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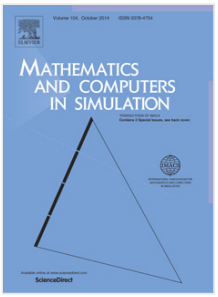

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Modelling pulsed immunotherapy of tumour-immune interaction

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Abstract

We develop a mathematical model that describes the tumour-immune interaction and the effect on it of pulsed immunotherapy, based on the administration of adoptive cellular immunotherapy (ACI) combined with interleukin-2 (IL-2). The stability conditions for the tumour-free periodic solution are provided with different frequencies of ACI applications and IL-2 infusions. Furthermore, the effects of period, dosage and times of drug deliveries on the amplitudes of the tumour-free periodic solution were investigated. The most feasible immunotherapy strategy was determined by comparing immunotherapy with ACI treatment with or without IL-2. However, to investigate how to enhance the efficacy of chemotherapy (radiotherapy) and reduce its side-effects, we developed a model involving periodic applications of immunotherapy with chemotherapy (radiotherapy) applied only when the density of the tumour reached a given threshold. The results revealed that the initial densities, the effector cell: tumour cell ratios, the periods T and a given critical number of tumour cells C_T are crucial for cancer treatment, which confirms that it is important to customise treatment strategies for individual patients.

Keywords: Cancer, Immunotherapy, Periodic solution, Combined therapy,

Threshold

1. Introduction

Cancer is an aggressive disease with high mortality rates. Without treatment, malignant tumour cells can grow uncontrollably and often metastasize from their initial site to other parts of the body with fatal consequences. Common therapies include surgery, radiotherapy, chemotherapy, immunotherapy or combinations thereof [37]. Immunotherapy, used to stimulate a strong immune response to target tumours, has become one of the most common approaches in cancer therapy [4, 29, 30].

Various mathematical models have been developed to describe tumour-immune dynamics. Mathematical models of tumour-immune dynamics not only help understanding of the involvement of immune cells and cancer cells and how they interact, but can also provide a useful tool to predict the results of immunotherapy and indicate improved treatment strategies. Many researchers have used ordinary differential equations (ODEs) to model populations of immune cells and tumour cells [28, 14, 5, 20, 19, 8, 21, 35, 38]. In these studies, the effects of the immune response and immunotherapy treatment on tumour growth and eradication have been studied in detail.

The preferred treatment for cancer depends on its stage and grade at diagnosis and the dosage, frequency and duration of immunotherapy are important for its success or failure. Optimal schedules for drug administration in immunotherapy have been widely investigated [9, 13, 16, 23, 24]. In 1994, Kuznetsov developed a tumour-immune model that was described by two ordinary differential equations, where the immune cells play the role of the predator, while the tumour cells are the prey: many complex dynamics were examined including immunostimulation of tumour growth, sneaking through of the tumour, and formation of a tumour dormant state [22]. Later, Kirschner and Panetta extended this work by incorporating tumour-immune dynamics together with interleukin-2 (IL-2) dynamics. The continuous administration of immunotherapy treatment was considered and short-term oscillations in tumour size as well as long-term tumour relapse were discussed [20].

Recently, the mathematical model of tumour-immune interaction developed by Kirschner and Panetta has been re-considered with pulsed immunotherapy described by impulsive differential equations [37] and a bifurcation analysis related to key parameters and its biological implications were discussed briefly. Note that Adoptive Cellular Immunotherapy (ACI) refers to the injection of cultured effector cells that have anti-tumour activity into

the tumour site [20], so that ACI acts directly on the tumour cells. However, sufficient lead time is needed for inputs of IL-2 to stimulate a strong immune response to fight against tumour cells. Therefore, what we need to show is how the time interval between injection of ACI and input of IL-2 affects the efficacy of immunotherapy. So we consider a more general case in this paper: ACI is applied only at each impulsive point τ_n, and at each impulsive point λ_m there is an impulsive injection of IL-2. These modifications result in the following model based on the two impulsive point series:

$$\begin{cases} \left.\begin{aligned} &\frac{dE(t)}{dt} = cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L}, \\ &\frac{dT(t)}{dt} = r_2 T(1 - bT) - \frac{aET}{g_2 + T}, \\ &\frac{dI_L(t)}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 I_L, \end{aligned}\right\} t \neq \tau_n, t \neq \lambda_m, \\ \left.\begin{aligned} &E(\tau_n^+) = E(\tau_n) + s_1, \\ &T(\tau_n^+) = T(\tau_n), \\ &I_L(\tau_n^+) = I_L(\tau_n), \end{aligned}\right\} \quad t = \tau_n, \\ \left.\begin{aligned} &E(\lambda_m^+) = E(\lambda_m), \\ &T(\lambda_m^+) = T(\lambda_m), \\ &I_L(\lambda_m^+) = I_L(\lambda_m) + s_2, \end{aligned}\right\} \quad t = \lambda_m, \end{cases} \tag{1}$$

with initial conditions: $E(0) = E_0, T(0) = T_0, I_L(0) = I_{L_0}$. Where $E(t)$, $T(t)$ and $I_L(t)$ represent the number of effector cells, tumour cells, and the concentration of IL-2, respectively. The parameter c models the antigenicity of the tumour, $1/\mu_2$ is the average lifespan of the effector cells, r_2 denotes the growth rate of the tumour, $1/b$ is the tumour carrying capacity, μ_3 represents loss/degradation rate of IL-2. s_1 is an ACI treatment term that represents an external source of effector cells such as lymphokine-activated killer (LAK) or tumour infiltrating lymphocyte (TIL) cells, s_2 is a treatment term that represents an external input of IL-2 into the system. Moreover, the interactions between the tumour and the immune system are modelled by Michaelis-Menten kinetics, g_1 is the semi-saturation point, and p_1 is the maximal production rate of an effector cell, while the meanings of g_2, g_3, a, and p_2 are similar to g_1 and p_1. Finally, $\tau_n (n = 1, 2, ...)$ and $\lambda_m (m = 1, 2, ...)$ are impulsive point series at which ACI (such as LAK or TIL cells) and inputs of IL-2 are applied, respectively. Based on system (1), de Pillis and his co-workers modelled tumour growth with respect to a total cell count

by including the influence of several immune cell effector subpopulations, namely tumour antigen-activated $CD8^+T$ cells, natural killer (NK) cells and total circulating lymphocytes, in addition to the concentrations of IL-2 and chemotherapy drug in the blood [14, 15]. It is found that the models proposed in [14, 15] are much more realistic and complex compared to Kirschner and Panetta's work. Our goal in this work is to show how pulsed immunotherapy with different frequencies of ACI applications and IL-2 infusions affect the growth and eradication of the tumour cells. Therefore, in order to provide detailed mathematical analyses and focus on the effects of pulse control strategies the simple model without pulse control is employed in the present work rather than the complex one.

Note that chemotherapy (or radiotherapy) which have direct impacts on tumour cells are the most commonly used methods in some cancer treatments. Until now, chemotherapy remains an important local treatment for malignant tumours. However, many negative side effects occur when a patient receives chemotherapy, such as micronuclei and DNA breakage in circulating lymphocytes and so on [27, 18]. Pre-clinical data and phased clinical studies have highlighted the potential therapeutic benefit of combining immunotherapy with chemotherapy [17, 11, 14, 15]. For example, work with murine models suggests that local radiotherapy plus injection of intra-tumoural syngeneic dendritic cells (DC) can mediate immunologic tumour eradication. Immunotherapy, can not only enhance the efficacy of chemotherapy, kill the residual tumour cells or cells with radiotherapy resistance effectively and prevent tumour metastasis and recurrence, but can also reduce the toxic reaction caused by chemotherapy, alleviate patient suffering, prolong their survival, and improve their life quality. Therefore, based on system (1), we propose a novel hybrid impulsive model with a threshold combining chemotherapy (radiotherapy) with immunotherapy, i.e., the chemotherapy is applied only when the critical number of tumour cells (denote by C_T) is observed and the immunotherapy is applied at the impulsive point series τ_n. Then the hybrid impulsive model can be described by:

$$
\begin{cases}
\dfrac{dE(t)}{dt} = cT - \mu_2 E + \dfrac{p_1 E I_L}{g_1 + I_L}, & t \neq \tau_n, \\
\dfrac{dT(t)}{dt} = r_2 T(1 - bT) - \dfrac{aET}{g_2 + T}, & T < C_T, \\
\dfrac{dI_L(t)}{dt} = \dfrac{p_2 ET}{g_3 + T} - \mu_3 I_L, & t \neq \tau_n, \\
\left.\begin{array}{l} E(\tau_n^+) = E(\tau_n) + s_1, \\ T(\tau_n^+) = T(\tau_n), \\ I_L(\tau_n^+) = I_L(\tau_n) + s_2 \end{array}\right\} & t = \tau_n, \\
\left.\begin{array}{l} E(\lambda_m^+) = E(\lambda_m) - p_0 E(\lambda_m), \\ T(\lambda_m^+) = T(\lambda_m) - p_1 T(\lambda_m), \\ I_L(\lambda_m^+) = I_L(\lambda_m), \end{array}\right\} & T = C_T,
\end{cases}
\tag{2}
$$

