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Dynamic aspects of tumour–immune system interaction under a periodic immunotherapy

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We study a mathematical model proposed in the literature with the aim of describing the interactions between tumor cells and the immune system, when a periodic treatment of immunotherapy is applied. Combining some techniques from non-linear analysis (degree theory, lower and upper solutions, and theory of free-homeomorphisms in the plane), we give a detailed global analysis of the model. We also observe that for certain therapies, the maximum level of aggressiveness of a cancer, for which the treatment works (or does not work), can be computed explicitly. We discuss some strategies for designing therapies. The mathematical analysis is completed with numerical results and conclusions.

Key words: Tumour, immune system, interacting populations, periodic therapies, global dynamics

2020 Mathematics Subject Classification: 37N25, 37C70, 37E30 (Primary); 47H11, 37C25 (Secondary)

1 Introduction

Biological tissue is composed by cells and their molecular products. These cells grow and die in mass following a determined pattern. However, cancer begins when the cells of a tissue proliferate in an uncontrolled manner. This fast growth produces an accumulation of cells in the affected area which turns out in the so-called tumour cells. During this period, new tumour cells variant may emerge with various mutations which further increase the overall resistance to immune attack and invade new healthy tissues.

Developing dynamical models which can be employed to describe and predict a tumour evolution has been the focus of a considerable amount of research papers in recent decades (see, e.g., [2, 3, 4, 8, 18, 19, 20, 21, 28, 29, 33, 35, 37, 39, 42, 43, 48, 51, 52, 53, 54, 55, 56]). The majority of these works are based on mathematical models describing the competition interaction between immune cells and cancer cells, which can be described by a system of Lotka–Volterra type equations (see, e.g., [18, 19, 20, 21, 28, 37, 39, 41, 48, 51, 52, 56]). Analysing the most known finite dimensional models in the literature (in the absence of therapy), one may observe the following features:

- Existence of a tumour-free equilibrium (that is a certain state where the immune cells exist in the absence of the tumour cells).

- Depending on the biological parameters involving the interaction between the immune and tumour system, there is a possibility that the tumour size may tend to $+\infty$.
- Possible existence of a small size tumour equilibrium which coexists with the tumour-free one.

Oncology is not sufficient to explain these basic phenomena, and it also requires strategies to better fight and hopefully eradicate the disease [16, 23]. The efforts in this direction are focused in combining therapies from different orientations. The most known are the so-called *hormonal therapies, chemotherapies, radiotherapies, targeted therapies* and *the immunotherapy*. However, if one adds a therapy in the above-mentioned models, many complex dynamical properties appear. In this framework, it is hard to find explicitly the domains of attraction for the tumour non-linear dynamics and so looking for its possible eradication.

Focusing our attention on the immunotherapy models, in [51], the authors proposed a Volterra-like model to study the interaction between a population of tumour cells (denoted by X) and a population of immune cells (denoted by Y) defined by:

$$\begin{aligned} X' &= aX - bXY, \\ Y' &= dXY - fY - \kappa X + u + \theta(\omega\tau). \end{aligned} \tag{1.1}$$

For the tumour cells, assumed a growth rate proportional to X and the rate of death is proportional to the interaction rate between the tumour cells and the immune cells. The growth rate of immune cells is proportional to the interaction with tumour cells and also to the flux per unit time of immune cells to the place of interaction. This last term characterises the diffusion process of immune cells that takes place in the surroundings of the tumour assuming a constant immune cells flux. The decrease rate depends on two factors, natural death and growth of tumour cells related to the effective area of tumour interacting directly with the immune cells. In order to introduce the effects produced by the treatment with cytokines (a type of immunotherapy) in the process of activation of the immune system, a periodic function is added that imitates the periodic dosage.

This model has been studied in depth both in the case of absence of therapy and in the case of a particular therapy using as a test function $\theta(\tau) := 0.5A(1 + \cos(4\pi\tau\nu))$, with $\nu > 0$. The studies show that the model fits data well from experimental and *in vivo* tumours in early stage (see, e.g., [38]), but it is physically inconsistent if the tumour size is large (see [19]). However, this model was of great interest because it connects the killing of immune cells with a function depending on the size tumour, which may cause in some cases generalised immunosuppression (see, e.g., [13, 49] and their references).

Inspired by this model, A. d'Onofrio suggested in [19] a general family of models based on this consideration (a general influx function in the immune system) and including other biologically reasonable classic models. That is,

$$\begin{aligned} X' &= X(\alpha\xi(X) - \phi(X)Y), \\ Y' &= -\Psi(X)Y + \nu g(X) + \theta(\omega\tau), \end{aligned} \tag{1.2}$$

X and Y are variables interpreted as in the Sotolongo model. The biological meaning of the functions appearing are summarized in Table 1.

