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.
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

\[
\frac{dC_S}{dt} = q_1C_S \left( 1 - \frac{C_S + CR}{K_1} \right) - \alpha_1C_SH - uF[Z]C_S - \frac{p_1C_SZ}{a_1 + C_S},
\]

\[
\frac{dC_R}{dt} = q_2C_R \left( 1 - \frac{C_S + CR}{K_1} \right) - \alpha_2C_RH + uF[Z]C_S,
\]

\[
\frac{dH}{dt} = \beta_1HR(t - \tau) - d_1H - \alpha_3H[C_S + C_R] - \frac{p_2HZ}{a_2 + H},
\]

\[
\frac{dR}{dt} = q_3R \left( 1 - \frac{R}{K_2} \right) - \beta_1HR(t - \tau) - \frac{p_3RZ}{a_3 + R},
\]

\[
\frac{dZ}{dt} = \Phi - \left( \zeta + \frac{g_1C_S}{a_1 + C_S} + \frac{g_2H}{a_2 + H} + \frac{g_3R}{a_3 + R} \right)Z,
\]

where \(C_S\) and \(C_R\) are the concentration of drug sensitive and resistant cells (kg/m³), respectively, \(H\) is the concentration of hunting cells (kg/m³), \(R\) is the concentration of resting cells (kg/m³), \(Z\) is the concentration of drug resistant cancer cells, and \(\Phi\) is the rate of dose-dense protocols.

Figure 1. Schematic representation of the model.
of the chemotherapeutic agent (mg/m^2), t is the time (day), \( \tau \) is the delay time from resting to hunting cells, and \( F(Z) \) is a function defined as

\[
F(Z) = \begin{cases} 
0, & Z = 0 \\
1, & Z > 0. 
\end{cases}
\]  

(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:
\[ c_s = C_s/K_T, \quad c_i = C_i/K_T, \quad h = H/K_T, \quad r = R/K_T, \quad \text{and} \quad z = \zeta Z, \]
where \( K_T = K_1 + K_2 \) and \( t = t/d \). 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, \( \xi^* = \xi \) day, \( q_i^* = q_i \) day, \( a_i^* = a_i K_T \) day, \( p_i^* = p_i/\zeta K_T \) day, \( g_i^* = g_i \) day, and \( \alpha_i^* = \alpha_i K_T \) (\( i = 1, 2, 3 \)). Redefining the variables and removing the stars, we obtain

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

(7)

\[
\frac{dc_i}{dt} = q_2 c_i \left(1 - \frac{c_s + c_i}{K_1}\right) - \alpha_2 c_i h + uF[z]c_s,
\]

(8)

Table 1. Parameters values according to the literature.

| Parameter | Value(s) | Description |
|-----------|----------|-------------|
| \( q_1 \) | 0.18 day | Proliferation |
| \( q_2 \) | 0.18 day | Rate [31, 32] |
| \( q_3 \) | 0.0245 day | |
| \( d_1 \) | 0.0412 day | Death rate [33] |
| \( \beta_1 \) | 6.2 × 10^{-9} (cells/day) | Conversion rate [33] |
| \( \Phi \) | 0–200 mg/m^2/day | Chemotherapy [34, 35] |
| \( \zeta \) | 0.2 day | Absorption rate [20] |
| \( u \) | 10^{-3} day | Mutation rate [25] |
| \( a_1, a_2 \) | 1.101 × 10^7 (cells/day) | Competition |
| \( a_3 \) | 3.422 × 10^10 (cells/day) | Coefficients [33] |
| \( K_1 \) | 5 × 10^6 cells | |
| \( K_2 \) | 1 × 10^7 cells | Capacity [31, 32] |
| \( \tau \) | 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 |
| \( \beta_1 \) | 9.3 × 10^{-2} |
| \( \beta_2 \) | 1 × 10^{-3} |
| \( \beta_3 \) | 1 × 10^{-3} |
| \( \alpha_1 \) | 1 × 10^{-4} |
| \( \alpha_2 \) | 1 × 10^{-4} |
| \( \alpha_3 \) | 1 × 10^{-4} |
| \( g_1, g_2, g_3 \) | 0.1 |
| \( a_1, a_2 \) | 1.6515 |
| \( a_3 \) | 5.133 × 10^{-3} |
| \( K_1 \) | 1/3 |
| \( K_2 \) | 2/3 |