where $\tau_n (n = 1, 2, ...)$ is an impulsive point series at which the immunotherapy is applied normally, and λ_m is the time series at which the number of tumour cells reach the threshold C_T and then the chemotherapy is applied. All the parameter values and their meanings are the same as in system (1). Compared to immunotherapy, the chemotherapy can be viewed as an instantaneous process, with parameter $p_i (i = 0, 1)$ representing instant killing rate of tumour and effector cell populations due to the application of chemotherapy, and we assume that $p_i \in [0, 1)$ to keep all solutions of system (2) from being negative, where p_i is largely dependent on $K_E, K_T, M_0, \delta_E, \delta_T$ and can be described by $p_0 = K_E(1 - \exp(-\delta_E M_0))$ and $p_1 = K_T(1 - \exp(-\delta_T M_0))$, $K_E(K_T)$ represents the rate of effector (tumour) cell depletion from medicine toxicity, M_0 is the chemotherapy drug concentration in the blood stream and $\delta_E(\delta_T)$ denotes medicine toxicity coefficient [14, 15]. In previous studies [14, 15], the chemotherapy drug concentration is described by a differential equation including terms of decay rate and infusion rate. In fact, when the chemotherapy drug is injected, it would stabilize at an equilibrium level quickly. Therefore, it is reasonable to assume that the chemotherapy drug concentration M_0 is a constant.

The paper is organized as follows: In section 2, we focus on system (1) and investigate its dynamic behaviour. The existence and stability of the tumour-free periodic solution are studied under different cases. Section 2.2 reports on the sensitivity of the amplitude of the tumour-free periodic solution and the applicability of the immunotherapy, and includes discussion of some biological implications. Moreover, in section 3, the hybrid impulsive

model (2) with a threshold is investigated numerically. Finally, we present a conclusion.

2. Mathematical analysis of system (1)

2.1. Existence and stability of the tumour-free periodic solution

In this subsection, we investigate the tumour-free periodic solution. By observation, we note that system (1) can be reduced to the following subsystem when tumour cells are eradicated, which can be described by:

$$\begin{cases} \left.\begin{aligned} &\frac{dE(t)}{dt} = E(-\mu_2 + \frac{p_1 I_L}{g_1 + I_L}), \\ &\frac{dI_L(t)}{dt} = -\mu_3 I_L, \end{aligned}\right\} t \neq \tau_n, t \neq \lambda_m, \\ \left.\begin{aligned} &E(\tau_n^+) = E(\tau_n) + s_1, \\ &I_L(\tau_n^+) = I_L(\tau_n) \end{aligned}\right\} t = \tau_n, \\ \left.\begin{aligned} &E(\lambda_m^+) = E(\lambda_m), \\ &I_L(\lambda_m^+) = I_L(\lambda_m) + s_2, \end{aligned}\right\} t = \lambda_m, \end{cases} \tag{3}$$

there are two impulsive point series when ACI and input of IL-2 are applied. Therefore, it is possible to rank the different patterns of applications of ACI in terms of their dynamic effects in relation to the timing of injection of IL-2. We consider several different cases in terms of the timing of controlling the tumour cells [34].

Case 1 ACI is applied more frequently than inputs of IL-2.

Assume $\lambda_{m+1} - \lambda_m \equiv T_N$ for all $m(m \in \mathcal{N})$, where T_N is the period of impulsive injections of IL-2. For this case, system (1) is said to be a T_N periodic system if there exists a positive integer k_p such that

$$\tau_{n+k_p} = \tau_n + T_N.$$

This implies that in each period T_N, ACI is applied k_p times.

Note that the variable E does not appear in the second equation of system (3). Therefore, for the dynamics of I_L we only need to consider the following subsystem:

$$\begin{cases} \dfrac{dI_L(t)}{dt} = -\mu_3 I_L(t), & t \neq \tau_n, t \neq \lambda_m, \\ I_L(\tau_n^+) = I_L(\tau_n), & t = \tau_n, \\ I_L(\lambda_m^+) = I_L(\lambda_m) + s_2, & t = \lambda_m, \end{cases} \tag{4}$$

Denote $\Delta_i = \tau_{i+1} - \tau_i$, $i = 0, 1, 2, ..., k_p$, where $\Delta_0 = \tau_1, \Delta_{k_p} = T_N - \tau_{k_p}$.

It is shown in Appendix A that there exists a globally stable T_N periodic solution $I_L^{T_N}(t)$ for system (4), substituting $I_L^{T_N}(t)$ into the first equation of (3) for $I_L(t)$, we get a positive tumour-free periodic solution with the complete expression $(E^{T_N}(t), 0, I_L^{T_N}(t))$ over the $h-$th time interval $hT_N < t \leq (h+1)T_N$ of system (1). Now we investigate the stability of the positive tumour-free periodic solution $(E^{T_N}(t), 0, I_L^{T_N}(t))$.

Theorem 2.1 If

$$R_0^1 = \exp(-\mu_2 T_N) \left(\frac{s_2 \exp(-\mu_3 T_N) + g_1(1 - \exp(-\mu_3 T_N))}{s_2 + g_1(1 - \exp(-\mu_3 T_N))} \right)^{\frac{-p_1}{\mu_3}} < 1,$$

and

$$R_0^2 = \exp\left(\int_{hT_N}^{(h+1)T_N} \left[r_2 - \frac{aE^{T_N}(t)}{g_2} \right] dt \right) < 1,$$

then the positive tumour-free periodic solution $(E^{T_N}(t), 0, I_L^{T_N}(t))$ of system (1) is locally asymptotically stable.

Proof. The local stability of the periodic solution $(E^{T_N}(t), 0, I_L^{T_N}(t))$ can be determined by considering the behaviour of small amplitude perturbations $(u(t), v(t), w(t))$ of the solution. Define

$$E(t) = E^{T_N}(t) + u(t), \quad T(t) = v(t), \quad I(t) = I^{T_N}(t) + w(t),$$

then it follows that

$$\begin{pmatrix} u(t) \\ v(t) \\ w(t) \end{pmatrix} = \Phi(t) \begin{pmatrix} u(0) \\ v(0) \\ w(0) \end{pmatrix},$$

where $\Phi(t)$ satisfies

$$\frac{d\Phi(t)}{dt} = \begin{pmatrix} -\mu_2 + \frac{p_1 I_L^{T_N}(t)}{g_1 + I_L^{T_N}(t)} & c & \frac{p_1 E^{T_N}(t)}{g_1 + I^{T_N}(t)} \\ 0 & r_2 - \frac{aE^{T_N}(t)}{g_2} & 0 \\ 0 & \frac{p_2 E^{T_N}(t)}{g_3} & -\mu_3 \end{pmatrix} \Phi(t),$$

with $\Phi(0) = I$ the identity matrix. The linearization of the re-setting impulsive condition of (1) becomes

$$\begin{pmatrix} u((h+1)T_N^+) \\ v((h+1)T_N^+) \\ w((h+1)T_N^+) \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} u((h+1)T_N) \\ v((h+1)T_N) \\ w((h+1)T_N) \end{pmatrix},$$

and

$$\begin{pmatrix} u((hT_N+\tau_i)^+) \\ v((hT_N+\tau_i)^+) \\ w((hT_N+\tau_i)^+) \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} u(hT_N+\tau_i) \\ v(hT_N+\tau_i) \\ w(hT_N+\tau_i) \end{pmatrix}.$$

Then the stability of the periodic solution $(E^{T_N}(t), 0, I_L^{T_N}(t))$ is determined by the eigenvalues of

$$\theta = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \Phi(T_N).$$

Therefore, all eigenvalues of θ are given by

$$\eta_1 = \exp\left(\int_{hT_N}^{(h+1)T_N} \left[-\mu_2 + \frac{p_1 I_L^{T_N}(t)}{g_1 + I_L^{T_N}(t)}\right] dt\right) = \prod_{j=0}^{k_p} \eta_1^j,$$

$$\eta_2 = \exp\left(\int_{hT_N}^{(h+1)T_N} \left[r_2 - \frac{aE^{T_N}(t)}{g_2}\right] dt\right) = R_0^2 < 1, \quad \text{and} \quad \eta_3 = e^{-\mu_3 T_N} < 1,$$

substitute $I^{T_N}(t)$ into η_1, then we get

$$\eta_1^0 = \exp\left(\int_{hT_N}^{\tau_1+hT_N} \left[-\mu_2 + \frac{p_1 I_L^* \exp[-\mu_3(t-hT_N)]}{g_1 + I_L^* \exp[-\mu_3(t-hT_N)]}\right] dt\right),$$

$$\eta_1^j = \exp\left(\int_{\tau_j+hT_N}^{\tau_{j+1}+hT_N} \left[-\mu_2 + \frac{p_1 I_L^* \exp[-\mu_3(\sum_{i=0}^{j-1}\Delta_i + t - \tau_j - hT_N)]}{g_1 + I_L^* \exp[-\mu_3(\sum_{i=0}^{j-1}\Delta_i + t - \tau_j - hT_N)]}\right] dt\right),$$

where $j = 1 \cdots k_p - 1$, and

$$\eta_1^{k_p} = \exp\left(\int_{\tau_{k_p}+hT_N}^{(h+1)T_N} \left[-\mu_2 + \frac{p_1 I_L^* \exp[-\mu_3(\sum_{i=0}^{k_p-1} \Delta_i + t - \tau_{k_p} - hT_N)]}{g_1 + I_L^* \exp[-\mu_3(\sum_{i=0}^{k_p-1} \Delta_i + t - \tau_{k_p} - hT_N)]} \right] dt \right),$$

then we replace I_L^* by $s_2/(1-\exp(-\mu_3 T_N))$, and by calculation, we have

$$\eta_1 = \exp(-\mu_2 T_N) \left(\frac{s_2 \exp(-\mu_3 T_N) + g_1(1-\exp(-\mu_3 T_N))}{s_2 + g_1(1-\exp(-\mu_3 T_N))} \right)^{\frac{-p_1}{\mu_3}} = R_0^1 < 1,$$