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Table 1. *Definition of the parameters in model* (1.2)*, where* $\Psi(X) = \mu(X) - \beta(X)$

Functions	Biological meaning
$\alpha\xi(X)$	Growth rate of the tumour
$\phi(X)Y$	Functional response
$g(X)$	External inflow of effector cells
$\beta(X)$	Tumour-stimulated proliferation rate of effector cells
$\mu(X)$	Tumour-induced loss of effector cells
$\nu g(X)$	Influx of effector cells
$\theta(\omega t)$	Immunotherapy

Table 2. *Definition of the parameters in model* (1.3)*, where* $\ell = d - \kappa$

Parameter	Biological meaning
a	Intrinsic growth rate of the tumour
b	Death malignant cells rate due to interaction with lymphocyte cells
d	Increased lymphocyte rate due to interaction with malignant cells
f	Death rate of the lymphocytes
κ	Immunosuppression coefficient
$\nu g(X)$	Influx external of effector cells
ω	Immunotherapy dosage frequency

Depending on the parameter Ψ, a cancer can be classified by its degree of aggressiveness against the immune system (see [22, p. 616]): if $\Psi(X) > 0$, the cancer is considered highly aggressive; on the contrary, if $\Psi(X)$ changes sign, it is lowly aggressive.

The objective of this paper is to study in depth a particular case of (1.2) and using this model to analyse the global dynamical behaviour of an aggressive cancer which fits well with its biological parameters. In particular, we shall analyse the model:

$$\begin{aligned} X' &= aX - bXY, \\ Y' &= \ell XY - fY + \nu g(X) + \theta(\omega\tau), \end{aligned} \tag{1.3}$$

where $\ell < 0$ (notice that here $\Psi(X) := f - \ell X$), θ is a non-negative τ_*-periodic therapy and $g : [0, +\infty) \to (0, +\infty)$ is a decreasing function satisfying

$$g(0) = 1, \qquad \lim_{X \to +\infty} g(X) = 0. \tag{1.4}$$

The parameters and their biological meaning of the system (1.3) are summarised in Table 2.

This paper is organised as follows. After this introduction and statements of the main result (see Section 2), in Section 3, we discuss some basic questions about the solutions of the Cauchy problem for (1.3). In Section 4, we explicitly compute the varying tumour-free solution and we investigate its local stability; it is here where we prove Theorem 1 (see Section 4.2). Section 5 is dedicated to analyse the coexistence state between tumour and immune cells to provide the proofs of Theorems 2 and 3 (see Section 5.3). This is where one needs to apply some techniques from non-linear analysis (degree theory, lower and upper solutions, and free-homeomorphism theory). In Section 6, we use all the information obtained up to that moment in order to prove Theorems 4

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and 5 (see Remarks 5 and 6, respectively). We close this section with various examples, showing the applicability of these results with particular therapies. We finalise this paper with a final section of conclusions with numerical results.

2 Statements of the main results

In this model, there is a periodically varying tumour-free solution of the form $(0, Y_P(\tau))$, where $Y_P(\tau)$ is the unique $\tau_*/\omega-$periodic solution of the linear equation:

$$Y' = -fY + \theta(\omega\tau) + \nu.$$

The result below shows that the local behaviour of this solution is in accordance with the clinical evidences, displaying that in some cases the immune system is able to eliminate small tumours (see, e.g., [6]). Precisely, we will discuss the conditions under which this solution is asymptotically stable or unstable. To formulate this result, we introduce the number:

$$\overline{\theta} := \frac{1}{\tau_*}\int_0^{\tau_*} \theta(s)ds.$$

Theorem 1 *There exists* $(X_P, Y_P) : \mathbb{R} \to \mathbb{R}^2$ *a unique* $\tau_*/\omega-$*periodic solution of* (1.3) *lying in the first quadrant of the plane, such that* $\min_{\tau\in\mathbb{R}} X_P(\tau) = 0$ *(and hence* $X_P \equiv 0$*). Moreover, assuming that*

$$\overline{\theta} > \frac{af - \nu b}{b}, \tag{2.1}$$

the solution is asymptotically stable. Otherwise, it is unstable if

$$\overline{\theta} < \frac{af - \nu b}{b}. \tag{2.2}$$

We will prove this result in Section 3. under a general framework, that is, here we still do not require that $\ell < 0$. Moreover, following the terminology adopted in [19], from Theorem 1, we point out that if $\frac{af}{\nu b} < g(0) = 1$ the immune system works well and it is able to destroy small tumours in absence of therapy (i.e., tumour-free equilibrium is asymptotically stable when $\theta = 0$); or on the contrary, there is immunosuppression (i.e., tumour-free equilibrium is unstable when $\theta = 0$) if $\frac{af}{\nu b} > g(0) = 1$.

