# Model for tumour growth with treatment by continuous and pulsed chemotherapy

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#### Abstract

In this work we investigate a mathematical model describing tumour growth under a treatment by chemotherapy that incorporates time-delay related to the conversion from resting to hunting cells. We study the model using values for the parameters according to experimental results and vary some parameters relevant to the treatment of cancer. We find that our model exhibits a dynamical behaviour associated with the suppression of cancer cells, when either continuous or pulsed chemotherapy is applied according to clinical protocols, for a large range of relevant parameters. When the chemotherapy is successful, the predation coefficient of the chemotherapic agent acting on cancer cells varies with the infusion rate of chemotherapy according to an inverse relation. Finally, our model was able to reproduce the experimental results obtained by Michor and collaborators [Nature, 435, 1267 (2005)] about the exponential decline of cancer cells when patients are treated with the drug glivec.

Keywords: tumour, delay, chemotherapy

#### 1. Introduction

Cancer is the name given to a cluster of more than 100 diseases that presents a common characteristic, the disorderly growth of cells that invade tissues and organs [1, 2]. These cells may spread to other parts of the body rapidly forming tumours [3].

An important mechanism of body defence against a disease caused by a virus, bacteria or tumour is the destruction of infected cells or tumours by actived cytotoxic T-lymphocytes (CTL) cells also known as hunter lymphocytes. CTL are able to kill cells or to induce a programmed cell death (apoptosis). The biological activation process occurs efficiently when the CTL receive impulses generated by T-helper cells  $(T_H)$ . The stimuli occur through the release of cytokines. This phenomenon is not instantaneous; besides the time elapsed to convert resting T-lymphocytes in CTL, there is also a natural delay of the cytological process [4, 5]. Banerjee and Sarkar studied the dynamical behaviour of tumour and immune cells using delay differential equations [6]. They observed the existence of oscillations in tumour cells when a time delay was considered in the growth of T-cells.

A possible way to stop the growing of cancer cells is chemotherapy. That is, the treatment with a drug or combination of drugs through some protocol. There are many experimental and theoretical studies about the

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effects of the chemotherapy on the cells. Moreover, mathematical models have been considered to simulate the growth of cancer cells [7], as well as, tumour-immune interactions with chemotherapy [8].

In this paper we investigate a mathematical model for the growth of tumours that not only take into consideration the time delay character of the lymphocytes dynamics, but also the effect of the chemotherapy. We extend the model of Sarkar and Banerjee [6] by adding the chemotherapy, and by considering some clinically plausible protocols. Firstly, a continuous chemotherapy is analysed. Secondly, the traditional or pulsed chemotherapy protocol is analysed, in which the drug is administered periodically. According to experimental protocols, we have used both a constant amplitude [9] and an oscillatory amplitude [10] for the continuous infusion rate of chemotherapy [11].

One of our main results is to show that there are a large range of relevant parameters that lead to a successful chemotherapy. In a successful chemotherapy is that the predation coefficient of the chemotherapic agent acting on the cancer cells and the infusion rate of the chemotherapy are inversely related. For the continuous chemotherapy, we have ensured the stability of the non-cancer state (i.e., a successful chemotherapy) by calculating the Lyapunov exponents of the non-cancer solution. Finally, our model was able to reproduce the experimental results obtained by Michor and collaborators [12] about the exponential decline of cancer cells when patients are treated with the drug glivec.

#### 2. The model

We extend a mathematical model proposed by Banerjee and Sarkar [13] including the chemotherapic agent. The model is based on the predator-prey system. The T-lymphocyte is the predator, while the tumour cell is the prey that is being attacked. The predators can be in a hunting or a resting state. The resting cells do not kill tumour cells, but they can become hunters. The activation occurs not only due to cytokines released by macrophages that absorb tumour cells, but also by direct contact between resting and tumour cells. As a result, the resting cells suffer a degradation while the hunting cells are actived. The activated cells do not return to the resting state. This way, the predator-prey model is a three dimensional deterministic system, consisting of tumour cells, hunting cells, and resting cells. We added the chemotherapic agent in the equations as a predator on both cancerous and lymphocytes cells. The time delay of about 60 days considered in our model was observed by Balduzzi and collaborators [14, 15], when they were realising experiments about lymphoblastic leukaemia. It incorporates many different phenomena in the system. It is one order of magnitude larger than the one observed in Ref. [16]. In our model, the time delay represents the total time interval for cancer cells to be identified by T-cell receptors and transfer this information to the killer cells, and the time related to the process of cytolytic information in the resting cells [16, 17]. The model is then given by