According to Floquet theory [1, 2], the tumour-free periodic solution $(E^{T_N}(t), 0, I_L^{T_N}(t))$ is locally asymptotically stable. This completes the proof.

Case 2 Inputs of IL-2 are more frequent than applications of ACI.

Assume $\tau_{n+1} - \tau_n \equiv T_p$ for all n ($n \in \mathcal{N}$, if $n = 1$, then this special case is considered by Wei and Lin [37]), where T_p is the period of the applications of ACI. For this case, system (1) is said to be a T_p periodic system if there exists a positive integer k_N such that

$$\lambda_{m+k_N} = \lambda_m + T_p.$$

This implies that in each period T_p, inputs of IL-2 are applied k_N times.

Similarly, denote $\Delta_i = \lambda_{i+1} - \lambda_i$, $i = 0, 1, 2, ..., k_N$, where $\Delta_0 = \lambda_1, \Delta_{k_N} = T_p - \lambda_{k_N}$. Note that the variable E does not appear in the second equation of system (3). Therefore, for the dynamics of $I_L(t)$ we only need to consider the following subsystem:

$$\begin{cases} \dfrac{dI_L(t)}{dt} = -\mu_3 I_L(t), & t \neq \tau_n, t \neq \lambda_m, \\ I_L(\lambda_m^+) = I_L(\lambda_m) + s_2, & t = \lambda_m, \\ I_L(\tau_n^+) = I_L(\tau_n), & t = \tau_n, \end{cases} \tag{5}$$

It is shown in Appendix B that there exists a tumour-free periodic solution with the complete expression $(E^{T_p}(t), 0, I_L^{T_p}(t))$ over the $h-$th time interval $hT_p < t \leq (h+1)T_p$ of system (1).

Theorem 2.2 If

$$R_1^1 = \exp\left(\int_{hT_p}^{(h+1)T_p} \left[-\mu_2 + \frac{p_1 I_L^{T_p}(t)}{g_1 + I_L^{T_p}(t)} \right] dt \right) < 1,$$

and

$$R_1^2 = \exp\left(\int_{hT_p}^{(h+1)T_p}\left[r_2 - \frac{aE^{T_p}(t)}{g_2}\right]dt\right) < 1,$$

then the positive tumour-free periodic solution $(E^{T_p}(t), 0, I_L^{T_p}(t))$ of system (1) is locally asymptotically stable.

The Proof is similar to that of Theorem 2.1, so we omit it here.

When the applications of ACI and inputs of IL-2 are employed with different periods, we assume that $\lambda_{m+1} - \lambda_m \equiv T_N$ for all m, and $\tau_{n+1} - \tau_n \equiv T_p$ for all n. In this case, T_N is the period of impulsive injections of IL-2, T_p is the period of ACI infusions, $m, n \in \mathcal{N}$. Denote $\rho = T_p/T_N$, then ρ either is rational (i.e. T_p and T_N are rational dependent) or is irrational (i.e. T_p and T_N are rational independent). If ρ is rational, then $\rho = \frac{p}{q}$, $p, q \in \mathcal{N}$ and p, q are relatively prime. Let $T_0 = pT_N(= qT_p)$, then system (1) is a T_0 periodic system. This means that if ρ is rational, model (1) can be investigated by using similar methods as those in Cases 1 and 2; if ρ is irrational, then the dynamical behaviour of model (1) becomes more complex and is quite difficult to investigate theoretically (for details see [26]).

From the analyses of Case 1 and Case 2, it is shown that there exists a positive locally stable tumour-free periodic solution in system (1), and the periodic solution reflects the periodic oscillations of the concentrations of effector cells and IL-2 when injections of ACI and inputs of IL-2 are applied. However, the tumour-free periodic solution becomes unstable when the conditions of Theorem 2.1 and Theorem 2.2 do not hold, then the tumour will not be eradicated and would oscillate periodically. This case is too complicated to investigate theoretically, so we present numerical investigations in the following.

2.2. Sensitivity analyses and biological implications

In this subsection, we will investigate the applications of model (1) numerically with the aim of mimicking the natural patterns of ACI treatment and inputs of IL-2 so that the tumour population can be controlled or eradicated with immunotherapy. Based on the literature [12, 14, 15, 20, 22, 31], we use the parameter values given in Table 1 for sensitivity analyses and numerical studies.

Table 1: Parameter values for the model (1)

Parameter	Value	Parameter	Value	Parameter	Value
c	0-0.05	μ_2	0.03	μ_3	10
p_1	0.1245	p_2	5	r_2	0.18
a	1	b	10^{-9}	g_1	2×10^7
g_2	10^5	g_3	10^3	K_E	0.6
K_T	0.9	$\delta_E(\delta_T)$	1.8328	M_0	$0.6 - 0.75$

2.2.1. Sensitivity analysis

For Case 1, the tumour-free periodic solution $(E^{T_N}, 0, I_L^{T_N})$ was obtained theoretically, meanwhile, the maximum amplitudes of E^{T_N} and $I_L^{T_N}$ represent the maximum number of the effector cells and the largest concentration of IL-2 with pulsed immunotherapy. Figs. 1(a) and (b) show how the inputs of dosage and infusion times of s_1 affect the maximum amplitude of E^{T_N} and indicate that the maximum amplitude of E^{T_N} increases when inputs of dosage and infusion times of s_1 increase correspondingly. Figs. 1(c) and (d) show the effects of inputs of dosage s_2 and the period T_N on the maximum amplitude of $I_L^{T_N}$; note that the maximum amplitude of $I_L^{T_N}$ decreases and is maintained at a certain level when T_N increases. Moreover, the maximum amplitude of $I_L^{T_N}$ increases as inputs of dosage s_2 increase. These results suggest that infusions of s_2 should be administered carefully, because a high-dose of s_2 often becomes toxic [14, 4].

Note that the dynamics are very sensitive to parameter c [20, 37]. What we want to address is how it will impact the efficacy of pulsed immunotherapy for Case 1. Fig. 2 shows that the combined immunotherapy under Case 1 is effective, the tumour cells were cleared while the effector cells and IL-2 oscillate periodically. We found that the number of tumour cells and the time for tumour eradication increased dramatically when c decreased, and the number of effector cells increased when c increased. Further, the change of c did not lead to the change of periodic infusions of IL-2 so that the concentration of IL-2 did not change when c increased or decreased. Moreover, the tumour size may tend to its carrying capacity when c is small enough, indicating that c plays an important role in immunotherapy.

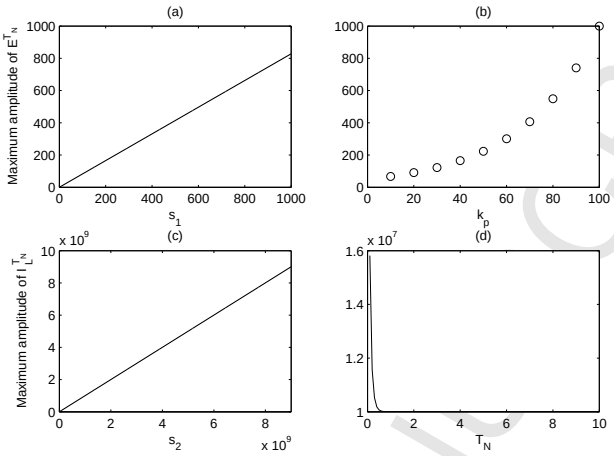

Figure 1: The effects of input dosages, the period T_N and the number of ACI applications on the maximum amplitudes of E^{T_N} and $I_L^{T_N}$. (a) $T_N = 9$ and $k_p = 2$. (b) $s_1 = 1000$, $s_2 = 1 \times 10^7$, $T_N = 100$ and $k_p = 1, 2, 3, ..., 10$ with $\Delta_i \equiv \Delta$. (c) $T_N = 9$, $k_p = 2$ and $s_1 = 1000$. (d) $s_1 = 1000$, $s_2 = 1 \times 10^7$ and $k_p = 2$. The rest of the parameter values are as those in Table 1.