Following our study, we will assume from now on that $\ell < 0$. In this setting, the stimulation of the immune system by an external treatment in such a way that (2.1) holds can lead to a periodic coexistence state (the tumour and immune cells are uniformly persistent in time). The result below also asserts that the occurrence of such a cancer-present state depends strongly on the initial population size of these cells.

Theorem 2 *There exists* $(X_T, Y_T) : \mathbb{R} \to \mathbb{R}^2$ *a* $\tau_*/\omega-$*periodic solution of* (1.3) *such that*

$$\min_{\tau\in\mathbb{R}} X_T(\tau) > 0, \qquad \min_{\tau\in\mathbb{R}} Y_T(\tau) \geq 0, \tag{2.3}$$

if and only if (2.1) *holds. Moreover,* (X_T, Y_T) *is the unique solution of* (1.3) *satisfying this property.*

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Although this statement could be regarded as a mathematical curiosity rather than a biological relevant state, it will play a crucial role to understand the global dynamics of this model. Indeed, depending on the initial population size of tumour and immune cells before starting with a treatment, the model exhibits one of the following dynamics:

- The population of tumour cells will grow uncontrollably.
- The population of tumour cells will disappear.
- The population of tumour cells will tend to the above-mentioned periodic coexistence state, which will be denoted by (X_T, Y_T) from now on.

To state this result rigorously, we introduce some notation. In what follows, we denote by $(X(\tau, X_0, Y_0), Y(\tau, X_0, Y_0))$ the unique solution of the Cauchy problem for the equation (1.3); that is, the solution of (1.3) satisfying $X(0) = X_0$ and $Y(0) = Y_0$. Biologically, $X_0 \geq 0$ (resp. $Y_0 \geq 0$) is connected with the population size of tumour cells (resp. immune cells) just before starting with the therapy. Hence, $X(\tau, X_0, Y_0)$ (resp. $Y(\tau, X_0, Y_0)$) is connected with the number of tumour cells (resp. immune cells) at time $\tau \geq 0$. Now we can set the following result.

Theorem 3 *Assume* (2.1). *Then, there exist* $0 \leq Z_0 < Z_1 \leq +\infty$, *an interval* $J \subseteq \mathbb{R}$ *and a continuous function* $\hat{\Phi} : J \to \mathbb{R}$ *which is increasing such that its graph:*

$$W := \left\{ (X, \hat{\Phi}(X)) : X \in J \right\},$$

divides the first quadrant of the plane into two regions:

$$D_- := \{(X, Y) : Y > \hat{\Phi}(X)\} \cup (0, Z_0) \times [0, +\infty),$$
$$D_+ := \{(X, Y) : Y < \hat{\Phi}(X)\} \cup [Z_1, +\infty) \times [0, +\infty).$$

Here either $J = [Z_0, Z_1)$ *if* $Z_0 > 0$ *or* $J = (0, Z_1)$ *otherwise. These regions determine the dynamics of the solutions to the system* (1.3) *in the following way:*

- *If* $(X_0, Y_0) \in D_- \implies X(\tau, X_0, Y_0) \to 0$ *as* $\tau \to +\infty$.
- *If* $(X_0, Y_0) \in D_+ \implies X(\tau, X_0, Y_0) \to +\infty$ *as* $\tau \to +\infty$.
- *If* $(X_0, Y_0) \in W \implies |X_T(\tau) - X(\tau, X_0, Y_0)| + |Y_T(\tau) - Y(\tau, X_0, Y_0)| \to 0$ *as* $\tau \to +\infty$.

After proving this theorem in Section 5, we can distinguish four dynamical cases where the expectancies of cure are qualitatively different (see Figure 4). However, if one desires to obtain quantitative implications in oncology, from an analytical point of view, the set W has to be analysed. As we will see, this is where determined characteristics of the therapy will play an important role.

In what follows, we shall consider the function:

$$p : \mathbb{R} \to \mathbb{R}, \qquad p(t) := \frac{af - b\theta\left(\frac{\omega t}{a}\right)}{a^2}. \tag{2.4}$$

The result below shows that if

$$\limsup_{t \to +\infty} \frac{1}{t} \int_0^t \int_0^s p(r) dr ds < +\infty \tag{2.5}$$

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we can discard the cases (a) and (b) in Figure 4. Condition (2.5) is strongly connected with the type of therapy applied in the region affected by the cancer and whereas it is not true that all therapies verifying (2.1) satisfy (2.5), it is true that many do so increasing its intensity.