\[
\frac{dh}{dt} = \beta_1 h(r - \tau) - d_1 h - \alpha_3 h[c_s + c_i] - \frac{p_2 h z}{a_2 + h},
\]

(9)

\[
\frac{dr}{dt} = q_3 r \left(1 - \frac{r}{K_2}\right) - \beta_1 h(r - \tau) - \frac{p_3 r z}{a_3 + r},
\]

(10)

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

(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 \( c_s(0) = 0.18, c_i(0) = 0.0, h(0) = 0.01, r(0) = 0.48, \) and \( z(0) = 0.0 \).

3.1 Continuous chemotherapy treatment

Figure 2 displays the behaviour of the time evolution of \( c_s \) (red line), \( c_i \) (blue line), \( h \) (black line), and \( r \) (green line) when there is no cancer drug resistance \( (\alpha = 0) \) for a continuous chemotherapy treatment. Increasing the value of chemotherapy dose \( \Phi \) 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 \( \Phi \) from 0.02
(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 $\Phi$ (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 $\Phi$ 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 × time interval). We do not observe a significant difference between the protocols $5 \times 23$ (red line) and $1 \times 10$ (black line). However, both are better than the protocol $2 \times 15$ (blue line) and $1 \times 10$ (black line). In our simulations, we use periodically pulsed chemotherapy and analyse different rest periods to find cancer remission. For $u = 0.001$, we consider the protocols (days of administration × time interval): $5 \times 23$ (red line), $2 \times 15$ (blue line), and $1 \times 10$ (black line).
Figure 6. Parameter space $\alpha_2 \times \tau$ for the protocol $5 \times 23$. (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 $5 \times 23$, and about 450 days for the protocols $2 \times 15$ and $1 \times 10$.

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 ($\alpha_2$), and the delay time from resting to hunting cells ($\tau$). Figure 6 exhibits the parameter space $\alpha_2 \times \tau$ for the protocol $5 \times 23$, 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 $\Phi$ from 0.2 (figure 6a) to 0.25 (figure 6b) the cancer remission region decreases. Therefore, for larger $\Phi$ value, the cancer remission is obtained for smaller $\tau$ value.

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

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

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): $5 \times 23$, $2 \times 15$, and $1 \times 10$. The protocols $2 \times 15$ and $1 \times 10$ 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 $5 \times 23$. 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.