2.2.2. Immunotherapy with ACI or IL-2 alone ($s_1 = 0$ or $s_2 = 0$)

Now, we keep the parameter values as shown in Table 1 and fix the period $T_N = T_p = 9$ (for Figs. 2 to Fig. 6, the initial values are set as $(10^4, 10^4, 10^7)$). Fig. 3 shows results of immunotherapy with ACI treatment alone ($s_1 = 2400$) and IL-2 ($s_2 = 1 \times 10^7$) alone, respectively, showing that the tumour cells are stabilized at a fixed level. Although the tumour cells are not cleared, their numbers in Fig. 3(c) are smaller than those in Fig. 3(d). This indicates that the efficacy of immunotherapy with ACI treatment alone is better than inputs of IL-2 alone, because sufficient lead time is needed for inputs of IL-2 to stimulate a strong immune response, while ACI treatment acts directly on the tumour cells. Besides, the tumour can be eradicated in a short treatment period or by a large dosage of s_1 alone (see Fig. 4(a), (c) and (e)), but the IL-2 treatment alone cannot clear the tumour, in agreement with previous research [3, 20, 37].

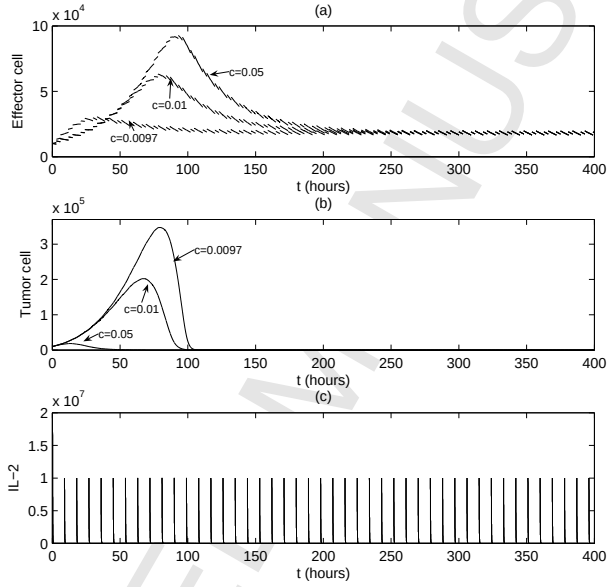

Figure 2: The effects of c (the tumour antigenicity) on the evolution of effector cells (a), tumour cells (b) and concentration of IL-2 (c) of system (1) for Case 1, where $c = 0.0097, 0.01, 0.05$ for three curves, $T_N = 9$, $k_p = 2$, $\Delta_i \equiv \Delta$, $s_1 = 2400$ and $s_2 = 1 \times 10^7$, from Fig. 2 to Fig. 6, the initial values are set as $(10^4, 10^4, 10^7)$. The rest of the parameter values are as those in Table 1.

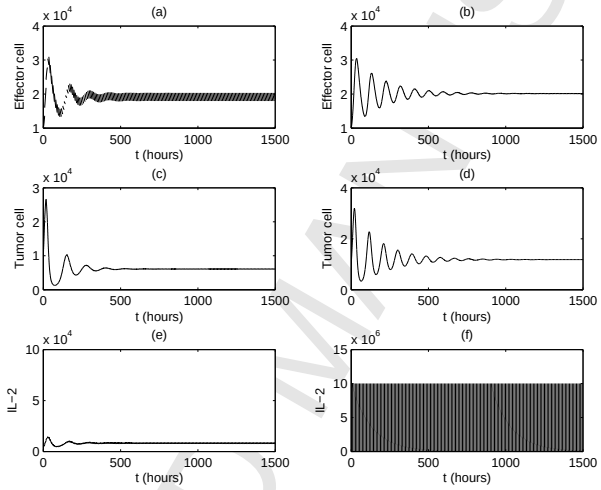

Figure 3: The effects of immunotherapy with ACI alone on the evolution of effector cells, tumour cells and concentration of IL-2 of system (1) (as shown in (a), (c) and (e) with $s_1 = 2400$ and $s_2 = 0$), and the effects of immunotherapy with IL-2 alone on the evolution of effector cells, tumour cells and concentration of IL-2 of system (1) (as shown in (b), (d) and (f) with $s_1 = 0$ and $s_2 = 1 \times 10^7$), where $T_N = T_p = 9$, we set $c = 0.05$. The rest of the parameter values are as those in Table 1.

2.2.3. Immunotherapy with both ACI and IL-2 ($s_1 > 0, s_2 > 0$)

First of all, we consider a special case, i.e. simultaneous application of ACI treatment and inputs of IL-2 (for example, $T_N = T_p = 9$, $s_1 = 2400$ and $s_2 = 1 \times 10^7$, see Fig. 4(b), (d) and (f)), in which the effector cells, the tumour cells and the concentration of IL-2 oscillate periodically. This shows that the result of such a combination would be no different from that of treating with ACI only, i.e. IL-2 could not stimulate a strong immune response targeted at the tumour population when ACI treatment and inputs of IL-2 are applied at the same time. Also, we could shorten the treatment period or increase the dosage of inputs of s_1 to clear the tumour cells (not shown here).

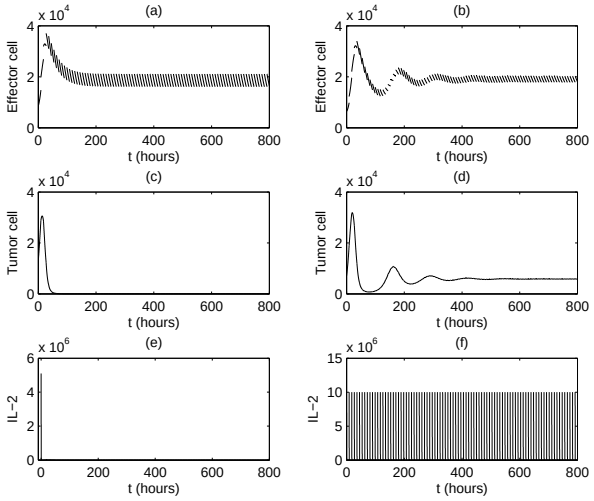

Figure 4: Simulations of the effects of immunotherapy with ACI alone, here $s_1 = 4000$, $s_2 = 0$ and $T_N = T_p = 9$ in (a), (c) and (e). Simulation of the effects of immunotherapy with both ACI and IL-2 at the same time, where $s_1 = 4000$, $s_2 = 1 \times 10^7$ and the period set as 9 in (b), (d) and (f). We set $c = 0.05$ and the rest of the parameter values are as those in Table 1.

From the analyses of Cases 1 and 2 in section 2.1, we know that with different frequencies of the external inputs of s_1 and s_2, for the system (1) there exists a locally stable tumour-free periodic solution. To substantiate our theoretical results and supply reasonable immunotherapy for the patients,

in Case 1, we also assume that $T_N = 9$ and let $k_p = 2$. With fixed $s_1 = 2400$ and $s_2 = 1 \times 10^7$, the stable tumour-free periodic solution is shown in Figs. 5 (a), (c) and (e). At the beginning of period $T_N = 9$, IL-2 is injected once and then ACI treatment is applied twice every three hours during this period. The tumour is cleared under this regime of immunotherapy, while the number of effector cells and the concentration of IL-2 oscillates periodically. Only when looking at tumour cells does it appear that different decrease kinetics may be noted when the dosage of ACI treatment is increased, the tumour cells being eradicated more rapidly with a higher rather than a lower dose. For Case 2, we also set $T_p = 9$ and $k_N = 2$, with the values of s_1 and s_2 the same as in Case 1. At the beginning of the period $T_p = 9$, ACI treatment is applied once and then IL-2 is injected twice every three hours during this period (see Fig. 5(b), (d) and (f)). It is shown that the tumour population stabilizes at a high level, but the effector cells and the concentration of IL-2 oscillate periodically. This indicates that the treatment of Case 1 is more effective than treatment of Case 2 with the same initial conditions, drug dosages, period and frequency of drug deliveries. Moreover, for Case 2, if we want to eradicate the tumour cells, it suggests that the reduction of the medication period (Fig. 6(a), (c) and (e)), the increased times of inputs of s_2, or increased dosages of inputs of s_1 and s_2 (Fig. 6(b), (d) and (f)) are necessary.

3. Hybrid impulsive model (2) with threshold

As mentioned before, initial treatment with chemotherapy and / or radiotherapy will often have a direct impact on tumour cells and reduce the tumour size. However, the dosage, time course and frequency of the chemotherapy (radiotherapy) are pivotal in treatment and prolonged use of chemotherapy does not result in tumour destruction. After chemotherapy, there are often many painful side-effects suffered by the patients. To enhance the efficacy of chemotherapy and reduce toxic reactions caused by chemotherapy, we propose a novel hybrid impulsive model (2) with a threshold, combining chemotherapy with immunotherapy. In system (2), for simplification, we assume that $\tau_{n+1} - \tau_n = T$ for all $n (n \in \mathcal{N})$, i.e. periodic infusions of ACI and IL-2 are applied.