Theorem 4 *Suppose* (2.5) *and*

$$\theta_{min} := \min_{t\in\mathbb{R}} \theta(t) > \frac{af - \nu b}{b}.$$

Then the following estimate holds

$$Z_0 \geq \widetilde{x}\, e^{-\frac{2a(1+p^*)}{f}} > 0.$$

Here, $\widetilde{x}$ *is implicitly defined by:*

$$g(\widetilde{x}) - \frac{|\ell| a}{\nu b}\widetilde{x} = \max\left\{\frac{af - b\theta_{min}}{\nu b}, 0\right\}, \text{ and } p^* := \sup_{t\in[0,+\infty)} \frac{1}{t}\int_0^t \int_0^s p(r)drds.$$

In order to understand the applicability of this result, it is useful to introduce the number:

$$\mu_* := \widetilde{x} e^{-\frac{2a(1+p^*)}{f}}, \tag{2.6}$$

where $\widetilde{x} > 0$ and $0 \leq p^* < +\infty$ are defined by Theorem 4. This number is explicit and it can be computed taking into account the characteristics of the detected cancer. Its main property consists in estimating analytically the effectiveness of a treatment with the characteristics of Theorem 4, by knowing the type of cancer and the sizes of populations involved, just before to start it. Indeed, denoting by $X_0 \geq 0$ the initial population size of tumour cells, under the assumptions of Theorem 4, if $X_0 \leq \mu_*$ then either the cancer will disappear or (only if $X_0 = \mu_*$) the cancer may tend towards a coexist state with the immune cells (see Figure 1).

In contrast with some studies in the literature dealing with non-aggressive tumours, Theorem 3 shows that the immunotherapy is not able to guarantee the global eradicability of a highly aggressive tumour without depending on the initial values X_0 and Y_0. However, Theorem 4 connects well with such studies through the following corollary:

Corollary 1 *Assume that*

$$\theta_{min} \geq \frac{af}{b}. \tag{2.7}$$

Then, $\mu_* \to +\infty$ *as* $\frac{\nu b}{|\ell|} \to +\infty$.

This result asserts that the expectancies of cure to a treatment satisfying (2.7) increase as the value $\frac{\nu b}{|\ell|}$ grows, becoming arbitrary large if $\frac{\nu b}{|\ell|}$ is so. In particular, Corollary 1 connects with [22, Proposition 7.1], which may be formulated in our setting as:

Theorem (d'Onofrio [22]) *Assume* (2.7) *and* $\ell = 0$. *Then under a therapy modelled by* θ, *the tumour cells will be eradicated independently from the initial tumour burden.*

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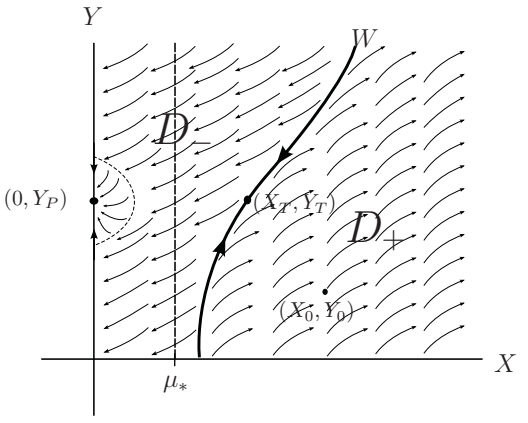

FIGURE 1. The $x-$ and $y-$ axes are connected with the variables X and Y of the model (1.3), respectively, that is, indicates the amount of initial tumour and immune cells coexisting in the affected region before starting the therapy. The asymptotic behaviour of a solution of the form $(X(\tau, X_0, Y_0), Y(\tau, X_0, Y_0))$ is shown in the image with a black arrow that begins from the point (X_0, Y_0), being particularly relevant to the asymptotic behaviour of $X(\tau, X_0, Y_0)$ as $\tau \to +\infty$ (see Theorem 3). In this sense, the points (X_T, Y_T) and $(0, Y_P)$ are the initial states that lead to two periodically varying solutions: the first one is connected with a cancer-present solution, whereas the second one is connected with a tumour-free solution. Finally, μ_* estimates analytically the density of tumour cells that a patient with cancer should initially have to improve during the treatment period.

An analogous study reveals that under the condition:

$$\liminf_{t\to+\infty} \frac{1}{t} \int_0^t \int_0^s p(r)drds > -\infty \tag{2.8}$$

one may discard the cases 4b and 4d shown in Figure 4. In this setting, Z_1 defined in Theorem 3 can be estimated. In fact, we can provide even more information estimating the function $\hat{\Phi}$ (introduced in Theorem 3) in a neighbourhood of Z_1.

