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# A SIMPLE MODEL FOR CONTROL OF TUMOR CELLS

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The Kirschner-Panetta model describes the poblational competition between effector cells and tumor cells. We analize external changes in the parameters and mechanisms to obtain the decreasing of tumor cells. These variations were performed by three different ways: Oscillations, spikes with the natural frequency of the system, and spikes with Normal Distribution. It was observed that the amount of tumor cells decreases to zero if we change simultaneously the parameters properly.

*Keywords*: Tumor; Immune System; Immunotherapy.

## 1. Introduction

Cancer is the leading cause of death worldwide. In the body, depending on the organ or tissue, the cells duplicate having a expected time of death; this process maintains a balance of the cell number. Cancer occurs when cells lose the ability to die after a given number of duplications resulting in their uncontrolled proliferation. In this case, these cells form accumulations that can affect significantly the normal functioning of the organs, to spreading to other organs and eventually leading to death.[1]

Immunotherapy is the process by which the immune system is stimulated to fight against cancer. Unlike other therapies, it offers smaller and lighter side effects than chemiotherapy, radiotherapy and surgery.[2] One alternative of this therapy is to introduce antigens in the tumor, allowing immune cells,[3] such as lymphocytes (which are involved in cell-mediated immunity), to recognize cancer cells enhancing the immune response.

Currently, the relation between mathematical models and the response of the immune system is making big strides trying to help and give alternative treatments.

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From Kutnesov[4] in 1994, who applied the Lotka-Volterra model for modeling the interaction between tumor cells and effector cells from immune system, Kirschner and Panetta[5] (here after call KP) introducing effector molecules used extensively in intercellular communication by the immune system, up to Arciero[6] (2004) and Tsygvintsev[7] (2013) who based in the KP model have obtained values for the parameters from experimental data. In their work they affirm that some of model parameters have temporal dependence, leaving a new point of view to introduce new experiments and tests to control tumors growth.

In this work, we propose new ways to control the growing of tumor cells based in KP model by using experimental data given by Arciero[6] and following Tsygvintsev's[7] observations, from temporal variation of some parameters which can be modified externally as a therapy.[6] This paper is organized as follows, In Sec. 2 we introduce the model and the parameters which are relevant to the problem. The dynamics of the model is shown in Sec. 3. Secion 4 is devoted to the analysis of simultaneous variations in parameters. Finally, Sec. 5 summarize some conclusions.

## 2. Methodology

The KP model is a competition model between effector cells from immune system and tumor cells ($T$). T-cells are generally homogeneous with logistic growth and ($E$) represent those cells that have been stimulated and are ready to respond to the foreign matter (See Refs. 5, 6 and 7 for more details), the equations that describe the dynamics are given by:

$$\dot{E} = cT - \mu E + p\frac{E}{E+f} + s. \tag{2.1}$$

$$\dot{T} = rT(1 - bT) - a\frac{ET}{T+g}. \tag{2.2}$$

The meaning of the parameters involved in this model, and the values from experimental data,[6] are depicted in Table 1.

Considering that all biological systems have intrinsic noise,[8,9] we introduced it in Eqs. (2.1) and (2.2). Therefore KP model in baseline is modified as:

$$\dot{E} = cT - \mu E + p\frac{E}{E+f} + s + \left\{\zeta_a\sqrt{cT} - \zeta_b\sqrt{\mu E} + \zeta_c\sqrt{p\frac{E}{E+f}} + \zeta_d\sqrt{s}\right\}, \tag{2.3}$$

$$\dot{T} = rT(1 - bT) - a\frac{ET}{T+g} + \left\{\zeta_e\sqrt{rT(1-bT)} - \zeta_f\sqrt{a\frac{ET}{T+g}}\right\}, \tag{2.4}$$

where $\zeta_i$, $i = a, b, c, d, e$ and $f$ are random variables with Normal Distribution $\sigma = 1$, $\mu = 0$ then $N(0, 1)$.

