dY}{dt} = dX(t - T)Y(t - T) - fY - kX + u + G(t) \]  

(2)

where \( G(t) = F \cos^2 \omega t \), and \( T \) is the time the immune system takes to react over the malignant cells once recognized. We want to point out that the delay time is absent in the other interaction term \( bXY \), since it represents the direct action of the already present T-lymphocytes and, therefore, it already exist at time \( t \).

If \( F = k = u = 0 \), we recover the classical delayed Lotka-Volterra model [15] with characteristic time \( t_e = 1/\sqrt{\alpha f} \). This time will be used to rescale the system as:

\[ \frac{dx}{dt} = \alpha x - xy \]
\[ \frac{dy}{dt} = x(t - \tau)(t - \tau) - x(t - \tau)t - \frac{1}{\alpha}y - kx + \sigma + H(\tilde{t}) \]  

(3)

being \( H(\tilde{t}) = V \cos^2 \beta \tilde{t} \)
where
\[ \tilde{t} = t/t_c, \quad \tau = T/t_c, \quad x = \frac{d}{\sqrt{a f}} X, \quad y = \frac{b}{\sqrt{a f}} Y \]
and
\[ \kappa = \frac{kb}{d \sqrt{a f}}, \quad \alpha = \sqrt{\frac{\sigma}{\tau}}, \quad \sigma = \frac{ub}{af} \]
\[ V = \frac{Fb}{af}, \quad \beta = \frac{w}{\sqrt{a f}} \]
To simplify notation, from now on we make \( \tilde{t} = t \).

### 2.2 Estimation of some parameters

To get some insight about the numerical range of the parameters to include in the model, let us estimate the values of the parameters \( a, f, T, u, b, d, k \) as well as \( X_0 \), using days as time unit.

It is known that the time a solid tumor takes to reach twice its initial volume is about 70 days [16]. Obviously, this “representative” value is useful only to have an idea of the orders of magnitude; there are tumors that duplicate their volume in 20 days, whereas others can do it in 100 days. Tumors like those of colon or rectal cancer take a few years to duplicate. We admit that in the absence of lymphocytes the growth is exponential so our parameters to include in the model, let us estimate the values of tumor cells that block the flow of lymphocytes to the region occupied by the tumor, it can be assumed the existence of a initial population \( X_0 \) of about \( 10^6 \) cells and, in the absence of lymphocytes, we can make an initial appreciation of \( k \approx 1.2 \times 10^{-2} \) days. All these estimates are in good agreement with particular values collected in the literature (see [17] and references therein).

These estimates of the parameters in (3), are shown in Table 1.

| min   | max   | typical |
|-------|-------|---------|
| \( \alpha \) | \( \sim 10^{-2} \) | \( \sim 1 \) | 1.5 |
| \( \kappa \) | \( \sim 10^{-2} \) | \( \sim 10 \) | 0.95 |
| \( \sigma \) | \( \sim 10^{-2} \) | \( \sim 10^3 \) | 0.5 |
| \( \tau \) | \( \sim 10^{-3} \) | \( \sim 10^2 \) | \( \sim 1 \) |
| \( X_0 \) | \( \sim 10^{-1} \) | \( \sim 10^2 \) | 0.1 |

Table 1: Ranges for the orders of magnitude of the dimensionless parameter values of equation (3) as well as initial condition for tumour cell population. In the last column, typical values used in the simulations reported in this work.