Theorem 5 *Suppose* (2.1) *and* (2.8). *Then either*

$$Z_1 \leq \widehat{x}\, e^{\frac{2a|p_*|}{f}} < +\infty$$

or

$$\hat{\Phi}(X) \geq \frac{a}{b}\left(1 - |p_*| + \frac{f}{2a} \ln\left(\frac{X}{\widehat{x}}\right)\right) \quad \textit{for } X \in \left(\widehat{x}e^{\frac{2a|p_*|}{f}}, Z_1\right).$$

Here, $\widehat{x}$ *is implicitly defined by:*

$$g(\widehat{x}) - \frac{|\ell|a}{\nu b}\widehat{x} = -\max\left\{\frac{b\theta_{max} - af}{\nu b}, 0\right\}, \textit{ and } p_* := \inf_{t\in[0,+\infty)} \frac{1}{t}\int_0^t \int_0^s p(r)drds,$$

where $\theta_{max} := \max_{t\in\mathbb{R}} \theta(t)$.

In order to discuss this result, it is useful to consider now the number:

$$\mu^* := \widehat{x}e^{\frac{2a|p_*|}{f}}, \tag{2.9}$$

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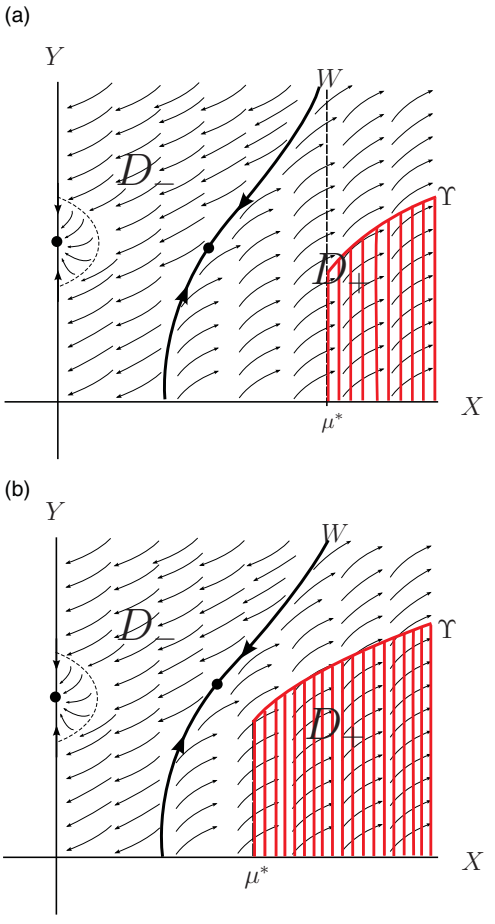

FIGURE 2. Figures 2(a) and (b) graphically show the two possibilities described by Theorem 5. In both cases, the shaded area is included in D_+. Here, $\Upsilon : [\mu^*, +\infty) \to \mathbb{R}$, $\Upsilon(X) := \frac{a}{b}\left(1 - |p_*| + \frac{f}{2a} \ln\left(\frac{X}{\widehat{x}}\right)\right)$.[1]

where $\widehat{x} > 0$ and $-\infty < p_* \leq 0$ are defined by Theorem 5. As in the above case (we refer to Theorem 4), this number is explicit and it can be computed depending on the characteristics of the detected cancer. Intuitively speaking, μ^* is connected with the inefficiency of a treatment of immunotherapy satisfying (2.1) and (2.8), and hence it plays a significant role in the proliferation and invasion of the tumour cells (see Figure 2).

As a consequence of Theorem 5, in terms of μ^*, we can state

Corollary 2 *Suppose* (2.1) *and* (2.8)*. If*

$$X_0 \geq \mu^*, \qquad Y_0 < \frac{a\left(1 - |p_*| + \frac{f}{2a} \ln\left(\frac{X_0}{\widehat{x}}\right)\right)}{b}, \tag{2.10}$$

$X(\tau, X_0, Y_0) \to +\infty$ *as* $\tau \to +\infty$*. In particular,* (2.10) *holds when* $X_0 \geq \mu^*$ *and* $Y_0 < \frac{a}{b}$.

[1]This figure comes from Figure 1, therefore we adopt its elements and terminology for convenience.

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See, for example [22, Section 7] (see also, e.g., [19, Proposition 1]) for more results in this direction.

Before jumping into the next section, we would like to underline the originality of the study also from a theoretical point of view, involving an important topic in mathematics: the *non-linear forced systems*. Some papers\books in this direction are (a not exhaustive list) [1, 9, 10, 11, 12, 14, 15, 24, 25, 26, 30, 31, 34, 36, 40, 44, 47, 50, 57], but there is not a huge literature where a model of this type is globally analysed using topological techniques.

