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Effects of drug resistance in the tumour-immune system with chemotherapy treatment

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Abstract. Cancer is a term used to refer to a large set of diseases. The cancerous cells grow and divide and, as a result, they form tumours that grow in size. The immune system recognises the cancerous cells and attacks them, though it can be weakened by the cancer. One type of cancer treatment is chemotherapy, which uses drugs to kill cancer cells. Clinical, experimental, and theoretical research has been developed to understand the dynamics of cancerous cells with chemotherapy treatment, as well as the interaction between tumour growth and immune system. We study a mathematical model that describes the cancer growth, immune system response, and chemotherapeutic agents. The immune system is composed of resting cells that are converted to hunting cells to combat the cancer. In this work, we consider drug sensitive and resistant cancer cells. We show that the tumour growth can be controlled not only by means of different chemotherapy protocols, but also by the immune system that attacks both sensitive and resistant cancer cells. Furthermore, for all considered protocols, we demonstrate that the time delay from resting to hunting cells plays a crucial role in the combat against cancer cells.

Keywords. Tumour-immune; chemotherapy; drug resistance.

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1. Introduction

An abnormal growth of cells can cause a malignant or cancerous tumour to invade nearby tissues and possibly to spread to other organs [1]. Cancer is a group of diseases, being a public health problem in all countries of the world [2]. Many types of treatment have been developed to eliminate cancer cells, such as surgery [3], chemotherapy [4], and radiation [5]. One of the chemotherapeutic treatments is the immunotherapy [6].

Mathematical models have been used to study different types of cancer and stages of tumour progression [7, 8]. In 1972, Greenspan [9] constructed a mathematical model of tumour growth to analyse the evolution of carcinoma. A model of tumour induced capillary growth was proposed by Balding and McElwain [10] in 1985. In the 1990s, Tracqui *et al.* [11] and Panetta [12] added chemotherapy to study the effects of chemotherapeutic agents on spatio-temporal growth and tumour recurrence, respectively. Recently, López

et al. [13, 14] formulated a model of tumour growth with cytotoxic chemotherapeutic agents to analyse the role of dose-dense protocols.

The main function of the immune system is to protect the body against infection and illness. It can recognise the cancerous cells and eliminate them, though the cancer can weaken the immunity [15]. The cancer treatment that takes advantage of the immune system is known as immunotherapy [16]. Some therapies based on the immune system consist of monoclonal antibodies, vaccines, and T-cell transfer [17]. Mathematical and computational studies of cancer immunotherapy have been performed to understand the interactions between immunity and tumour growth [18, 19]. Borges *et al.* [20] presented a tumour-immune model with chemotherapy treatment. They considered a time-delay between the conversion from resting to hunting cells, the main immune system reaction. Ren *et al.* [21] demonstrated analytical result for impulse chemotherapy parameter to eliminate the cancer cells.

Cancers can develop resistance to chemotherapeutic agents [22]. Drug resistance is a phenomenon that occurs when cancer cells are unaffected by chemotherapy. Experiments have yielded information about the mechanisms of cancer drug resistance [23]. Sun *et al.* [24] modelled drug sensitive and resistant cancer cells in response to chemotherapeutic treatment. Trobia *et al.* [25] created a model of brain tumour growth with drug resistance. They demonstrated that the time interval of the drug application plays an important role in the treatment to eliminate the cancerous cells.

In this work, we include drug resistance in the tumour-immune model proposed by Borges *et al.* [20] and analyse its effect on the system. In our mathematical model, the immune system is composed of resting and hunting cells, while the cancer is separated into drug sensitive and drug resistant cells. We consider chemotherapy to combat the tumour growth. However, the chemotherapeutic agents also attack the immune system. We show that the tumour growth can be controlled by means of different chemotherapy protocols.

The paper is organised as follows. In section 2, we introduce the tumour-immune system with drug resistance. Section 3 presents our results about the effects of the drug resistance. In the last section, we draw our conclusions.