$$\frac{dC(t)}{dt} = q_1 C(t) \left( 1 - \frac{C(t)}{K_1} \right) - \alpha_1 C(t) H(t) 
- \frac{p_1 C(t)}{a_1 + C(t)} Z(t), 
\frac{dH(t)}{dt} = \beta_1 H(t) R(t - \tau) - d_1 H(t) - \alpha_2 C(t) H(t) 
- \frac{p_2 H(t)}{a_2 + H(t)} Z(t), 
\frac{dR(t)}{dt} = q_2 R(t) \left( 1 - \frac{R(t)}{K_2} \right) - \beta_1 H(t) R(t - \tau) 
- \frac{p_3 R(t)}{a_3 + R(t)} Z(t), 
\frac{dZ(t)}{dt} = \Delta - \left( \xi + \frac{g_1 C(t)}{a_1 + C(t)} + \frac{g_2 H(t)}{a_2 + H(t)} \right) 
+ \frac{g_3 R(t)}{a_3 + R(t)} Z(t),$$
(1)

where C, H and R are the number of cancerous, hunting and resting cells, respectively, t is the time and Z is the concentration of the chemotherapic agent. The cancerous and resting cells have a logistic growth. The term  $-d_1H(t)$  represents the natural death of the hunting cells. The terms  $-\alpha_1C(t)H(t)$  and  $\alpha_2C(t)H(t)$  are the losses due to encounters between the cancerous and hunting cells. The term  $\beta_1H(t)R(t-\tau)$  is associated with the conversion of resting to hunting state, where  $\tau$  is the delay in the conversion. The terms with Z correspond to interaction of the chemotherapic agent with the cells.

Table 1 shows the parameters obtained from the literature, according to experimental evidence, and Table 2 shows the definition of some of the parameters. Table 3 presents the values that we consider in our simulations for the sake of numerical integration.

Table 1: Parameters according to experimental evidence.

Parameter	Definition	Value	Ref.
$q_1$	growth rate of malig-	$0.18 \ day^{-1}$	[18]
	nant tumour cells		
$K_1$	carrying capacity of	$5 \times 10^6 \text{ cells}$	[18]
	tumour cells		
$lpha_1$	decay rate of tumour	$1.101 \times 10^{-7}$	[19]
	cells by hunting cells	$\mathrm{cells^{-1}\ day^{-1}}$	
$lpha_2$	decay rate of hunting	$3.422 \times 10^{-10}$	[19]
	cells by tumour cells	$cells^{-1} day^{-1}$	
$d_1$	death rate of hunting	$0.0412 \ \mathrm{day^{-1}}$	[19]
	cells		
$q_2$	growth rate of resting	$0.0245 \ \mathrm{day^{-1}}$	[6]
	cells		
au	time delay in conver-	$45.6  \mathrm{day}$	[6]
	sion from resting cells		
	to hunting cells		
$K_2$	carrying capacity of	$1 \times 10^7$ cells	[6]
	resting cells		
$eta_1$	conversion rate from	$6.2 \times 10^{-9}$	[19]
	resting to hunting cells	$cells^{-1} day^{-1}$	

Table 2: Parameters according to the literature.

Parameter	Definition	Ref.
$p_i$	predation coefficients of chemotherapic	[11]
	agent on cells (C, H, R)	
$a_i$	determine the rate at which C, H, R,	[11]
	in the absence of competition and	
	predation, reach carrying capacities	
$g_i$	represent the combination rates of the	[11]
	chemotherapic agent with the cells	
$\Delta$	represents the infusion rate	[11]
	of chemotherapy	
ξ	washout rate of chemotherapy	[11]