With the combined effects of chemotherapy and immunotherapy, we can control the tumour cells below a prescribed threshold. However, the elements which may influence the therapeutic effect can vary, such as the ef-

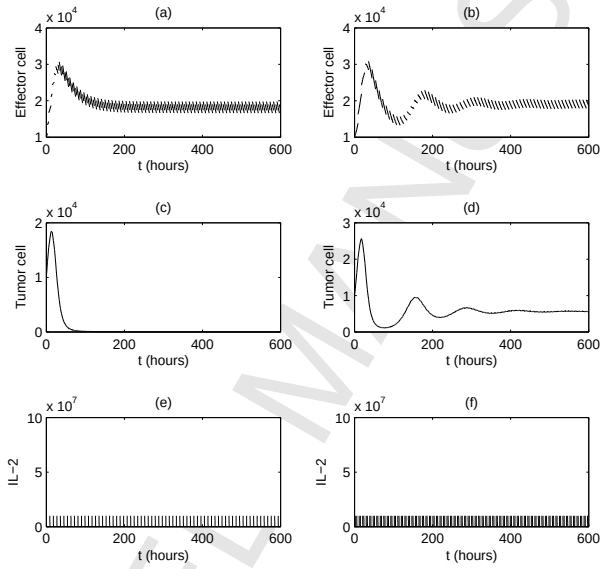

Figure 5: Simulations of the effects of immunotherapy with both ACI and IL-2 for Case 1 (as shown in (a), (c) and (e)), simulations of the effects of immunotherapy with both ACI and IL-2 for Case 2 (as shown in (b), (d) and (f)), where $T_N = T_p = 9$, $k_p = k_N = 2$, $s_1 = 2400$ and $s_2 = 1 \times 10^7$, we set $c = 0.05$. The rest of the parameter values are as those in Table 1.

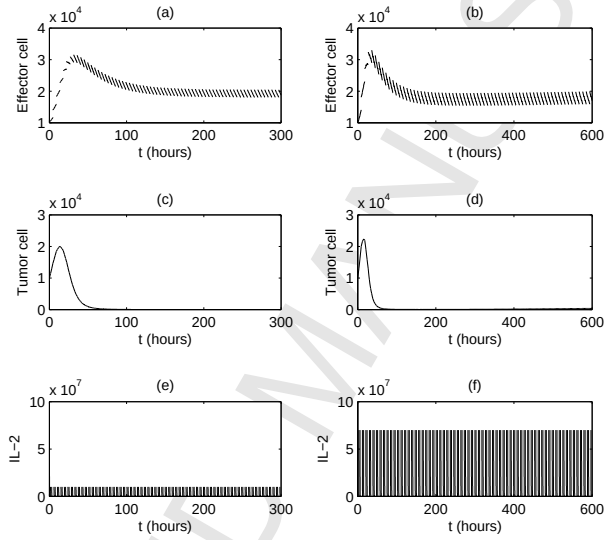

Figure 6: Simulations of the effects of the reduction period on immunotherapy with both ACI and IL-2 for Case 2, where $T_p = 4.5$, $k_N = 2$, $s_1 = 2400$ and $s_2 = 1 \times 10^7$ in (a), (c) and (e). Simulation of the effects of increased frequencies of inputs of s_1 and s_2 on immunotherapy with both ACI and IL-2 for Case 2, where $T_p = 9$, $k_N = 2$, $s_1 = 4000$ and $s_2 = 7 \times 10^7$ in (b), (d) and (f). We set $c = 0.05$ and the rest of the parameter values are as those in Table 1.

fector:tumour cell ratios of patients, the dosage, time course and frequency of the chemotherapy and immunotherapy. How do these factors affect the therapeutic strategies? In particular, what we want to know is how the threshold C_T, the period of the applications of immunotherapy and various effector:tumour cell ratios affect the chemotherapy control strategies. Note that model (2) is a hybrid impulsive system with fixed time pulses and state-dependent control actions, which indicates that it is impossible to provide theoretical analyses for model (2). To this end, it is essential to resort to numerical investigations to address the proposed problems.

For a given C_T, we suggest that the applications of chemotherapy control strategies largely depend on the initial concentration of effector:tumour cell ratios. To show this, we fix all parameter values as those in Table 1, the controlling parameters are shown in Fig. 7. In Fig. 7(a) the initial densities are set as $(1.5 \times 10^4, 1.3 \times 10^4, 0)$ and the simulation result indicates that the system is free from the need for chemotherapy after one application of it, that is to say, after one application of chemotherapy, immunotherapy can control the tumour cells below the given threshold C_T. If we set the initial densities as $(1.5\times10^4, 1.42\times10^4, 0)$ and $(1.5\times10^4, 1.47\times10^4, 0)$, Fig. 7(b) and Fig. 7(c) indicate that the system is free from the need for chemotherapy after two or four applications of it, respectively. Further, if the initial conditions are set as $(1.5 \times 10^4, 1.48 \times 10^4, 0)$, then the frequency of chemotherapy applications needed is significantly increased (Fig. 7(d)). From Fig. 7, it is found that the applications of chemotherapy control strategies largely depend on the initial concentrations of effector:tumour cell ratios. Furthermore, the smaller the effector:tumour cell ratio is, the higher the frequency of applications of chemotherapy needed. Moreover, after one time application of chemotherapy, it can be seen that the tumour size reduced remarkably.

Furthermore, for a given C_T, we show that the immunotherapy period T plays an important role relevant for the chemotherapy application control strategies. We fix all parameter values as those in Table 1 and initial densities are set as $(1.6 \times 10^4, 1.5 \times 10^4, 0)$, the controlling parameters are shown in Fig. 8. In Fig. 8(a) the immunotherapy period T is 6 and it is shown that the density of the tumour cells never reaches the given C_T, which implies that the tumour cells can be controlled below the given threshold C_T with immunotherapy only and the chemotherapy is not applied. If we set the immunotherapy period T as 12 or 14.1, Fig. 8(b) and Fig. 8(c) indicate that the system is free from the need for chemotherapy after one or two applications of it, and then the density of tumour cells never reaches the

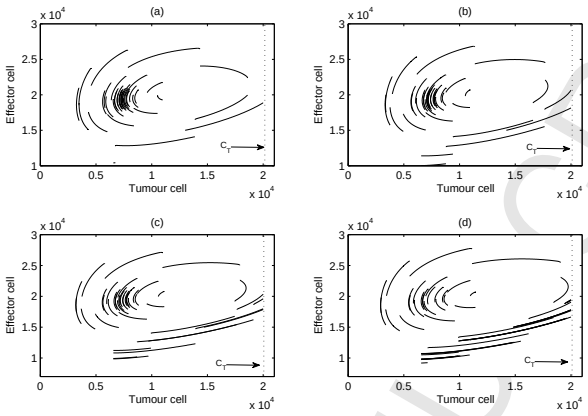

Figure 7: Illustration of the effects of C_T and initial number of effector cells and tumour cells of system (2) on the chemotherapy control strategies. The control parameters are fixed as: $s_1 = 2400$, $s_2 = 7 \times 10^7$, $M_0 = 0.75$, $C_T = 2 \times 10^4$ and $T = 12$. Initial densities (a) $(1.5 \times 10^4, 1.3 \times 10^4, 0)$; (b) $(1.5 \times 10^4, 1.42 \times 10^4, 0)$; (c) $(1.5 \times 10^4, 1.47 \times 10^4, 0)$ and (d) $(1.5 \times 10^4, 1.48 \times 10^4, 0)$. We set $c = 0.05$ and the rest of the parameter values are as those in Table 1.

given C_T with immunotherapy alone. If we further increase $T = 15$, the frequency of chemotherapy applications needed is significantly increased, as shown in Fig. 8(d).

Moreover, many other numerical simulations (not shown here) with different effector:tumour cell ratios, different periods T, and different dosages of ACI and IL-2 showed that there are only three possible cases that model (2) has: (1) infinite repeats of chemotherapy; (b) finite numbers of chemotherapy; (c) no chemotherapy required. These results show that the applications of chemotherapy are greatly affected by above factors which influence the therapeutic output, and that the tumour can be controlled below a threshold when immunotherapy is implemented in conjunction with chemotherapy. Thus the model proposed here can help us to understand interactions between effector cells and tumour cells and assist in the improvement of control strategies against tumour cells.