2. Mathematical model

Cancer drug resistance has been a difficulty in chemotherapy cancer treatment [26], and the challenge is how to identify and avoid the resistance [27]. Many researchers have carried out tests to find new strategies in the treatment of tumours associated with drug resistance [28].

In this work, we proposed a mathematical model that describes cancerous cell growth, where we include cancer drug resistance. The cancer cells are separated into sensitive and resistant cells, as they are attacked by the immune system. In the immune system, the resting cells are converted to hunting cells. We consider that the cancerous and resting cells have a logistic growth, while the hunting cells have a form of programmed cell death, known as apoptosis. The chemotherapeutic agent is applied to kill the cancer; it affects all cells, except the drug resistant cancer cells, as shown in figure 1. The model is given by

$$\frac{dC_S}{dt} = q_1 C_S \left(1 - \frac{C_S + C_R}{K_1}\right) - \alpha_1 C_S H - uF[Z]C_S$$
$$- \frac{p_1 C_S Z}{a_1 + C_S}, \tag{1}$$

$$\frac{dC_R}{dt} = q_2 C_R \left[1 - \frac{C_S + C_R}{K_1}\right] - \alpha_2 C_R H + uF[Z]C_S, \tag{2}$$

$$\frac{dH}{dt} = \beta_1 HR(t - \tau) - d_1 H - \alpha_3 H[C_S + C_R]$$
$$- \frac{p_2 HZ}{a_2 + H}, \tag{3}$$

$$\frac{dR}{dt} = q_3 R \left(1 - \frac{R}{K_2}\right) - \beta_1 HR(t - \tau) - \frac{p_3 RZ}{a_3 + R}, \tag{4}$$

$$\frac{dZ}{dt} = \Phi - \left(\zeta + \frac{g_1 C_S}{a_1 + C_S} + \frac{g_2 H}{a_2 + H} + \frac{g_3 R}{a_3 + R}\right)Z, \tag{5}$$

where C_S and C_R are the concentration of drug sensitive and resistant cells (kg/m^3), respectively, H is the concentration of hunting cells (kg/m^3), R is the concentration of resting cells (kg/m^3), Z is the concentration
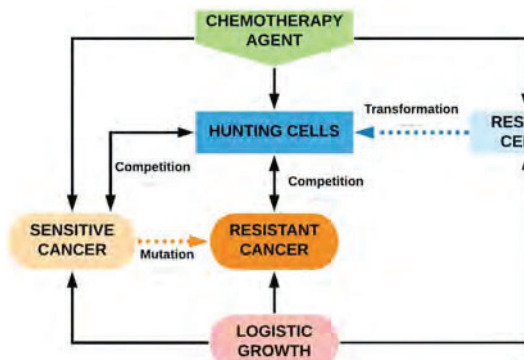

Figure 1. Schematic representation of the model.

of the chemotherapeutic agent (mg/m²), t is the time (day), τ is the delay time from resting to hunting cells, and $F(Z)$ is a function defined as

$$F(Z) = \begin{cases} 0, & Z = 0 \\ 1, & Z > 0 \end{cases}. \tag{6}$$

Besides that, p_i represents the predation coefficient of the chemotherapeutic agent, a_i corresponds to the rate at which the cells achieve the carrying capacity when there is no competition and predation, and g_i represents the combination rates of the chemotherapeutic agent with the cells [29]. The parameters p_i and g_i are related with the strength of the Holling type 2 interaction functions. Holling [30] proposed types of functional responses to different types of interactions. The type 2 function describes the response of many interacting predators and has the characteristics of decelerating the intake rate. The parameter values that we use in our simulations are given in table 1.