Introducing the following dimensionless variables

$$\bar{t} = \frac{t}{\text{day}}, \quad \bar{C} = \frac{C}{K_T}, \quad \bar{H} = \frac{H}{K_T},$$

$$\bar{R} = \frac{R}{K_T}, \quad \bar{Z} = \frac{Z}{\Delta_M \, \xi^{-1}},$$
(2)

where  $K_T = K_1 + K_2$  is the total carrying capacity and  $\Delta_M$  is equal 1 mg m<sup>-2</sup>day<sup>-1</sup>. Combining (2) with (1), and relabelling the variables  $\{\bar{t}, \bar{C}, \bar{H}, \bar{R}, \bar{Z}\}$  as t, C, H, R, Z, respectively, and the parameters  $\{\bar{q}_1, \bar{K}_1, \bar{\alpha}_1, \bar{p}_1, \bar{q}_1, \bar{a}_1, \bar{\beta}_1, \bar{d}_1, \bar{\alpha}_2, \bar{p}_2, \bar{q}_2, \bar{k}_2, \bar{p}_3, \bar{q}_3, \bar{a}_3, \bar{\Delta}, \bar{\xi}\}$  as  $\{q_1, K_1, \alpha_1, p_1, q_1, a_1, \beta_1, d_1, \alpha_2, p_2, g_2, a_2, q_2, K_2, p_3, g_3, a_3, \Delta, \xi\}$ , respectively, we obtain the same equations for C, H and R. However, the equation for Z presents a small alteration,

$$\frac{dZ(t)}{dt} = \Delta \xi - \left(\xi + \frac{g_1 C(t)}{a_1 + C(t)} + \frac{g_2 H(t)}{a_2 + H(t)} + \frac{g_3 R(t)}{a_3 + R(t)}\right) Z(t),$$
(3)

where we consider

$$\bar{q}_{1} = q_{1} \operatorname{day}, \quad \bar{\alpha}_{1} = \alpha_{1} K_{T} \operatorname{day}, \quad \bar{K}_{1} = \frac{K_{1}}{K_{T}}, 
\bar{p}_{1} = \frac{p_{1} \Delta_{M} \operatorname{day}}{K_{T} \xi}, \quad \bar{a}_{1} = \frac{a_{1}}{K_{T}}, \quad \bar{\beta}_{1} = \beta_{1} K_{T} \operatorname{day}, 
\bar{d}_{1} = d_{1} \operatorname{day}, \quad \bar{\alpha}_{2} = \alpha_{2} K_{T} \operatorname{day}, \quad \bar{g}_{1} = g_{1} \operatorname{day}, 
\bar{g}_{2} = g_{2} \operatorname{day}, \quad \bar{g}_{3} = g_{3} \operatorname{day}, \quad \bar{p}_{2} = \frac{p_{2} \Delta_{M} \operatorname{day}}{K_{T} \xi}, 
\bar{a}_{2} = \frac{a_{2}}{K_{T}}, \quad \bar{K}_{2} = \frac{K_{2}}{K_{T}}, \quad \bar{p}_{3} = \frac{p_{3} \Delta_{M} \operatorname{day}}{K_{T} \xi}, 
\bar{a}_{3} = \frac{a_{3}}{K_{T}}, \quad \bar{\Delta} = \frac{\Delta}{\Delta_{M}}, \quad \bar{q}_{2} = q_{2} \operatorname{day}, \quad \bar{\xi} = \xi \operatorname{day}.$$
(4)

Table 3: Dimensionless parameters

Table 5. Difficulties parameters.						
Parameter	Value	Parameter	Value			
$q_1$	0.18	$K_1$	1/3			
$lpha_1$	1.6515	$lpha_2$	$5.133 \times 10^{-3}$			
$d_1$	0.0412	$q_2$	0.0245			
au	45.6	$K_2$	2/3			
$eta_1$	$9.3 \times 10^{-2}$	$p_1$	$1 \times 10^{-3}$			
$p_2$	$1 \times 10^{-3}$	$p_3$	$1 \times 10^{-3}$			
$a_1$	$1 \times 10^{-4}$	$a_2$	$1 \times 10^{-4}$			
$a_3$	$1 \times 10^{-4}$	$g_1$	0.1			
$g_2$	0.1	$g_3$	0.1			
$\Delta$	$0 - 10^4$	ξ	0.2			

#### 3. Continuous chemotherapy

In this section we consider the continuous application of chemotherapy, without pause or interruption. That is, the value of the  $\Delta$  is constant in time.