4. Conclusion

Since the original pioneering work on the dynamics of the tumour-immune system contributing to immunotherapy, numerous papers have appeared on

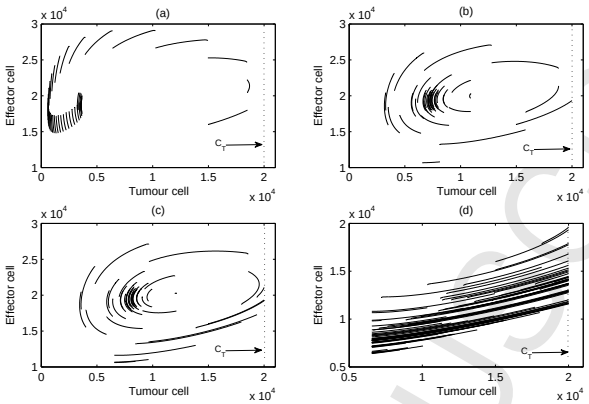

Figure 8: Illustration of the effects of C_T and the immunotherapy period T of system (2) on the chemotherapy control strategies. The control parameters are fixed as: $s_1 = 2400$, $s_2 = 7 \times 10^7$, $M_0 = 0.75$, $C_T = 2 \times 10^4$ and initial densities is $(1.6 \times 10^4, 1.5 \times 10^4, 0)$. The immunotherapy period T: (a) $T = 6$; (b) $T = 12$; (c) $T = 14.1$ and (d) $T = 15$. We set $c = 0.05$ and the rest of the parameter values are as those in Table 1.

the topic [31, 22, 20, 14, 9, 8, 24, 23]. Many researchers have used ODEs (ordinary differential equations), DDEs (delay differential equations) and PDEs (partial differential equations) to describe the tumour-immune interaction and investigate its dynamics. Recently, mathematical models of the tumour-immune interaction with pulsed immunotherapy have received much attention [14, 10, 6, 7, 37]. The theory of impulsive differential equations is increasingly being recognized, not only to be richer than the corresponding theory of differential equations without impulses, but also to represent a more natural framework for the mathematical modelling of real-world phenomena [33, 34, 36, 25]. However, no previous authors have expanded models of the tumour-immune interaction to include the effects of different frequencies of ACI injections and IL-2 infusions. The main subjects of this paper were to incorporate these effects into the tumour-immune system (1) and to address how they affect the dynamics. Moreover, in clinical therapies, immunotherapy combined with radiotherapy (chemotherapy) has been considered as a necessary and reasonable treatment for patients. So we proposed a novel hybrid impulsive model (2) with a threshold to see how the combined therapies affected the tumour population.

Two possible cases of system (1) were investigated at first, according to

the relations between the frequency of infusions of ACI and input frequencies of IL-2. Whatever IL-2 inputs took place, either more or less frequently than the ACI infusions, the threshold conditions which guarantee the existence and stability of the tumour-free periodic solution have been provided. To avoid toxicity from taking excessive drug concentrations [14, 4], the effects of the dosage, frequency and period of inputs of s_1 and s_2 on the maximum amplitude of E^{T_N} and $I_L^{T_N}$ were carefully studied. In particular, the maximum amplitude of E^{T_N} increased when inputs of dosage and infusion times of s_1 increased correspondingly, the maximum amplitude of $I_L^{T_N}$ increased as inputs of dosage s_2 increased, while the maximum amplitude of $I_L^{T_N}$ was maintained at a certain level when T_N increased. Furthermore, the antigenicity c plays an important role in immunotherapy treatment which suggests that appropriate immunotherapy should be applied carefully, according to different values of c.

In addition, for large amounts of s_1 alone, the effector cells increase and then lead to tumour eradication. However, for large amounts s_2 alone, the concentration of IL-2 increases markedly, while both the effector and tumour cells are not affected much. This implies that the use of only IL-2 cannot result in a tumour-free body [3, 20, 37]. In contrast, when ACI treatment and inputs of IL-2 are applied at the same time, it is found that the result of such a combination would not be different from that of treating with ACI alone. Simulations of a therapy associating ACI to IL-2 under Case 1 show that the tumour cells can be cleared and the effector cells and IL-2 can be maintained at acceptable levels. Furthermore, the applications of immunotherapy combining ACI with IL-2 under Case 2 do not help the patient, as additional actions are needed to clear the tumour, including the reduction of the medication period, increased times of s_2 inputs, or the increased dosages of inputs of both s_1 and s_2. Therefore, we conclude that the immunotherapy of Case 1 represents a better way to administer cancer immunotherapy.

The model which appeared in [32] refers to continuous differential equations, while system (1) is proposed with impulsive differential equations. The sufficient conditions for the local stability of the tumour-free equilibrium point have been given in [32]. However, in addition to the conditions for the local stability of the tumour-free equilibrium, it is emphasized that the immunotherapy under Case 1 is proved to be more effective than other cases. Thus the results in this paper extend and develop the research of previous studies [14, 10, 6, 7, 37, 32].

In practice, though chemotherapy could kill a large portion of tumour cells

in a short time, it is accompanied by many side effects. Then immunotherapy needs to be applied periodically to enhance the efficacy of chemotherapy and reduce its side effects. System (2) is proposed based on this ideal. We assumed that chemotherapy is applied only when the density of tumour cells reach the prescribed threshold C_T and periodic repeated applications of immunotherapy are applied. It is shown that the tumour size can be reduced significantly by using chemotherapy and the factors which affect chemotherapy frequency are discussed. The simulation results indicate that successful chemotherapy control strategies largely depend on the initial densities of effector and tumour cells, their ratios, the period T, the dosage of immunotherapy and the given C_T. This confirms that it is important to individualize treatment strategies for different patients. Therefore, we conclude that hybrid system (2) is helpful for understanding effector cell-tumour cell interactions and the design of appropriate control strategies against tumour cells.

For the sake of simplicity, in this paper the total NK cell population, total $CD8^+$T cell population, and total number of circulating lymphocytes are viewed as a total cell count. Recently, de Pillis and his co-workers modelled tumour growth by including the influence of these immune cell effector subpopulations [14, 15]. It is found that the models proposed in [14, 15] are much more realistic and complex compared to Kirschner and Panetta's work. Hence, the effect of pulsed immunotherapy and chemotherapy on the tumour cells will be studied by taking the updated model into consideration proposed by de Pillis and co-workers [14]. Based on their model, how this effect influences the growth and extinction of the tumour cells seems intriguing, and it will be presented in the future[14]. It is hoped that such research, planned for the near future and to be reported elsewhere, will be useful for oncologists and clinicians to help them to decide on treatment methods and dosages of drugs to be administered with the aim of improving optimal strategies for cancer treatment.

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Appendix A. Analyzing system (3) for Case 1

We begin by investigating the periodic solution of system (4). We consider any given time interval $(hT_N, (h+1)T_N]$, where h is a positive integer. Integrating the first equation of system (4) from hT_N to $\tau_1 + hT_N$ yields

$$I_L(t) = I_L(hT_N^+)\exp[-\mu_3(t - hT_N)], \quad t \in (hT_N, \tau_1 + hT_N].$$

At time $\tau_1 + hT_N$, we have

$$I_L((\tau_1 + hT_N)^+) = I_L(hT_N^+)\exp[-\mu_3\tau_1] = I_L(hT_N^+)\exp[-\mu_3\Delta_0].$$

Similarly, integrating the first equation of model (4) from τ_1+hT_N to τ_2+hT_N yields

$$I_L(t) = I_L((\tau_1 + hT_N)^+)\exp[-\mu_3(t - \tau_1 - hT_N)], \quad t \in (\tau_1 + hT_N, \tau_2 + hT_N].$$

And at time $\tau_2 + hT_N$, it follows that

$$I_L((\tau_2+hT_N)^+) = I_L((\tau_1+hT_N)^+)\exp[-\mu_3\Delta_1] = I_L(hT_N^+)\exp[-\mu_3(\Delta_0+\Delta_1)].$$

By induction, we can see that

$$I_L(t) = I_L(hT_N^+)\exp[-\mu_3(\Delta_0 + \Delta_1 + \cdots + \Delta_{k_p-1})]\exp[-\mu_3(t - \tau_{k_p} - hT_N)],$$

for all $t \in (\tau_{k_p} + hT_N, (h+1)T_N]$. At time $(h+1)T_N$, then IL-2 is injected once and

$$I_L((h+1)T_N^+) = I_L(hT_N^+)\exp[-\mu_3 T_N] + s_2.$$

Denote $I_h = I_L(hT_N^+)$, then we have the following difference equation:

$$I_{h+1} = \exp[-\mu_3 T_N]I_h + s_2,$$

solving the equation yields a unique steady state:

$$I_L^* = \frac{s_2}{1 - \exp[-\mu_3 T_N]}.$$

Clearly, $\exp[-\mu_3 T_N] < 1$, therefore, system (4) has a globally stable T_N periodic solution (denoted by $I_L^{T_N}(t)$), which can be calculated as follows:

$$I_L^{T_N}(t) = \begin{cases} I_L^* \exp[-\mu_3(t - hT_N)], & t \in (hT_N, \tau_1 + hT_N], \\ I_L^* \exp[-\mu_3\Delta_0] \exp[-\mu_3(t - \tau_1 - hT_N)], \\ t \in (\tau_1 + hT_N, \tau_2 + hT_N], \\ \vdots \\ I_L^* \exp[-\mu_3 \sum_{i=0}^{k_p-1} \Delta_i] \exp[-\mu_3(t - \tau_{k_p} - hT_N)], \\ t \in (\tau_{k_p} + hT_N, (h+1)T_N]. \end{cases} \tag{A.1}$$