Table 1. Parameter values for the model (Eqs. (2.1) and (2.2)).

| Name | Definition | Baseline (*Units*) | Range |
|---|---|---|---|
| $\mu$ | Mortality rate of effector cells E | 0.03 (1/day) | 0.03 |
| $p$ | Proliferation rate of $E$ | 0.1245 (1/day) | 0.1245 |
| $f$ | Half-sat for $E$ proliferation term | $10^{-3}$ (cells) | $[10^{-5}, 1]$ |
| $s$ | Immunotherapy term | 1 (cells/day) | $[10^{-2}, 10^{2}]$ |
| $c$ | Cancer antigenicity | 0.05 (1/day) | $[10^{-3}, 0.5]$ |
| $r$ | Cancer growth rate | 0.18 (1/day) | [0.1, 2] |
| $b$ | Cancer cell capacity(logistic growth) | $10^{-9}$ (1/cells) | $10^{-9}$ |
| $a$ | Cancer clearence term | 1 (1/day) | $[10^{-2}, 10^{2}]$ |
| $g$ | Half-saturation, for cancer clearance | $10^{5}$ (cells) | $10^{5}$ |

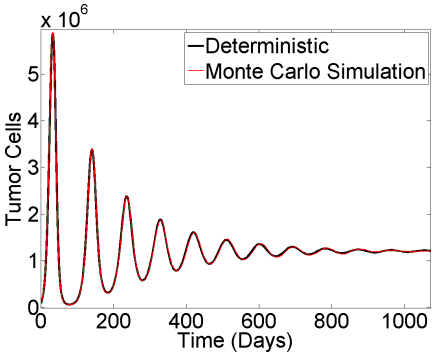



Fig. 1. Time series for tumor cells. When $T(0) = 10^5$ cells, the stochastic model tends to deterministic behavior.

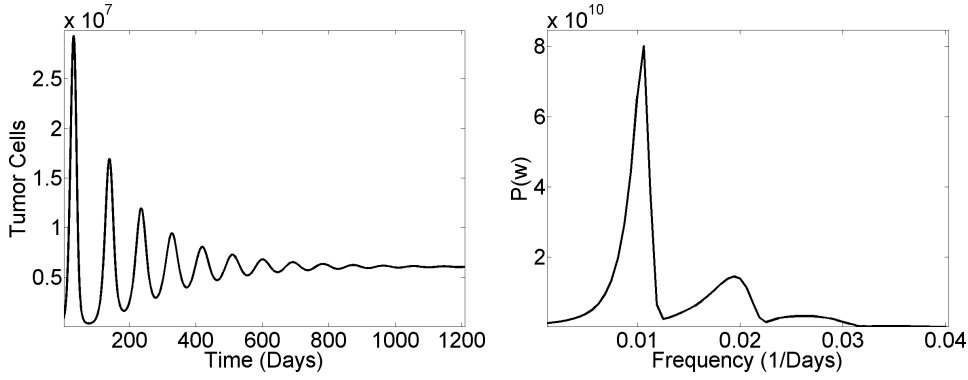
If the number of tumor cells is bigger than $\sim 10^5$, the stochastic simulation (by Monte Carlo's method) tends to deterministic behavior. The system, for these number of tumor cells, is robust under the effect of intrinsic noise. So, for sake of clarity in what follow, we work with the deterministic system with amount of tumor cells bigger than $10^5$.

Besides, by computed tomography, a solid tumor can be detected from about 2 mm of diameter, by using a mean value for individual tumor cell (which is smaller than normal cell), we are in the order of $5 \cdot 10^5$ tumor cells before the begining with our immunotherapeutic model. Then, the simulations were made with the initial conditions $T(0) = 5.10^5$ cells and $E(0) = 10^3$ cells (it is assumed that there is always a number of effector cells that fight the tumor), we found the solutions of the system as shown in Fig. 2.

In order to quantify the relation between initial and final amount of tumor cells, we define

$$J = \frac{Mean\ value\ of\ the\ total\ tumor\ cells}{Initial\ amount\ of\ tumor\ cells} = \frac{\overline{J_{\text{final}}}}{J_0}. \tag{2.5}$$

$J$ is in the steady state (*For baseline parameters*, $J = 12.09$).




(a) (b)

Fig. 2. Time series for tumor cells (Eq. (2.2)) and power spectrum of the same time series, with the natural frequency system is $\omega_{\text{system}} = 0.01016/\text{Days}$, therefore the $T_{\text{system}} = 98.42$ Days.

The results of tumor cells temporal evolution and its power spectrum can be observed in Figs. 2a and 2b. The cells reaches a plateau in the time series and a characteristic frequency in the power spectrum ($\omega_{\text{system}} = 0.01016/\text{Days}$).