#### 3.1. Cancer suppression

We consider the following initial conditions:  $C_0 = 0.18$ ,  $H_0 = 0.01$ ,  $R_0 = 0.48$  and  $Z_0 = 0$ . These initial conditions are in the limit cycle region of the model solution. The periodic behaviour implies that the tumor levels oscillate around a fixed point, a clinically observed behaviour known as Jeff's phenomenon. One cancer cell in the model (1) is equal to  $66 \times 10^{-9}$  in the dimensionless model. Our main aim is to find

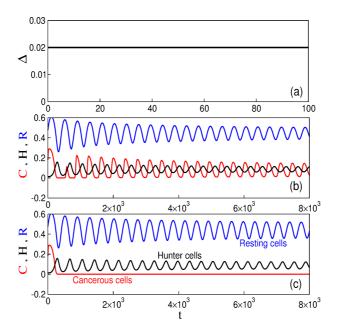


Figure 1: (Color online) Time evolution of the dimensionless quantities according to the model (2) using (3). (a) Continuous infusion rate of chemotherapy, (b)  $\Delta = 0.02$  and (c) cancer suppression considering  $\Delta = 0.025$ . The red line represents the cancerous cells, black line the hunter cells and blue line the resting cells.

parameters that make the chemotherapy successfully suppress cancer, but that preserves the lymphocytes population.

Figure 1 displays the time evolution of the dimensionless quantities and variables. Figure 1(a) shows the behaviour of the infusion rate of chemotherapy. For  $\Delta = 0.02$  [Fig. 1(b)] there is no cancerous suppression and the system presents stable oscillatory behaviour. If we increase the value of  $\Delta$  to 0.025 [Fig. 1(c)], the system may present cancerous suppression without the disappearance of lymphocytes. However, for larger  $\Delta$ , not only the cancer cells, but also lymphocytes disappear. To obtain a global picture of the parameters leading to different behaviour of our model, we construct the parameter space shown in Figure 2, for the parameters  $\Delta$  and the predation coefficient of chemotherapy,  $p_1$ . For  $p_1 = 0$  the rate of cancer cells proliferation is unaffected by the chemotherapic agent. This case may be interpreted as the use of inappropriated drugs or mechanisms related to drug resistance. When  $p_1$  is not null, there is drug-induced killing of cancer cells. These parameters are important due to the fact that they are directly related to the chemotherapy used in the treatment of cancer. We can identify three behaviours in this parameter space. In the white region there are cancer cells. The suppression of cancer occurs for the parameters in the black region. The grey region presents an undesired situation, the suppression of lymphocytes. Therefore, we observe that it is possible to achieve cancerous suppression by increasing infusion rate of the chemotherapy to a high enough value, but the threshold depends on the value of  $p_1$ . For the parameters  $\Delta$  and  $p_1$  in the black region the number of malignant tumour cells goes to zero preserving the immune cells. When the number of cancer cells is zero, the treatment can stop and the tumour will not return.

## 3.2. Lyapunov exponents

To verify whether the suppression of cancer (C=0) is stable, that is, the cancer will not return after its elimination, we calculate the spectra of Lyapunov exponents of our model with time delay. We present only the values of the two largest Lyapunov exponents  $\lambda_i(t)$  (i=1,2) at time t. We are interested in the maximal value of  $\lambda_i(t)$ . Firstly, we use a value of  $\Delta=0.01$ , in that the therapy does not eliminate the cancer. In this case, the system oscillates in a stable limit cycle (Fig. 3a). The largest Lyapunov exponent is about 0 and the second largest negative. To determine that no cancer is an unstable solution of the model, we calculate

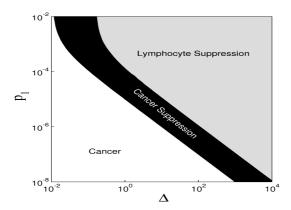


Figure 2: Parameter space  $p_1$  versus  $\Delta$ : the white region represents parameters that lead to the existence of cancer cells, the black region to cancer suppression, and the grey region to the disappearance of the cancer cells and lymphocytes. We consider the continuous application of chemotherapy, without pause or interruption.

the conditional Lyapunov exponents of the whole system but requiring the trajectory to lie in the subspace C=0. We obtain one positive Lyapunov exponent [20], which must be associated with the stability in this subspace since the Lyapunov exponents of the 3D reduced version of our model in (3), without the variable for C, are all negative. In other words, if  $\Delta=0.01$ , cancer will certainly not be eliminated.