### 3 Results

#### 3.1 System with \( G(t) = 0 \) and without delay (from [6])

Our system (3) without delay and with \( G(t) = 0 \) becomes:
\[ \frac{dx}{dt} = \alpha x - xy \]
\[ \frac{dy}{dt} = xy - \frac{1}{\alpha} y - \kappa x + \sigma \quad (4) \]

The stability of the stationary states of this system can be expressed as:

1. State \( L_0 = (0, \alpha \sigma) \), tumorless state
   - If \( \sigma > 1 \) \( \Rightarrow \) Stable node
   - If \( \sigma < 1 \) \( \Rightarrow \) Saddle point \hspace{1cm} (E1)

2. State \( L_1 = \left( \frac{1-\sigma}{\alpha-\kappa}, \alpha \right) \)
   - If \( \frac{\kappa}{\alpha} > \sigma > 1 \) or \( \frac{\kappa}{\alpha} > 3 \) \( \Rightarrow \) Saddle point \hspace{1cm} (E2)
   - If \( \frac{\kappa}{\alpha} < \sigma < 1 \) \( \Rightarrow \) Stable node or focus \hspace{1cm} (E3)
   - If \( \sigma < \frac{\kappa}{\alpha} < 1 \) \( \Rightarrow \) Unstable node or focus \hspace{1cm} (E4)
3.2 Delayed system without treatment

\((G(t) = 0)\)

In this case our system becomes:

\[
\begin{align*}
\frac{dx}{dt} &= \alpha x - xy \\
\frac{dy}{dt} &= x(t-\tau)y(t-\tau) - \frac{1}{\sigma}y - \kappa x + \sigma
\end{align*}
\]  

\((5)\)

Current techniques of delay differential equations give the following analytic results concerning stability of solutions \([7, 8, 9]\):

1. The stability of the tumorless state \(L_0\) is unaltered. Then (E1) is fulfilled \(\forall \tau \geq 0\).

2. The state \(L_1\) is kept unstable \(\forall \tau \geq 0\) in all cases given by (E2).

3. In the stability range given by (E3), a value of \(\tau\), i.e. \(\tau_c\), exists such that the stationary state \(L_1\) becomes unstable.

4. For the range given by (E4), the unstable state \(L_1\) preserves its instability.

![Figure 1: Function \(\tau_c(\alpha)\), the threshold above which the system becomes unstable. Here the values of \(\kappa = 0.95\), \(\sigma = 0.5\), within the physiological estimated range, were taken such that the system is stable for \(\tau = 0\). No immunological treatment \((V = 0)\) was considered.](image)

The value of \(\tau = \tau_c\) for which \(L_1\) becomes destabilized due to the presence of the delay can be computed analytically (see \([7]\) for details, or the appendix in \([13]\)). Figure 1 shows these values of \(\tau\) for which the system becomes unstable, as a function of the parameter \(\alpha\) (the same can be done applying the criteria in \([7]\) for the other parameters \(\kappa\) and \(\sigma\)). These values of \(\tau_c(\alpha)\) can be computed analytically within the range of parameters for which \(L_1\) has positive abscissa and where \(L_1\) is stable for \(\tau = 0\).

3.3 Results with delay and therapy

To make a useful phase diagram, numerical integration of the system \([3]\) can be performed for different values of the parameters and explore the values of \(\beta\) and \(\tau\) for which, given a set of values of the other parameters, the system becomes stable or unstable.

As the initial condition for the integration of the system of delay differential equations, the steps method can be used for which initial conditions need to be specified, giving the values of \(x(t)\) and \(y(t)\) in the interval \([-\tau, 0]\). We will take as a realistic initial condition, \(x(t) = x_0(0)e^{\alpha(1-\sigma)t}\), \(y(t) = \alpha \sigma\), in \(t \in [-\tau, 0]\), corresponding to an exponentially growing tumour, and an unaware immune system (\(\tau\)-delayed response).

We will perform the numerical integration of the system up to a time \(t_{\text{max}}\) corresponding to \(\sim 25\) years (from typical values estimated in \([2, 2]\) it can be obtained \(t_{\text{max}} \in [30, 10^3]\); we will consider \(t_{\text{max}} \leq 100\) in what follows). However, whenever the condition \(y \leq 0\) is met, that is, when the immune system becomes annihilated due to tumor aggressiveness, integration will stop before \(t = t_{\text{max}}\).