We analyze the system behavior by using three different time dependence on the parameters as pointed by Ref. 7 (*Immunotherapy term* ($s$), *Cancer antigenicity* ($c$), *Cancer clearance term* ($a$)). We considered the time dependence as the following functions $F(t)$:

(a) Periodic oscillations of each parameter ($c(t), a(t)$ and $s(t)$) with the system natural frequency

$$F(t) = (F_{\max} - F_{\min}) \cdot \sin(\omega_{\text{system}} t)^2 + F_{\min}. \tag{2.6}$$

(b) Train of spikes of each parameter ($c(t), a(t)$ and $s(t)$) with the system natural frequency

$$F(t) = \begin{cases} F_{\max} & \text{for } t = T_{\text{system}} \cdot K \text{ with } K = 1, 2, 3 \ldots \\ F_{\min} & \text{for } t \neq T_{\text{system}} \cdot K. \end{cases} \tag{2.7}$$

(c) Random train spikes on each parameter ($c(t), a(t)$ and $s(t)$).
If $x$ is a random variable with Normal Distribution $\sigma = 1, \mu = 0$

$$F(t) = \begin{cases} F_{\max} & \text{for } x \leq 0 \\ F_{\min} & \text{for } x > 0. \end{cases} \tag{2.8}$$

$F(t)$ is a positive function always, the Normal Distribution is only in order to give the same probability of occurrence for $F_{\max}$ or $F_{\min}$.

## 3. System Dynamic with Time Dependence Parameters

We analize the evolution of the system by changing one parameter at a time while the others remain constant. We start considering $c(t)$, after $s(t)$, and $a(t)$ successively. To associate the value $J$ with the different time dependence, we define:

$J_O$ for changes given by Eq. (2.6) (Oscillations).
$J_P$ for changes given by Eq. (2.7) (Periodic spikes).
$J_R$ for changes given by Eq. (2.8) (Random spikes).

- Variation of parameter $c$ (Antigenic term).

  This parameter is associated to the recognition of tumor cells and stimulates the duplication the effector cells to defeat the tumor. Its range is between $[10^{-3}, 0.5](1/\text{Days})$.

  As we can see in the Fig. 3, if the temporal variation of $c(t)$ is given by Eq. (2.6), we have $J = 0.9419$, meaning that the amount of the tumor cells decrease. However, if $c(t)$ is given by 2.8 and Eq. (2.7) $J > 1$, meaning that the amount of the tumor cells increase.

  The system where $c(t)$ is those given by Eq. (2.6) is oscillatory, but when $c(t)$ is those given by Eq. (2.7) or Eq. (2.8) the system tend to stabilize in a fixed point. As an observation can be said, that with periodic spikes, the system behavior is very similar to baseline conditions, although the final number of tumor cells is bigger.
- Variation of parameter $s$ (Immunotherapy term).

  It is related with the stimulation of the immune system. For example, by the entry of Cytokine-stimulated cells near to the tumor location. The range is $[10^{-2}, 10^2]$ (cells/Days units).

  Changing this parameters given by Eqs. (2.8), (2.7) and (2.6), we observed that the response of the system is always oscillatory (Fig. 4), there $J_O = J_P =$

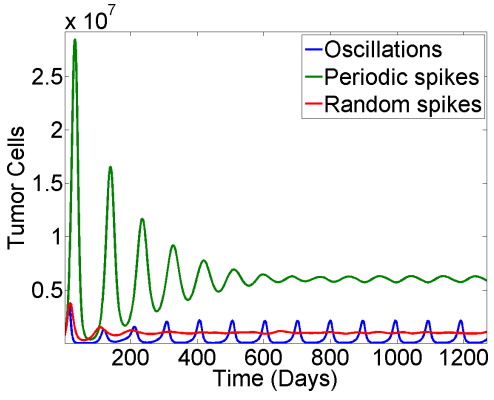



Fig. 3. Time series for tumor cells for different variations of $c$: $J_O = 0.9419$, $J_P = 12.03$, $J_R = 1.9893$.

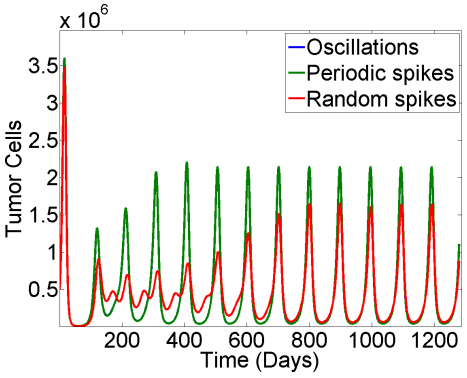



Fig. 4. Time series for tumor cells for different variations of $s$ : $J_O = 0.9403$, $J_P = 0.9403$ where both lines are superposed, $J_R = 0.8610$.