For  $\Delta=0.025$ , not only the cancer can be eliminated, but also the dynamics in the subspace C=0 is stable. Figure 3(b) shows that the behaviour of the system is a limit cycle. The result of the two largest Lyapunov exponents for the case  $\Delta=0.025$  is given in Figure 3(c). The maximum values  $\lambda_1(t)$  and  $\lambda_2(t)$ , for t>4400, are 0.0015 and -0.0001. Notice that this is only an upper bound for the real value and it indicates that the real value, whatever it is, needs necessarily to be smaller than 0.0015, a small number that we interpret as being 0, as required for a limit cycle.

## 4. Pulsed chemotherapy

Often chemotherapy treatments are carried out in cycles. The repeated application of drugs for a short time is a typical protocol for chemotherapy, called pulsed chemotherapy [21]. For example, in this protocol, one may use the drug doxorubicin combined with other drugs to treat some types of cancer. The chemotherapy with these drugs is given through cycles of treatment according to the type of cancer [22].

In the following, we will consider two clinical protocols for the chemotherapy with respect to their dependence on the rate  $\Delta$ . One protocol is to administer the drug at a constant  $\Delta$  and the other for two values of this rate ( $\Delta_1$  and  $\Delta_2$ ), both of which have been applied with a determined period P between two chemotherapic sessions. Our aim is to obtain the cancer suppression, while preserving the lymphocytes.

## 4.1. First protocol

Figure 4(a) exhibits the drug injection pattern for the first protocol. When  $\Delta = 0.2$ , P = 10, and parameters in Table 3, the tumour cell population does not vanish, as depicted in Figure 4(b). However, considering the same period P, it is possible to obtain cancer suppression for  $\Delta = 0.3$  (Fig. 4c).

The drugs have specific protocols of application according to the type of tumour. For this reason we study the period of the drug injection. Figure 5 exhibits the time interval P of the pulsed chemotherapy, where the points are used to denote the minimum value of the rate  $\Delta$  in which the cancer suppression occurs. When P increases, it is necessary to increase the intensity of the chemotherapy to obtain cancer suppression. As a matter of fact, the infusion rate versus the period shows a linear increase with the critical value of  $\Delta$  as P grows,  $\Delta_c(P) \sim P$ .

To verify the effect of the period on the behaviour of our model, we show the parameter space in Fig. 6, similar to the one shown in Figure 2, but considering pulsed chemotherapy with a period equal to 10.

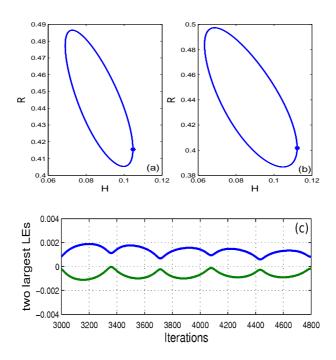


Figure 3: Phase space plot for the variables R and H, where the filled points is a Poincare map of the maximal values for the variable H. We consider the parameters according to Table 3, (a)  $\Delta=0.01$  and (b)  $\Delta=0.025$ . (c) Time evolution for the two largest Lyapunov considering  $\Delta=0.025$ .

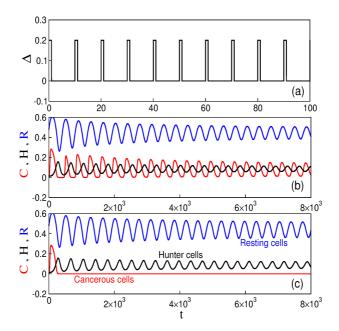


Figure 4: (Color online) (a) $\Delta$  versus t, where  $\Delta$  is not zero when the drug is applied with a period equal to 10 (P=10) with (b)  $\Delta=0.2$  and (c)  $\Delta=0.3$ .

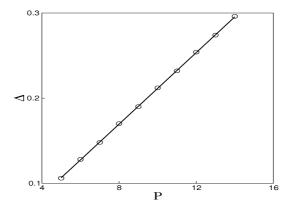


Figure 5:  $\Delta$  versus P, where the points represent the minimum value of  $\Delta$  for a given P to occur the cancer suppression.