To finish this section, we display a list of notation which is used throughout the paper: $\mathbb{R}$ is the set of real numbers, $\mathbb{R}^+ := (0, +\infty)$, $\mathbb{R}_+ := [0, +\infty)$, $\mathbb{R}^- := (-\infty, 0)$; and for $x \in \mathbb{R}$ we denote by $x^+ := \max\{x, 0\}$ and $x^- := \min\{-x, 0\}$. $C := C([0, T]; \mathbb{R})$, where $T > 0$, is the Banach space of continuous function $u : [0, T] \to \mathbb{R}$ with the norm:

$$\|u\|_\infty := \max\{|u(t)| : t \in [0, T]\};$$

$C(D_1; D_2)$, where $D_1, D_2 \subseteq \mathbb{R}$, is the set of continuous functions $u : D_1 \to D_2$;
$C^1 := C^1([0, T]; \mathbb{R})$ is the Banach space of continuous functions $u : [0, T] \to \mathbb{R}$ with continuous derivative, with the norm $\|u\|_{C^1} := \|u\|_\infty + \|u'\|_\infty$;

$L^1 := L^1([0, T]; \mathbb{R})$ is the Banach space of the integrable functions $u : [0, T] \to \mathbb{R}$ endowed with the norm:

$$\|u\|_1 := \int_0^T |u(s)|ds;$$

If $u \in C$, we denote by

$$m_u := \min_{t\in[0,T]} u(t), \qquad M_u := \max_{t\in[0,T]} u(t);$$

If $u \in C((r_1, r_2); \mathbb{R})$, where $-\infty \le r_1 < r_2 \le +\infty$, then

$$u(r_1^+) := \lim_{t\to r_1^+} u(t), \qquad u(r_2^-) := \lim_{t\to r_2^-} u(t);$$

If $q \in L^1$, we denote by

$$Q_+ := \int_0^T q^+(s)ds, \quad Q_- = \int_0^T q^-(s)ds, \quad Q_* := \max\{Q_+, Q_-\}.$$

The rest of the notation will be given as needed.

To simplify, throughout the article, we will assume that θ is a continuous function. However, experts in differential equations can easily extend the arguments for any bounded function $\theta \in L^\infty$. –

3 A first review of the mathematical model

This section is dedicated to testing two basic results about the solutions of equation (1.3). Here we point out that these results are probably not completely new because they necessarily should have been taken into account in earlier papers when the case was being examined (see e.g., [19, 21, 22]); however, we could not find them in a precise form.

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Lemma 1 *Every solution of* (1.3) *starting in the first quadrant of the plane remains in that region over time.*

Proof From the first equation of (1.3), we obtain that

$$X(\tau) = X(0) \exp\left\{\int_0^\tau (a - bY(s))ds\right\}. \tag{3.1}$$

Hence, $X(\tau) \geq 0$ for all $\tau \geq 0$ where the function X is defined.

We continue now arguing analogously as above but with the second equation of (1.3) in order to obtain that

$$Y(\tau) = \exp\left\{-\int_0^\tau \mu(s)ds\right\}\left(Y(0) + \int_0^\tau (\nu g(X(s)) + \theta(\omega s)) \exp\left\{\int_0^s \mu(r)dr\right\} ds\right), \tag{3.2}$$

where $\mu(s) = -\ell X(s) + f$ and $\tau \geq 0$. Hence, we conclude also that $Y(\tau) \geq 0$. □

Next, we shall show that actually the above-mentioned solutions are defined for all time. This result is stated below.

Lemma 2 *Let* $(X, Y) : [0, \tau_0) \to \mathbb{R}^2$ *be a solution of* (1.3) *defined on its maximal domain. Assuming that*

$$X(0) \geq 0, \qquad Y(0) \geq 0,$$

then $\tau_0 = +\infty$.

Proof We assume, on the contrary, that $\tau_0 \in [0, +\infty)$. Then, one of the following possibilities happens

$$\limsup_{\tau \to \tau_0^-} X(\tau) = +\infty \qquad \text{or} \qquad \limsup_{\tau \to \tau_0^-} Y(\tau) = +\infty.$$

However, taking into account that $Y \geq 0$, in view of (3.1), the first possibility does not occur. Thus, using that the function X is bounded, from (3.2), we conclude that the second possibility neither happens. Hence, we have a contradiction. □

Remark 1 *Notice that if* (X, Y) *is a solution of* (1.3) *such that* $X(\tau_0) = 0$, *then* $X \equiv 0$. *By using a similar argument, in general, it is easy to check that if there exists* $\tau_0 > 0$ *such that* $Y(\tau_0) \geq 0$, *then* $0 \leq Y(\tau) < +\infty$ *for all* $\tau \geq \tau_0$. *However, we cannot assure the non-negativeness of* Y *for times previous to* τ_0.