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References

[1] M Höckel and U Behn, Front. Oncol. 9, 416 (2019)
[2] R L Siegel, K D Miller and A Jamel, CA-Cancer J. Clin. 65, 5 (2015)
[3] M F Brennan, Gastric Cancer 8, 64 (2005)
[4] V T DeVita Jr and E Chu, Cancer Res. 68, 8643 (2008)
[5] C M Ronckers, C A Erdmann and C E Land, Breast Cancer Res. 7, 21 (2004)
[6] J Couzin-Frankel, Science 342, 1432 (2013)
[7] K C Iarosz, F S Borges, A M Batista, M S Baptista, R A N Siqueira, R L Viana and S R Lopes, J. Theor. Biol. 368, 113 (2015)
[8] H N Weerasinghe, P M Burragge, K Burragge and D V Nicolau Jr, J. Oncol. 2019, 1 (2019)
[9] H P Greenspan, Stud. Appl. Math. 52, 317 (1972)
[10] D Balding and D L S McElwain, J. Theor. Biol. 114, 53 (1985)
[11] P Tracqui, GC Cruywagen, DE Woodward, GT Bartoo, JD Murray and E C Alvord Jr, Cell Proliferation 28, 17 (1995)
[12] J C Panetta, Bull. Math. Biol. 58, 425 (1996)
[13] A G López, K C Iarosz, A M Batista, J M Seoane, R L Viana and M A Sanjuán, Commun. Nonlinear Sci. Numer. Simul. 79, 104918 (2019)
[14] A G López, K C Iarosz, A M Batista, J M Seoane, R L Viana and M A Sanjuán, Commun. Nonlinear Sci. Numer. Simul. 70, 307 (2019)
[15] H Gonzalez, C Hagerling and Z Werb, Genes Dev. 32, 1267 (2018)
[16] S Farkona, E P Diamandis and I M Blasutig, BMC Med. 14, 73 (2016)
[17] S J Oiseth and M S Aziz, J. Cancer Metastasis Treat. 3, 250 (2017)
[18] F Nani and H I Freedman, Math. Biosci. 163, 159 (2000)
[19] A Konstorum, A T Vella, A J Adler and R C Laubenbacher, J. R. Soc., Interface 14, 20170150 (2017)
[20] F S Borges, K C Iarosz, H P Ren, A M Batista, M S Baptista, R L Viana, S R Lopes and C Grebogi, Biosystems 116, 43 (2014)
[21] H P Ren, Y Yang, M S Baptista and C Grebogi, Phil. Trans. A 375, 20160221 (2017)
[22] G Housman, S Byler, S Heerboth, K Lapinska, M Longacree, N Snyder and S Sarkar, Cancers 6, 1769 (2014)
[23] M M Gottesman, Annu. Rev. Med. 53, 615 (2002)
[24] X Sun, J Bao and Y Shao, Sci. Rep. 6, 22498 (2016)
[25] J Trobia, T Kun, A M Batista, C Grebogi, H-P Ren, M S Santos, P R Protachevich, F S Borges, J D Szezech Jr, R L Viana, I L Caldas and K C Iarosz, arXiv: submit/3516727[physics.bio_ph] 15 Dec. 2020
[26] N Vasan, J Baselga and D M Hyman, Nature 575, 299 (2019)
[27] J P Godefridus, Cancer Drug Resist. 1, 1 (2018)
[28] J Rodriguez-Pascual, A Ayuso-Sácalo and C Beldi-Iniesta, Cancer Drug Resist. 2, 980 (2019)
[29] S T R Pinho, H I Freedman and F Nani, Math. Comput. Modell. 36, 773 (2002)
[30] C S Holling, Mem. Entomol. Soc. Canada 45, 1 (1965)
[31] H Siu, E S Vitetta, R D May and J W Uhr, J. Immunol. 137, 1376 (1986)
[32] S Banerjee and R R Sarkar, Biosystems 91, 268 (2008)
[33] V A Kuznetsova, I A Makalkin, M A Taylor and A S Perelson, Bull. Math. Biol. 56(2), 295 (1994)
[34] R Stupp, W P Mason, M J Van den Bent, M Weller, B Fisher, M J B Taphoorn, K Belanger, A A Branderes, C Marosi, U Bogdahn, J Curschmann, R C Janzer, S K Ludwin, T Gorlia, A Allgeier, D Lacombe, J G Cairncross, E Eisenhauer and R O Mirimanoff, N. Engl. J. Med. 352, 987 (2005)
[35] H M Strik, C Marosi, B Kaina and B Neumann, Curr. Neurol. Neurosci. Rep. 12, 286 (2012)
[36] C A von Roemeling, Y Wang, Y Qie, H Yuan, H Zhao, X Liu, Z Yang, M Yang, W Deng, K A Bruno, C K Chan, A S Lee, S S Rosenfeld, K Yun, A J Johnson, D A Mitche, W Jiang and B Y S Kim, Nat. Commun. 11, 1508 (2020)
[37] C Maletzki, L Wiegeli, I Nassar, J Stenzel and C Junghanss, J. Immunother. Cancer 7, 8 (2019)