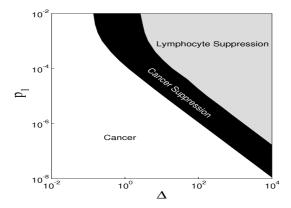


Figure 6: Parameter space  $p_1$  versus  $\Delta$ : the white region represents parameters that lead to the existence of cancer cells, the black region to cancer suppression, and the grey region to the disappearance of the cancer cells and lymphocytes. The drug is applied with a period equal to  $10 \ (P = 10)$ .

We also see the three behaviours: white regions represent parameters that lead to cancer, black regions represent parameters that lead to the suppression of cancer, and the grey region represent parameters that lead to the suppression of lymphocytes. Therefore, it is still possible to obtain a successful chemotherapy. However, the threshold of values of  $p_1$  and  $\Delta$  leading to a successful chemotherapy are larger in the pulsed chemotherapy with P=10, then these threshold values for a continuous chemotherapy. This is a realistic behaviour observed in treatments that prescribe chemotherapic drugs in a continuous or pulsed way.

#### 4.2. Second protocol

Another case for the pulsed chemotherapy consists in infusions of drugs with different concentrations and periods. There is recent research about the successful rate of each type of pulsed chemotherapy [10]. For instance, the treatment for colon cancer adding oxaliplatin to bolus, fluorouracil mixed with leucovorin has been used with different infusion rates [10]. Due to clinical treatment described in the literature, we consider  $\Delta$  to oscillate between two values.

Figure 7(a) shows the drug injection pattern with  $\Delta_1 = 0.3$ ,  $\Delta_2 = 0.1$ , and P = 10. For these values of  $\Delta$  the cancer cells do not disappear but they oscillate at regular intervals (Fig. 7b). On the other hand, fixing  $\Delta_1$  and increasing  $\Delta_2$  the cancer is suppressed, as can be observed in Figure 7(c).

When the infusion rate is constant and chemotherapy sessions are periodically repeated, the cancer suppression depends on the time interval P. For this reason we fix  $\Delta_1$  and vary P and  $\Delta_2$  that results in

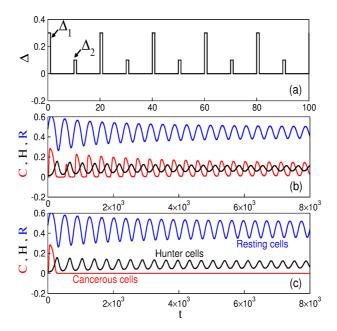


Figure 7: (Color online) (a)  $\Delta$  versus t, where  $\Delta_1=0.3$  and  $\Delta_2=0.1$ . (b) Time evolution according to model (3) with period equal 10,  $\Delta_1=0.3$  and  $\Delta_2=0.1$ . (c) Applications of P=10 with  $\Delta_1=0.3$  and  $\Delta_2=0.15$ .

the successful treatment of cancer. As a result, we see in Figure 8, the lines represent the minimal values of  $\Delta_2$  for a given P that lead to cancer suppression. The circles are for  $\Delta_1 = 0.212$  and the squares are for  $\Delta_1 = 0.3$ . Fixing  $\Delta_2$  and varying  $\Delta_1$ , we obtain the same result.

Through the Figure 5 and Figure 8, we can see a linear relation between  $\Delta$  and P. Defining the frequency as f = 1/P, the infusion rate versus the frequency will show a linear decreases with the critical value of  $\Delta$  as f decreases,  $\Delta_c(f) \sim f^{-1}$ . This way, when tuning the frequency, the value of the rate  $\Delta$  in that the cancer suppression occurs is altered.

The drug Diethylstilbestrol to prostate cancer can be used in treatment by continuous or pulsed chemotherapy. In a continuous treatment may be administered 50 mg (oral) per day, every day, while in a pulsed treatment this drug may be administered 500 mg (infusion) once per week, many weeks. Comparing, we can see that the value of the pulsed is ten times the value of the continuous. Then, the values that we used are in accordance with realistic values.

## 4.3. Exponential decline of cancer cells

Michor and collaborators [12] analysed 169 chronic myeloid leukaemia patients, a cancer of the white blood cell, or leukocytes. They studied the dynamics of different treatment responses to tyrosine kinase inhibitor imatinib, which is also known as glivec. The imatinib is used to treat some types of leukaemia and soft tissue sarcoma. The treatment with this drug causes the death of cancer cells by inhibiting the signals exchanged by the cancer cells responsible to produce the growth and the division of the cancer cells.