To close this section, we introduce the following transformation:

$$X = \frac{ax}{\ell}, \quad Y = \frac{ay}{b}, \quad \tau = \frac{t}{a}, \tag{3.3}$$

obtaining that the equation (1.3) can be rewritten as:

$$\begin{aligned} x' &= x - xy, \\ y' &= xy - \alpha y + \rho\widetilde{g}(x) + \gamma\theta(\beta t). \end{aligned} \tag{3.4}$$

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Here, $\alpha := f/a$, $\rho := \nu b/a^2$, $\gamma := b/a^2$, $\beta := \omega/a$ and $\widetilde{g}(x) := g(ax/\ell)$. The new variables are defined in the following region:

$$(\operatorname{sgn}\ell)\, x \geq 0, \qquad y \geq 0, \qquad t \geq 0. \tag{3.5}$$

Furthermore, since θ is τ_*-periodic, with respect to the new variables of the function:

$$t \in [0, +\infty) \mapsto \theta(\beta t),$$

is $T-$periodic, for any $T \in (a\tau_*/\omega)\mathbb{N}$. From now on, we shall refer to the above function as a $T-$periodic function (with $T = a\tau_*/\omega$). It is easy to check that

$$\overline{\theta} = \frac{1}{T}\int_0^T \theta(\beta s)ds. \tag{3.6}$$

In the forthcoming sections, we are taking into account the above discussion and we shall find $T-$periodic solutions of (3.4) in order to prove the main results of this paper.

4 Tumour growth under a periodic therapy. Particular cases

This section is dedicated to the study of the existence and uniqueness of a $\tau_*/\omega-$periodic solution to the equation (1.3) (resp. a $T-$periodic solution to the equation (3.4)) under certain assumptions which simplify the problem. Afterwards, we shall analyse the asymptotic behaviour of such solution. As we mentioned above, throughout this paper, we shall always refer to the number T thinking that $T = a\tau_*/\omega$, and thus (3.6) holds (we will not refer more to this observation).

4.1 Tumour growth under stationary therapy

We study the system under a stationary therapy, that is, $\theta(\beta t) = \overline{\theta} > 0$. With this aim in view, we consider (3.4). In particular, the system has a tumour-free stationary state:

$$P_{\text{free}} := \left(0, \frac{\rho + \gamma\overline{\theta}}{\alpha}\right),$$

for which the Jacobian matrix has the form:

$$J = \begin{pmatrix} 1 - \frac{\rho+\gamma\overline{\theta}}{\alpha} & 0 \\ \\ \frac{\rho+\gamma\overline{\theta}}{\alpha} + \rho\widetilde{g}'(0) & -\alpha \end{pmatrix}.$$

By using the classical theory of stability of the equilibria points for an autonomous system, we can show the following result, which can be seen as a particular case of our Theorem 1.

Corollary 3 *Assume* (2.1). *Then the tumour-free equilibrium point is asymptotically stable. Otherwise, it is unstable when* (2.2) *holds.*

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4.2 Tumour-free equilibrium under non-stationary therapy. Proof of Theorem 1

If for the system (3.4), we have that $x(t) = 0$ (the system is tumour-free), then we obtain the following first order differential equation:

$$y' = -\alpha y + \rho + \gamma\theta(\beta t). \tag{4.1}$$

Direct computations show the following result.

Lemma 3 *For the system (3.4), the solution* $(0, y_P(t))$ *is* $T-$*periodic and lies in the first quadrant of the plane. Here,*

$$y_P(t) = \int_0^t \xi_*(s)e^{\alpha(s-t)}ds + \frac{1}{e^{\alpha T}-1}\int_0^T \xi_*(s)e^{\alpha(s-t)}ds, \tag{4.2}$$

where $\xi_*(t) := \rho + \gamma\theta(\beta t)$ *for every* $t \geq 0$. *This is the unique* $T-$*periodic solution to equation* (4.1).

Lemma 4 *Assume that* (2.1) *(resp.* (2.2)*) holds. Then, the solution* $(0, y_P(t))$ *of* (3.4) *is asymptotically stable (resp. unstable). Here,* $y_P(t)$ *is defined by* (4.2).

Proof If we consider the linearisation of the system (3.4) in a neighbourhood of $(0, y_P(t))$, we obtain

$$\begin{aligned}\varphi_1'(t) &= (1 - y_P(t))\varphi_1(t),\\ \varphi_2'(t) &= (y_P(t) + \rho\widetilde{g}'(0))\varphi_1(t) - \alpha\varphi_2(t).\end{aligned}$$

From the first equation of this system, we can deduce an explicit solution:

$$\varphi_1(t) = \varphi_1(0)\exp\left[\int_0^t (1 - y_P(s))ds\right].$$

Similarly for $\varphi_2(t)$,

$$\varphi_2(t) = e^{-\alpha t}\left(\int_0^t (y_P(s) + \rho\widetilde{g}'(0))\varphi_1(s)e^{\alpha s}ds + \varphi_2(0)\right). \tag{4.3}$$