Substituting $I_L^{T_N}(t)$ into the first equation of (3) for $I_L(t)$, we have

$$\begin{cases} \dfrac{dE(t)}{dt} = E\left(-\mu_2 + \dfrac{p_1 I_L^{T_N}(t)}{g_1 + I_L^{T_N}(t)}\right), \quad t \neq \tau_n, t \neq \lambda_m, \\ E(\tau_n^+) = E(\tau_n) + s_1, \qquad t = \tau_n, \\ E(\lambda_m^+) = E(\lambda_m), \qquad t = \lambda_m, \end{cases} \tag{A.2}$$

Then integrating the first equation of system (A.2) from hT_N to $\tau_1 + hT_N$ yields

$$\begin{aligned} E(t) &= E(hT_N^+) \exp\left(\int_{hT_N^+}^t \left(-\mu_2 + \tfrac{p_1 I_L^{T_N}(s)}{g_1 + I_L^{T_N}(s)}\right) ds\right) \\ &= E(hT_N^+) \exp[-\mu_2(t - hT_N)] \exp\left(p_1 \int_{hT_N^+}^t \tfrac{I_L^{T_N}(s)}{g_1 + I_L^{T_N}(s)} ds\right). \end{aligned} \tag{A.3}$$

From system (4), when $hT_N^+ \leq b_1 \leq b_2 \leq (\tau_1 + hT_N)$, we have

$$\begin{aligned} \exp\left(p_1 \int_{b_1}^{b_2} \tfrac{I_L^{T_N}(t)}{g_1 + I_L^{T_N}(t)} dt\right) &= \exp\left(\tfrac{-p_1}{\mu_3} \int_{b_1}^{b_2} \tfrac{-\mu_3 I_L^{T_N}(t)}{g_1 + I_L^{T_N}(t)} dt\right) \\ &= \exp\left(\tfrac{-p_1}{\mu_3} \int_{b_1}^{b_2} \left(\tfrac{d \ln(g_1 + I_L^{T_N}(t))}{dt}\right) dt\right) \\ &= \exp\left(\tfrac{-p_1}{\mu_3} \ln\left(\tfrac{g_1 + I_L^{T_N}(b_2)}{g_1 + I_L^{T_N}(b_1)}\right)\right) \\ &= \left(\tfrac{g_1 + I_L^{T_N}(b_2)}{g_1 + I_L^{T_N}(b_1)}\right)^{\frac{-p_1}{\mu_3}}. \end{aligned} \tag{A.4}$$

From equation (A.3) and (A.4), when $hT_N < t \leq (\tau_1 + hT_N)$, it follows that

$$E(t) = E(hT_N^+)\exp[-\mu_2(t-hT_N)]\left(\frac{g_1+I_L^{T_N}(t)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}}.$$

At time $\tau_1 + hT_N$, ACI is applied once and

$$E((\tau_1+hT_N)^+) = E(hT_N^+)\exp(-\mu_2\Delta_0)\left(\frac{g_1+I_L^{T_N}(\tau_1+hT_N)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}} + s_1.$$

Again, integrating the first equation of system (A.2) from τ_1+hT_N to τ_2+hT_N yields

$$\begin{aligned} E(t) &= E((\tau_1+hT_N)^+)\exp[-\mu_2(t-\tau_1-hT_N)]\left(\frac{g_1+I_L^{T_N}(t)}{g_1+I_L^{T_N}((\tau_1+hT_N)^+)}\right)^{\frac{-p_1}{\mu_3}} \\ &= E(hT_N^+)\exp[-\mu_2(\Delta_0+t-\tau_1-hT_N)]\left(\frac{g_1+I_L^{T_N}(t)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}} \\ &+ s_1\exp[-\mu_2(t-\tau_1-hT_N)]\left(\frac{g_1+I_L^{T_N}(t)}{g_1+I_L^{T_N}((\tau_1+hT_N)^+)}\right)^{\frac{-p_1}{\mu_3}}, \end{aligned}$$

At time $\tau_2 + hT_N$, ACI is applied again and it is easy to get $E((\tau_2+hT_N)^+)$,

$$\begin{aligned} E((\tau_2+hT_N)^+) &= E(hT_N^+)\exp[-\mu_2(\Delta_0+\Delta_1)]\left(\frac{g_1+I_L^{T_N}((\tau_2+hT_N)^+)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}} \\ &+ s_1\left(1+\exp(-\mu_2\Delta_1)\left(\frac{g_1+I_L^{T_N}((\tau_2+hT_N)^+)}{g_1+I_L^{T_N}((\tau_1+hT_N)^+)}\right)^{\frac{-p_1}{\mu_3}}\right), \end{aligned}$$

by induction, we can see that

$$\begin{aligned} E(t) = E(hT_N^+)\exp(-\mu_2(\sum_{i=0}^{k_p-1}\Delta_i))\exp(-\mu_2(t-\tau_{k_p}-hT_N))\left(\frac{g_1+I_L^{T_N}(t)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}} \\ +s_1A, \end{aligned}$$

for all $t \in (\tau_{k_p}+hT_N, (h+1)T_N]$, where

$$A = \sum_{i=1}^{k_p}\exp(-\mu_2(t-\tau_i-hT_N))\left(\frac{g_1+I_L^{T_N}(t)}{g_1+I_L^{T_N}((\tau_i+hT_N)^+)}\right)^{\frac{-p_1}{\mu_3}}.$$

At time $(h+1)T_N$, ACI is not applied, and we get $E((h+1)T_N^+)$,

$$E((h+1)T_N^+) = E(hT_N^+)\exp(-\mu_2 T_N)\left(\frac{g_1+I_L^{T_N}((h+1)T_N^+)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}} + s_1 A_1,$$

where

$$A_1 \;=\; \sum_{i=1}^{k_p}\exp(-\mu_2(T_N-\tau_i))\left(\frac{g_1+I_L^{T_N}((h+1)T_N^+)}{g_1+I_L^{T_N}((\tau_i+hT_N)^+)}\right)^{\frac{-p_1}{\mu_3}}.$$

Denote $E_h = E(hT_N^+)$, then we get the following difference equation:

$$E_{h+1} = E_h\exp(-\mu_2 T_N)\left(\frac{g_1+I_L^{T_N}((h+1)T_N^+)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}} + s_1 A_1, \tag{A.5}$$

where

$$s_1A_1>0, \quad \text{and} \quad 0<\exp(-\mu_2 T_N)\left(\frac{g_1+I_L^{T_N}((h+1)T_N^+)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}}<1,$$

then for equation (A.5) there exists a unique positive steady state

$$E^* = \frac{s_1A_1}{1-\exp(-\mu_2T_N)\left(\frac{g_1+I_L^{T_N}((h+1)T_N^+)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}}},$$

consequently, the subsystem (A.2) has a globally stable T_N periodic solution (denote by E^{T_N}), which can be calculated as follows:

$$E^{T_N}(t) = \begin{cases} E_1(t), & t\in(hT_N,\tau_1+hT_N],\\ E_2(t), t\in(\tau_1+hT_N,\tau_2+hT_N],\\ \vdots\\ E_{k_p+1}(t), t\in(\tau_{k_p}+hT_N,(h+1)T_N], \end{cases} \tag{A.6}$$

where

$$E_1(t) \;=\; E^*\exp[-\mu_2(t-hT_N)]\left(\frac{g_1+I_L^{T_N}(t)}{g_1+I_L^{T_N}(hT_N^+)}\right)^{\frac{-p_1}{\mu_3}},$$

$$
\begin{aligned}
E_2(t) &= E^* \exp[-\mu_2(\Delta_0 + t - \tau_1 - hT_N)] \left(\frac{g_1 + I_L^{T_N}(t)}{g_1 + I_L^{T_N}(hT_N^+)} \right)^{\frac{-p_1}{\mu_3}} \\
&+ s_1 \exp[-\mu_2(t - \tau_1 - hT_N)] \left(\frac{g_1 + I_L^{T_N}(t)}{g_1 + I_L^{T_N}((\tau_1 + hT_N)^+)} \right)^{\frac{-p_1}{\mu_3}},
\end{aligned}
$$

and

$$
\begin{aligned}
E_{k_p+1}(t) = E^* \exp[-\mu_2(\sum_{i=0}^{k_p-1} \Delta_i)] \exp(-\mu_2(t - \tau_{k_p} - hT_N)) \left(\frac{g_1 + I_L^{T_N}(t)}{g_1 + I_L^{T_N}(hT_N^+)} \right)^{\frac{-p_1}{\mu_3}} \\
+ s_1 A.
\end{aligned}
$$

Appendix B. Analyzing system (3) for Case 2

Here, we investigate the periodic solution of subsystem (5). We consider any given time interval $(hT_p, (h+1)T_p]$, where h is a positive integer. Integrating the first equation of system (5) from hT_p to $\lambda_1 + hT_p$ yields

$$
I_L(t) = I_L(hT_p^+) \exp[-\mu_3(t - hT_p)], \quad t \in (hT_p, \lambda_1 + hT_p].
$$