In Ref. [12] was showed that a successful therapy using imatinib leads to a biphasis exponential decline of leukaemic cells in time. The value of the first slope (quantifying the exponential time decay rate of cancer cells) is approximately -0.05, and represents the death of leukaemic differentiated cells. The second slope is around -0.008, and is due to the death of leukaemic progenitors. If the imatinib therapy is interruped the slope is approximately 0.09. Without imatinib the differentiated leukaemic cells arise from leukaemic stem cells. Figure 9 shows the slopes obtained through the model (2). We consider P = 10,  $\Delta = 0.3$ , and two values for  $p_1$ . We use for the time interval  $0 < t \le 175$  that produces the first slope (black line)  $p_1 = 0.0001$ , and for the time interval  $175 < t \le 300$  that produces the second slope (blue line)  $p_1 = 0.0009$ . For t > 300,

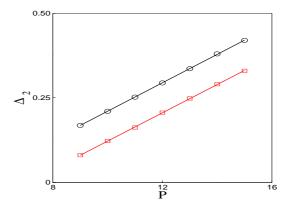


Figure 8:  $\Delta_2$  versus P, where the lines correspond to cancer suppression.  $\Delta_1 = 0.212$  is for circles and  $\Delta_1 = 0.3$  for squares.

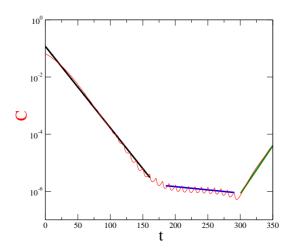


Figure 9: (Color online) Time evolution of the dimensionless quantity C according to the model (2) using (3), where we consider P = 10 and  $\Delta = 0.3$ . The value of the first slope is -0.06 (black line), the second is -0.005 (blue line), and the third is 0.08 (green line).

time interval that produces the third slope (green line) there is not chemotherapy. As a result, we obtain the slopes -0.06, -0.005, and 0.08, which are remarkably similar with the slopes obtained in Ref. [12].

In our model, the case without therapy can be simulated by setting the parameter  $p_i$  equal to zero. This parameter can be also used to simulate a case where the cancer cells become resistante to the drug. The leukaemic cells may present resistance to imatinib therapy. Resistance can be modelled decreasing the effect of chemotherapy to cancer cells (i.e., decreasing  $p_1$ ), while leaving the effect on immune cells constant (maintaining  $p_2$  and  $p_3$ ).

## 5. Conclusions

We propose a delay differential equations model for the evolution of cancer under the attack of both the immune system and chemotherapy. The novelty in this model is the introduction of the chemotherapy and the adjustment of parameters according to recent experimental evidence. We considered some types of protocols aiming at the cancer suppression.

We studied a continuous administration of drugs. The solutions of the system are stable, presenting a limit cycle behaviour. We identified domains of cancer suppression for a wide parameter range of the

predation coefficient  $p_1$  of the chemotherapic agent and of the continuous infusion rate of chemotherapy,  $\Delta$ . Our main results in this session was to show that (i)  $p_1$  and  $\Delta$  that lead to a successful cancer treatment (elimination of cancer cells) are inversely related; (ii) too large values of  $p_1$  and  $\Delta$  eliminate cancer but also eliminate the lymphocytes.

The success of the chemotherapic treatment is highly dependent on the values of the parameters  $p_1$  and  $\Delta$ , responsible for the interactions between the tumour and the drug. By varying  $p_1$  we were able to obtain the biphasic exponential decline observed in chronic myeloid leukaemia [12]. Moreover, the variation of  $p_1$  permits to simulate cases in which the tumour develops drug resistance.

We examined the behaviour of the cancer cells with pulsed chemotherapy and its dependence on the chemotherapic dosing regime. We verified the possibility of cancer suppression through two clinical protocols. In fact, we investigated infusions of drugs with equal and different concentrations. The protocol with different concentrations is more used in the case of drug combination. Our results enabled us to predict the values of the relevant parameters for cancer suppression through protocols related to the treatment of ill people.

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