The result of the integration of \([3]\) with these initial conditions and this stop conditions \((y > 0\) and \(t < t_{\text{max}}\)), quite surprisingly, leads to a division of the \((\beta, \tau)\) plane into three regions instead of two as could be expected, with an interesting “transition region” in which, being the system unstable, the instability manifests itself only “asymptotically”, i.e., only when a very long time has elapsed.

The region marked as stable in figure 2 denotes that the system remains stable at any “biologically meaningful” time, that is, tumour growth is controlled by the cytokine treatment. The one marked as unstable denotes, for the chosen values of the parameters, those values of the frequency \(\beta\) and the delay \(\tau\) for which, the system becomes unstable in a finite time (less than \(t_{\text{max}}\)) leading to an unlimited tumor growth and total annihilation of the immune system \([3]\).
Unstable

Asymptotically stable

Figure 2: Representation of stable and unstable regions in the phase plane ($\beta, \tau$). The values of the other parameters in this case are: $\kappa = 0.95$, $\sigma = 0.5$, $\alpha = 1.5$, $V = 0.5$, all of them within the estimated physiological range. The initial conditions were thus taken as $x_0 = 0.1$, $y_0 = \sigma \alpha = 0.75$. Dashed line delimits the asymptotically stable region where tumour size remains controlled after $t = 100$. Solid line limits the “marginally stable” region, where tumor grows in an uncontrollable way after a dimensionless time $t_{\text{max}} = 10$.

The marginally stable region corresponds to unstable states where instabilities manifest themselves after such a long time (for $t > t_{\text{max}}$) that they have not a practical sense. In the above case, inside this region the instabilities manifest only for times in the order of tens of years, an unpractical value in the medical sense. The limit between this marginally stable region and the unstable one in figure 2 depends strongly on the initial conditions ($x_0$, $y_0$ as well as on the hypotheses about their history) used for the numerical calculation.

4 Discussion and Conclusions

We have studied the effect of the chemical signal and B-lymphocytes mediated interaction between (T-)lymphocytes and cancer cells (that is, the time delay) upon the development and growth of a cancer tumor. We have found that an increase in this body reaction time will un-stabilize a system in which the tumor has evolved to a latent state. As far as this delay is a body characteristic time, it will classify cancer situations into stable (that is, limited by the immune system and thus curable) and unstable (those which cannot be controlled by the immune system). These states will be characterized by the particular dynamical system parameter values, which must be estimated as shown in section 2.2 from real available data. Furthermore, the mathematical form of the evolution equations determines parameter combinations (in the form of dimensionless groups) which are more suitable to describe and classify the dynamics.

For a fixed time delay, numerical simulations show that tumors evolve under cytokine treatment as follows. For an initially unstable system, above the $\tau_c$ critical value, immunotherapy treatment helps to stabilize this state. For low dosage frequency $\beta$, tumor evolves so slowly that the system behaves as stable for times larger than a given $t_{\text{max}}$ (taken of the order of decades, see conditions in 3.3). Above a threshold the system becomes also asymptotically stable. Therapy does not lead to the full annihilation of tumor cells, but keeps tumor size in a controlled state, allowing the inclusion of other methods, like surgery, or more directed therapies like radiation, aimed to a localized and controlled tumoral mass.

Finally, when the system is not stable but instability does not lead to uncontrolled tumor growth for, at least, $t_{\text{max}}$ (taken of the order of two decades), $\beta$ dosage values larger than a critical one may lead to system unstabilization as well as to its stabilization if the frequency is further increased, in a way sensitive to the initial state of the tumour and the particular value of $\tau$. In general, we conclude that there exist one critical low dosage frequency that makes the system unstable (for limited times smaller than a $t_{\text{max}}$) and another higher frequency that takes the system back to stability (long time stability, in this case). These particular values will depend on the immune system delay ($\tau$), as well as on the dose burden ($V$) and other parameters of the system.

It is of paramount importance to notice that for some practical range of cytokine dosage frequencies ($\beta \gtrsim 0.75$ in the particular case shown in figure 2), a particular value of the immune system delay may fall above the region of stability (asymptotic as well as transitory), making the use of immunotherapy useless.
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