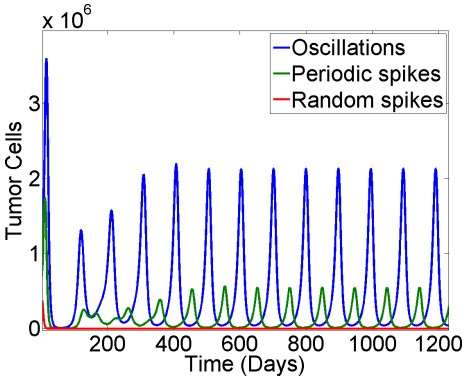



Fig. 5. Time series for tumor cells for different variations of $a$ : $J_O = 0.9409$, $J_P = 0.2705$, $J_R = 0.2705$.

$0.9403, J_R = 0.8610$. That behavior shows a high maximum value of tumor cells and a minimum value near to zero.

- Variation of parameter $a$ (clearance term).

  This is clearance term of cells tumor by interaction with effector cells. $[10^{-2},10^{2}](1/\text{Days units})$.

  In Fig. 5 we observed, that if $a(t)$ is given by Eqs. (2.6) and (2.7), the system has an oscillatory behavior. $J_O = 0.9409$ but with high value of tumor cells, instead, $J_P = 0.2705$ and $J_R = 0$, which is our expected value.

## 4. Simultaneous Variation of the Parameters

This section is devoted to analize the dynamic when three parameters ($a(t), c(t)$ and $s(t)$) have the same time dependence, using the same parameters range as previous