We introduce the following dimensionless variables: $c_s = C_S/K_T$, $c_r = C_R/K_T$, $h = H/K_T$, $r = R/K_T$, and $z = \zeta Z$, where $K_T = K_1 + K_2$ and $t^* = t/$day. We consider $K_1^* = K_1/K_T$, $K_2^* = K_2/K_T$, $u^* = u$ day, $d_1^* = d_1$ day, $\beta_1^* = \beta_1 K_T$ day, $\Phi^* = \Phi$ day, $\zeta^* = \zeta$ day, $q_i^* = q_i$ day, $\alpha_i^* = \alpha_i K_T$ day, $p_i^* = p_i/(\zeta K_T)$ day, $g_i^* = g_i$ day, and $a_i^* = a_i/K_T$ ($i = 1, 2, 3$). Redefining the variables and removing the stars, we obtain

$$\frac{dc_s}{dt} = q_1 c_s \left(1 - \frac{c_s + c_r}{K_1}\right) - \alpha_1 c_s h - uF[z]c_s$$
$$- \frac{p_1 c_s z}{a_1 + c_s}, \tag{7}$$

$$\frac{dc_r}{dt} = q_2 c_r \left[1 - \frac{c_s + c_r}{K_1}\right] - \alpha_2 c_r h + uF[z]c_s, \tag{8}$$

Table 1. Parameters values according to the literature.

Parameter	Values	Description
q_1	0.18 day⁻¹	Proliferation
q_2	0.18 day⁻¹	Rate [31, 32]
q_3	0.0245 day⁻¹	
d_1	0.0412 day⁻¹	Death rate [33]
β_1	6.2×10^{-9} (cells/day)	Conversion rate [33]
Φ	0–200 mg/m²/day	Chemotherapy [34, 35]
ζ	0.2 day⁻¹	Absorption rate [20]
u	10^{-3} day⁻¹	Mutation rate [25]
α_1, α_2	1.101×10^{-7} (cells/day)	Competition
α_3	3.422×10^{-10} (cells/day)	Coefficients [33]
K_1	5×10^6 cells	Carrying
K_2	1×10^7 cells	Capacity [31, 32]
τ	45.6 days	Time delay [32]

Table 2. Dimensionless parameters.

Parameter	Values
q_1	0.18
q_2	0.18
q_3	0.0245
d_1	0.0412
β_1	9.3×10^{-2}
p_1	1×10^{-3}
p_2	1×10^{-3}
p_3	1×10^{-3}
a_1	1×10^{-4}
a_2	1×10^{-4}
a_3	1×10^{-4}
g_1, g_2, g_3	0.1
α_1, α_2	1.6515
α_3	5.133×10^{-3}
K_1	1/3
K_2	2/3

$$\frac{dh}{dt} = \beta_1 hr(t - \tau) - d_1 h - \alpha_3 h[c_s + c_r] - \frac{p_2 hz}{a_2 + h}, \tag{9}$$

$$\frac{dr}{dt} = q_3 r \left(1 - \frac{r}{K_2}\right) - \beta_1 hr(t - \tau) - \frac{p_3 rz}{a_3 + r}, \tag{10}$$

$$\frac{dz}{dt} = \Phi\zeta - \left(\zeta + \frac{g_1 c_s}{a_1 + c_s} + \frac{g_2 h}{a_2 + h} + \frac{g_3 r}{a_3 + r}\right)z, \tag{11}$$

The dimensionless parameter values are given in table 2.

3. Tumour drug resistance

Many different powerful chemicals and clinical protocols have been used to eliminate a wide variety of cancers. In this work, we consider both continuous and pulsed chemotherapy treatments. In our simulations, the initial conditions are given by $c_s(0) = 0.18$, $c_r(0) = 0.0$, $h(0) = 0.01$, $r(0) = 0.48$, and $z(0) = 0.0$.

3.1 *Continuous chemotherapy treatment*

Figure 2 displays the behaviour of the time evolution of c_s (red line), c_r (blue line), h (black line), and r (green line) when there is no cancer drug resistance ($u = 0$) for a continuous chemotherapy treatment. Increasing the value of chemotherapy dose Φ from 0.02 (figure 2a) to 0.025 (figure 2b), we observe that the cancer (red line) is killed while the cells of the immune system (black and green lines) remain alive.