At time $\lambda_1 + hT_p$, input of IL-2 occurs and

$$
I_L((\lambda_1 + hT_p)^+) = I_L(hT_p^+) \exp(-\mu_3 \lambda_1) + s_2 = I_L(hT_p^+) \exp(-\mu_3 \Delta_0) + s_2.
$$

Similarly, integrating the first equation of model (5) from $\lambda_1 + hT_p$ to $\lambda_2 + hT_p$ yields

$$
\begin{aligned}
I_L(t) &= I_L((\lambda_1 + hT_p)^+) \exp[-\mu_3(t - \lambda_1 - hT_p)] \\
&= (I_L(hT_p^+) \exp(-\mu_3 \Delta_0) + s_2) \exp[-\mu_3(t - \lambda_1 - hT_p)],
\end{aligned}
$$

where $t \in (\lambda_1 + hT_p, \lambda_2 + hT_p]$. And at time $\lambda_2 + hT_p$, IL-2 is injected again and

$$
\begin{aligned}
I_L((\lambda_2 + hT_p)^+) &= I_L((\lambda_1 + hT_p)^+) \exp[-\mu_3 \Delta_1] + s_2 \\
&= I_L(hT_p^+) \exp[-\mu_3(\Delta_0 + \Delta_1)] + s_2 \exp(-\mu_3 \Delta_1) + s_2,
\end{aligned}
$$

By induction, we can see that

$$
I_L(t) = \left(I_L(hT_p^+) \exp\left(-\mu_3 \left(\sum_{i=0}^{k_N - 1} \Delta_i \right) \right) + B \right) \exp[-\mu_3(t - \lambda_{k_N} - hT_p)],
$$

for all $t \in (\lambda_{k_N} + hT_p, (h+1)T_p]$, where

$$B = s_2 \left(\exp(-\mu_3(\sum_{i=1}^{k_N-2} \Delta_i)) + \exp(-\mu_3(\sum_{j=2}^{k_N-2} \Delta_j)) + \cdots + \exp(-\mu_3 \Delta_{k_N-2}) \right).$$

At time $(h+1)T_p$, there is no IL-2 injected and

$$\begin{aligned} I_L((h+1)T_p^+) &= I_L(hT_p^+)\exp[-\mu_3 T_p] + s_2[\exp(-\mu_3(\sum_{i=1}^{k_N-1} \Delta_i)) \\ &\quad + \exp(-\mu_3(\sum_{j=2}^{k_N-1} \Delta_j)) + \cdots + \exp(-\mu_3 \Delta_{k_N-1})] \\ &= I_L(hT_p^+)\exp[-\mu_3 T_p] + B_1. \end{aligned}$$

Denote $I_h = I_L(hT_p^+)$, then we have the following difference equation:

$$I_{h+1} = \exp[-\mu_3 T_p] I_h + B_1,$$

solving the equation yields a unique positive steady state:

$$I_L^* = \frac{B_1}{1 - \exp[-\mu_3 T_p]}.$$

Clearly, $B_1 > 0$ and $\exp[-\mu_3 T_p] < 1$ always holds, therefore, system (5) has a globally stable T_p periodic solution (denoted by $I_L^{T_p}(t)$), which can be calculated as follows:

$$I_L^{T_p}(t) = \begin{cases} I_L^* \exp[-\mu_3(t - hT_p)], & t \in (hT_p, \lambda_1 + hT_p], \\ (I_L^* \exp(-\mu_3 \Delta_0) + s_2)\exp[-\mu_3(t - \lambda_1 - hT_p)], \\ t \in (\lambda_1 + hT_p, \lambda_2 + hT_p], \\ \vdots \\ \left(I_L^* \exp[-\mu_3(\sum_{i=1}^{k_N-1} \Delta_i)] + B \right) \exp[-\mu_3(t - \lambda_{k_N} - hT_p)], \\ t \in (\lambda_{k_N} + hT_p, (h+1)T_p], \end{cases} \tag{B.1}$$

Substituting $I_L^{T_p}(t)$ into the first equation of (3) for $I_L(t)$, we have

$$\begin{cases} \dfrac{dE(t)}{dt} = E\left(-\mu_2 + \dfrac{p_1 I_L^{T_p}(t)}{g_1 + I_L^{T_p}(t)} \right), & t \neq \tau_n, t \neq \lambda_m, \\ E(\lambda_m^+) = E(\lambda_m), & t = \lambda_m, \\ E(\tau_n^+) = E(\tau_n) + s_1, & t = \tau_n, \end{cases} \tag{B.2}$$

then integrating the first equation of (B.2) from hT_p to $\lambda_1 + hT_p$ yields

$$E(t) = E(hT_p^+)\exp[-\mu_2(t - hT_p)]\left(\frac{g_1+I_L^{T_p}(t)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}}.$$

obviously,

$$E((\lambda_1 + hT_p)^+) = E(hT_p^+)\exp(-\mu_2\Delta_0)\left(\frac{g_1+I_L^{T_p}((\lambda_1+hT_p)^+)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}}.$$

Again, integrating the first equation of (B.2) from $\lambda_1 + hT_p$ to $\lambda_2 + hT_p$ yields

$$\begin{aligned} E(t) &= E((\lambda_1 + hT_p)^+)\exp[-\mu_2(t - \lambda_1 - hT_p)]\left(\frac{g_1+I_L^{T_p}(t)}{g_1+I_L^{T_p}((\lambda_1+hT_p)^+)}\right)^{\frac{-p_1}{\mu_3}} \\ &= E(hT_p^+)\exp[-\mu_2(\Delta_0 + t - \lambda_1 - hT_p)]\left(\frac{g_1+I_L^{T_p}(t)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}}, \end{aligned}$$

at time $\lambda_2 + hT_p$, it is easy to get $E((\lambda_2 + hT_p)^+)$,

$$E((\lambda_2 + hT_p)^+) = E(hT_p^+)\exp[-\mu_2(\Delta_0 + \Delta_1)]\left(\frac{g_1+I_L^{T_p}((\lambda_2+hT_p)^+)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}}.$$

By induction, we can see that

$$E(t) = E(hT_p^+)\exp\left(-\mu_2(\sum_{i=0}^{k_N-1}\Delta_i)\right)\exp(t - \lambda_{k_N} - hT_p)\left(\frac{g_1+I_L^{T_p}(t)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}},$$

for all $t \in (\lambda_{k_N} + hT_p, (h+1)T_p]$. At time $(h+1)T_p$, ACI is applied once, and we get

$$E((h+1)T_p^+) = E(hT_p^+)\exp(-\mu_2 T_p)\left(\frac{g_1+I_L^{T_p}((h+1)T_p^+)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}} + s_1,$$

Denote $E_h = E(hT_p^+)$, then we get the following difference equation:

$$E_{h+1} = E_h\exp(-\mu_2 T_p)\left(\frac{g_1+I_L^{T_p}((h+1)T_p^+)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}} + s_1, \qquad \text{(B.3)}$$

where

$$0 < \exp(-\mu_2 T_p)\left(\frac{g_1 + I_L^{T_p}((h+1)T_p^+)}{g_1 + I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}} < 1.$$

Then for equation (B.3) there exists a unique steady state

$$E^* = \frac{s_1}{1 - \exp(-\mu_2 T_p)\left(\frac{g_1+I_L^{T_p}((h+1)T_p^+)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}}},$$

consequently, the subsystem (B.2) has a globally stable T_p periodic solution (denote by E^{T_p}), which can be calculated as follows:

$$E^{T_p}(t) = \begin{cases} E_1^1(t), & t \in (hT_p, \lambda_1 + hT_p], \\ E_2^1(t), t \in (\lambda_1 + hT_p, \lambda_2 + hT_p], \\ \vdots \\ E_{k_N+1}^1(t), t \in (\lambda_{k_N} + hT_p, (h+1)T_p], \end{cases} \tag{B.4}$$

where

$$E_1^1(t) = E^* \exp[-\mu_2(t - hT_p)]\left(\frac{g_1+I_L^{T_p}(t)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}},$$

$$E_2^1(t) = E^* \exp[-\mu_2(\Delta_0 + t - \lambda_1 - hT_p)]\left(\frac{g_1+I_L^{T_p}(t)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}},$$

and

$$E_{k_N+1}^1(t) = E^* \exp\left(-\mu_2(\sum_{i=0}^{k_N-1}\Delta_i)\right)\exp(t - \lambda_{k_N} - hT_p)\left(\frac{g_1+I_L^{T_p}(t)}{g_1+I_L^{T_p}(hT_p^+)}\right)^{\frac{-p_1}{\mu_3}}.$$

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1. We develop a novel mathematical model that describes the tumor-immune interaction with pulsed immunotherapy.

2. The existence and stability of the tumor free periodic solution are addressed.

3. The effects of ACI associated or not with IL-2 on immunotherapy are investigated numerically in detail.

4. The results showed that the tumor can be eradicated or controlled with combined therapies.