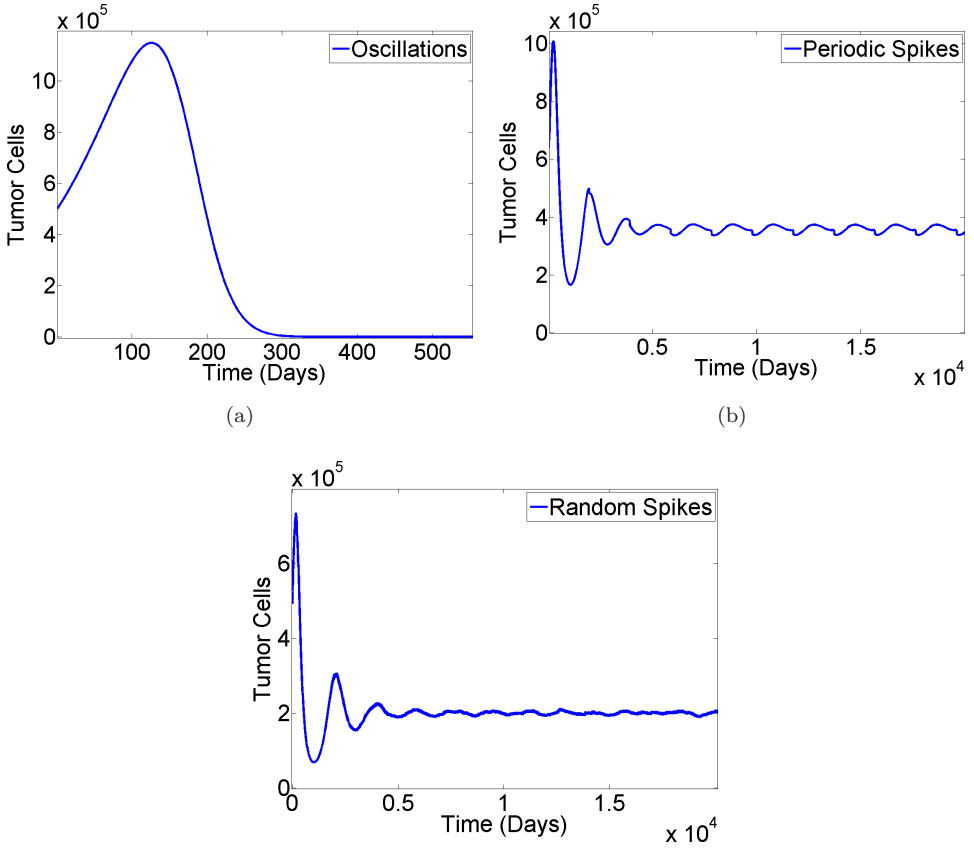


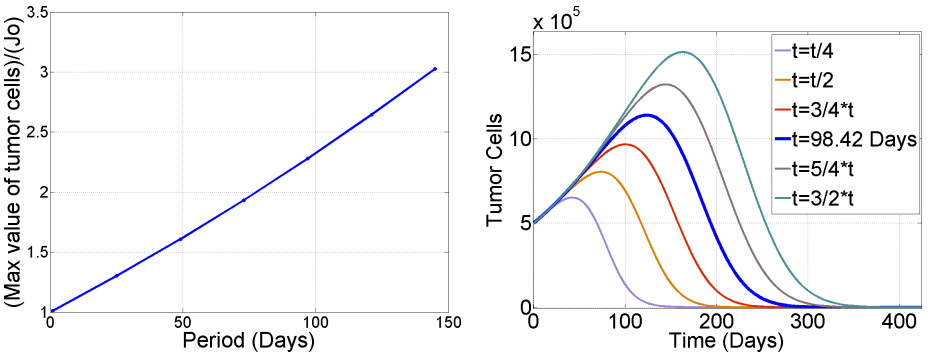

Fig. 6. Simultaneous variation for the parameters $a(t), c(t)$ and $s(t)$: (a) $J_O = 0$, suppression of tumor cells; (b) parameters in spikes modes $J_P = 3.0384$ with a the tumor growth; and (c) parameters in random spikes $J_R = 0.3892$, meaning a decrement of the tumor.

section. This implies that all the parameters will have the same temporal behavior between the minimum and maximum value of range expressed in Table 1.

Firstly, $a(t), c(t)$ and $s(t)$ are given by Eq. (2.6); Secondly, $a(t), c(t)$ and $s(t)$ are given by Eq. (2.7); and finally, $a(t), c(t)$ and $s(t)$ are those given by Eq. (2.8).

As we can see in Fig. 6a, with a simultaneous oscillation of the parameters by Eq. (2.6), the tumor cells decay to zero. If the temporal variation of the parameters are given by Eq. (2.8), we have $J_R < 1$, which is according with our expectations although quite difficult to perform externally (Fig. 6c). If the parameters are given by Eq. (2.7) (Fig. 6b), we have $J_P = 3.0384$, this does not avoid the growth of the tumor. Additionally, in the case the variation is given by Eq. (2.6), we have to remark $J_O = 0$.

Since, the clearance term $(a)$ is quite difficult to be modified externally, we think it is wise to kept it constant (in baseline value).




(a) (b)

Fig. 7. (a) Dependence on the number of tumor cells with time (measure in periods) for the simultaneously variation of the parameters given by Eq. (2.6), where the period $t = 2\pi/\omega_{\text{system}}$ and (b) Time evolution of tumor cell.

Therefore we performed the calculations with this value. No difference was found with the results previously discussed.

Bearing in mind that the best result is when $J = 0$, which is obtained by 2.6 with the two parameters ($c(t)$ and $s(t)$) are involved, we analyse the system behavior when the external entries varies with the frequency.

If we considered the external frequency less or greater than the natural one, we obtain the results shown in Fig. 7a and the system behaves as 7b. Notice that a initial increase of the tumoral cells decreases as the frequency (period) increases (diminish).

## 5. Conclusions

In order to search new ways to control of tumor cells, we can see that the KP model can be used in cases when tumor cells are present in the body, since otherwise the antigens would not recognize the tumor.

We also have shown if the parameters $c(t)$, $s(t)$ and $a(t)$ are given by Eq. (2.6) we have $J < 1$ (meaning the decrease of tumor cells). When $a(t)$ is given by Eqs. (2.7) and (2.8) we have obtained the lowest values de $J$.

If we wish to implement a random input in the parameters, we face with very complex experimental processes.

The best result is obtained when the temporal variation of the parameters is oscillatory (by Eq. (2.6)), where $J = 0$ and the period of external input decreases. Currently, there are therapies where the antigen is introduced through vaccines in the tumor itself and in neighboring zones for stimulate the immune system.[10–13] According with recent biological and medical researches, where explain how with periodic oscillations of antigen and effector cells ($c$ and $s$ in our case) by the use of vaccines, the tumor can decreases until disappear.[14,15]

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