Drug resistance is one of the many problems in the cancer therapy. This phenomenon is considered in our model when the mutation rate $u > 0$. In figure 3, we see the appearance of drug resistant cancer cells (blue line) due to $u = 0.001$. Increasing Φ from 0.02
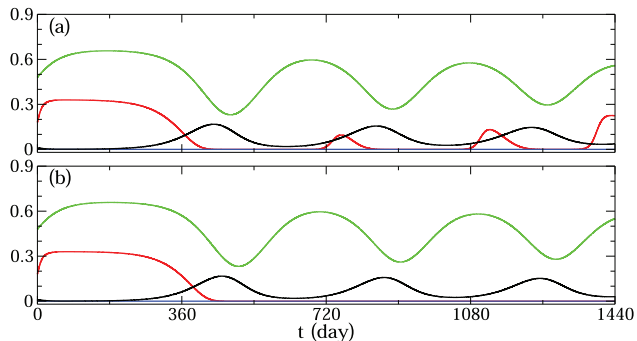
Figure 2. Time evolution of c_s (red line), c_r (blue line), h (black line), and r (green line) for (**a**) $\Phi = 0.02$ and (**b**) $\Phi = 0.025$.

Figure 4. Parameter space $p_1 \times \Phi$ for (**a**) $u = 0.0$ and (**b**) $u = 0.001$. We separate into three regions: cancer growth ($c_s > 0.001$, black), cancer remission ($c_s < 0.001$ and $0.0 \leq c_r < 0.01$, yellow), and hunting cells remission ($h < 0.001$, red).

(figure 3a) to 0.035 (figure 3b), we verify a temporary cancer remission ($c_s(t) < 0.0009$ and $c_r(t) < 0.0009$) for $t = 434$ and 557 days, respectively. The sensitive cancer cells are suppressed by the chemotherapy and the immune system. However, the immune system by itself is not sufficient to suppress the resistant cancer cells.

We compute the parameter space $p_1 \times \Phi$ to identify the regions in which the cancer remission occurs. Figure 4a displays the situation without drug resistance, i.e., for $u = 0$. We separate into three regions: cancer growth ($c_s > 0$), cancer remission ($c_s < 0.001$), and hunting cells remission ($h < 0.001$). The cancer grows for small values of p_1 and Φ (black region), but it is suppressed for larger values (yellow region). Higher values of these parameters not only lead to the killing of cancerous cells, but also weakening of the immune system with the remission of the hunting cells (red region). When there is drug resistance, a temporary cancer remission for 100 days ($0.0 \leq c_r < 0.01$) is observed for small values of p_1 and Φ for $u = 0.001$, as shown in figure 4b (yellow region).
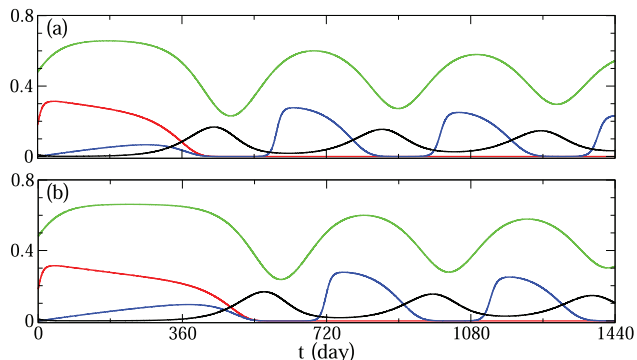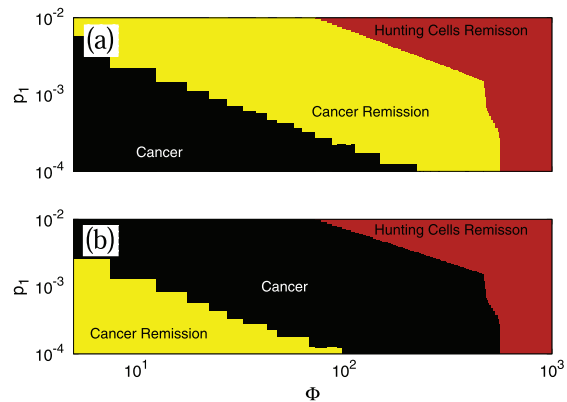
3.2 *Pulsed chemotherapy treatment*

Pulsed administration of chemotherapeutic drugs, also known as intermittent therapy, is a clinical protocol in which the drug is administered and followed by a rest period. In our simulations, we use periodically pulsed chemotherapy and analyse different rest periods to find cancer remission.

Figures 5a–d exhibit the time evolution of (a) c_s, (b) c_r, (c) h, and (d) r, respectively, for $\Phi = 0.2$, $u = 0.001$, and different protocols (days of administration $\times$ time interval). We do not observe a significant difference between the protocols 2×15 (blue line) and 1×10 (black line). However, both are better than the protocol 5×23 (red line), due to the fact that the times for suppression and remission of c_s and c_r, respectively, are shorter than 5×23. The suppression of c_s occurs for $t \simeq 625$ for 5×23, and about 500 for 2×15 and 1×10. The temporary remission

Figure 3. Time evolution of c_s (red line), c_r (blue line), h (black line), and r (green line) for $u = 0.001$, (**a**) $\Phi = 0.02$, and (**b**) $\Phi = 0.035$.
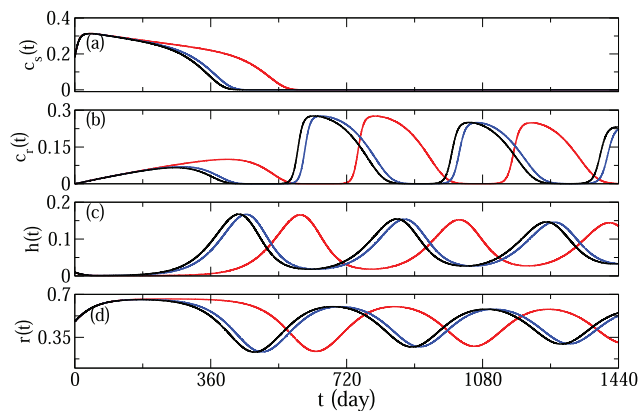
Figure 5. Time evolution of (**a**) c_s, (**b**) c_r, (**c**) h, and (**d**) r for $\Phi = 0.2$ and $u = 0.001$. We consider the protocols (days of administration $\times$ time interval): 5×23 (red line), 2×15 (blue line), and 1×10 (black line).
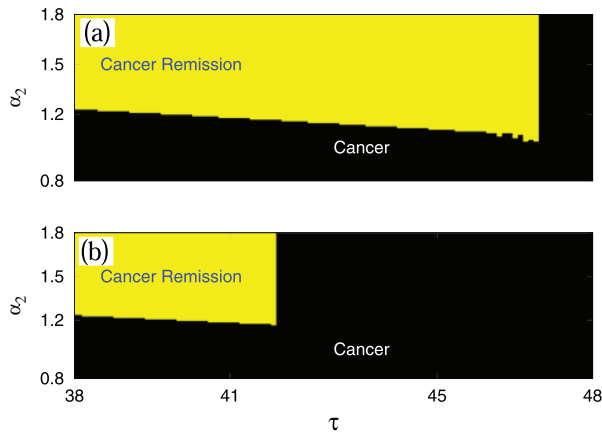
Figure 6. Parameter space $\alpha_2 \times \tau$ for the protocol 5×23. (**a**) $\Phi = 0.2$ and (**b**) $\Phi = 0.25$. The yellow and black regions correspond to the cancer remission and cancer.

($c_r < 0.1$) starts approximately 615 days after the chemotherapy treatment according to the protocol 5×23, and about 450 days for the protocols 2×15 and 1×10.

The immune system plays an important role in the combat against the cancer. To analyse the influence of the hunting cells on the resistant cancer, we vary the competition coefficient between the hunting and drug resistant cancer cells (α_2), and the delay time from resting to hunting cells (τ). Figure 6 exhibits the parameter space $\alpha_2 \times \tau$ for the protocol 5×23, where we consider cancer remission when $c_s < 0.0001$ and $c_r < 0.1$ (yellow region) for at least 100 days, and cancer for $c_s \geq 0.0001$ and $c_r \geq 0.1$ (black region). We verify that by increasing Φ from 0.2 (figure 6a) to 0.25 (figure 6b) the cancer remission region decreases. Therefore, for larger Φ value, the cancer remission is obtained for smaller τ value.
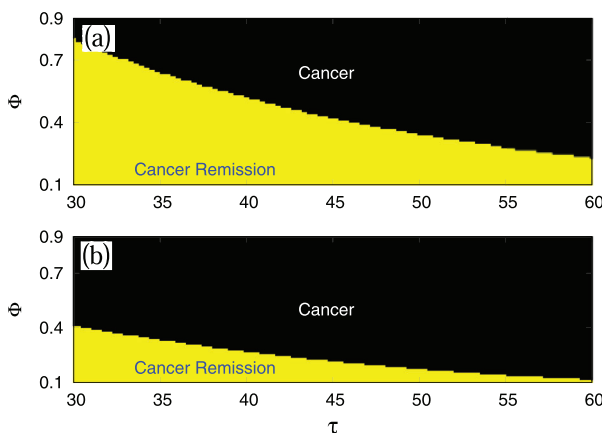

Figure 7. Parameter space $\Phi \times \tau$ for the protocols (**a**) 1×10 and (**b**) 5×23. The yellow and black regions correspond to the cancer remission and cancer.

We also compute the parameter space $\Phi \times \tau$ for the protocols 1×10 and 5×23, as shown in figures 7a and 7b, respectively. Comparing figures 7a and 7b, we see that not only Φ and τ are important, but also the type of protocol is relevant to increase the cancer remission region. The cancer remission region is smaller for 5×23 than for 1×10.

4. Conclusions

Drug resistance is responsible for a vast majority of cancer deaths and it is one of the major challenges in chemotherapy treatment. Initially some cancers are susceptible to chemotherapeutic agents; however, over time they can become resistant. Due to this fact, strategies have been used to eliminate resistant cancer cells.

In this work, we study the effects of the drug resistance in the tumour-immune system with chemotherapy treatment. The immune system is composed of resting cells that can transform into hunting cells. We separate the cancer into drug sensitive and drug resistant cells. In our simulations, we consider continuous and pulsed chemotherapy treatment.

In the continuous chemotherapy treatment, we verify that cancer remission is possible for smaller values of the chemotherapy intensity and the coefficient of chemotherapeutic agent on the sensitive cancer cells. The sensitive cells are eliminated, while the resistant cells are responsible for the remission. With regard to the pulsed chemotherapy, we analyse three types of protocols (days of administration $\times$ time interval): 5×23, 2×15, and 1×10. The protocols 2×15 and 1×10 exhibit almost the same results. In both protocols, the time for the elimination of sensitive cancer cells and the beginning of the temporary remission are less than the protocol 5×23. Furthermore, for all protocols, we show that the time delay from resting to hunting cells plays a crucial role in the combat against cancer cells.

Our results are in agreement with recent experimental findings related to chemo-immunotherapy. In 2020, von Roemeling *et al.* [36] carried out treatments to induce immune response against a type of brain tumour. They reported a therapeutic modulation that can generate potent hunting cells. In our model, the hunting cell efficiency is increased by means of the competition coefficient between hunting cells and cancer in which the hunting cells kill the cancerous cells. Maletzki *et al.* [37] in 2019 demonstrated that the combination of immune-stimulating vaccination and cytotoxic therapy can improve long-term survival. Depending on the protocol, they observed that mice became tumour free from 25 to 65 weeks. In our simulations, the mice became

tumour free in about 25 weeks. Nevertheless, for small time delay from resting to hunting cells in our model, it is possible to use different protocols aiming to maximise the tumour free time.

Acknowledgements

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