To prove that $(0, y_P)$ is asymptotically stable it is sufficient to show that

$$\varphi_1(t) \to 0, \qquad \varphi_2(t) \to 0.$$

On the contrary, if some of the above limits is $\pm\infty$, then $(0, y_P)$ is unstable. The remaining of the proof is devoted to check this issue. Indeed, we start by noting that

$$\begin{aligned}\varphi_1(T) &= \varphi_1(0)e^{T(1-\overline{y_P})},\\ \varphi_1(2T) &= \varphi_1(0)e^{2T(1-\overline{y_P})},\\ \varphi_1(3T) &= \varphi_1(0)e^{3T(1-\overline{y_P})},\\ &\vdots\\ \varphi_1(nT) &= \varphi_1(0)e^{nT(1-\overline{y_P})}.\end{aligned} \tag{4.4}$$

On the other hand, since y_P is a $T-$periodic solution of (4.1), by integrating this equation over the interval $[0, T]$ we obtain that

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$$\overline{y_P} = \frac{\rho + \gamma\overline{\theta}}{\alpha}.$$

Now, in view of (2.1) (resp. (2.2)), we deduce that $\overline{y_P} > 1$ (resp. $\overline{y_P} < 1$), whence by (4.4) we prove that $\varphi_1(t) \to 0$ (resp. $|\varphi_1(t)| \to +\infty$) as $t \to +\infty$.

Next, we shall show that $\varphi_2(t) \to 0$. Thus, using a contradiction argument, we assume that $\varphi_2(t) \not\to 0$. Consequently, the function:

$$t \mapsto \varphi_2(0) + \int_0^t (y_P(s) + \rho\widetilde{g}'(0))\varphi_1(s)e^{\alpha s}ds,$$

is unbounded (see (4.3)). However, by applying L'Hôpital's rule, we get

$$\begin{aligned}\lim_{t\to+\infty} \varphi_2(t) &= \lim_{t\to+\infty} \frac{\displaystyle\int_0^t (y_P(s) + \rho\widetilde{g}'(0))\varphi_1(s)e^{\alpha s}ds + \varphi_2(0)}{e^{\alpha t}} \\ &= \lim_{t\to+\infty} \left[\frac{y_P(t) + \rho\widetilde{g}'(0)}{\alpha}\right]\varphi_1(t) \\ &= 0,\end{aligned}$$

a contradiction. The proof is complete. □

To close this section, we prove Theorem 1. We have only to combine Lemmas 3 and 4 and use the transformation (3.3) introduced above.

Proof of Theorem 1 By Lemma 3, let $(0, y_P)$ be a $T-$periodic solution of (3.4). From (3.3), $(0, Y_P)$ is a $\tau_*/\omega-$periodic solution to (1.3). Here, $Y_P(\tau) := ay_P(a\tau)/b$. Thus, according to Lemma 4, if (2.1) (resp. (2.2)) holds then $(0, Y_P)$ is asymptotically stable (resp. unstable).

Finally, we claim that the above-mentioned solution is unique with this property. Indeed, if $(\hat{X}, \hat{Y})$ is a $\tau_*/\omega-$periodic solution of (1.3) with $\min_{\tau\in\mathbb{R}} \hat{X} = 0$, then $\hat{X} \equiv 0$, see Remark 1. By using the transformations in (3.3), $(0, \hat{y})$ is a $T-$periodic solution to (3.4), where $\hat{y}(t) := b\hat{Y}(t/a)/a$. The result follows directly taking into account that y_P is the unique function such that $(0, y_P)$ is a $T-$periodic solution of (3.4), i.e., $y_P \equiv \hat{y}$ and hence $Y_P \equiv \hat{Y}$. The proof is complete. □

5 Tumour growth under a periodic therapy. General case

We turn our attention to the most general case. The key here is that in order to tackle this problem, we need to deal with solutions of (1.3) whose first component is positive. Thus, we henceforth assume that any solution is positive, that is, we shall consider solutions in the form $(X, Y) : [0, +\infty) \to \mathbb{R}^2$ satisfying

$$X(\tau) > 0 \qquad \text{for } \tau \geq 0.$$

After applying the transformation introduced in (3.3), we obtain an equivalent system given by (3.4). Thus, from (3.5), we observe that the new solution $(x, y) : [0, +\infty) \to \mathbb{R}^2$ satisfies

$$(\operatorname{sgn}\ell)x(t) > 0 \qquad \text{for } t \geq 0.$$

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We shall only consider the case when $\ell < 0$. Hence, we deduce that

$$x(t) < 0 \qquad \text{for } t \geq 0.$$

An important tool will be the change of variables

$$z(t) = \ln |x(t)|, \qquad t \geq 0, \tag{5.1}$$

whence it follows that

$$z'(t) = 1 - y(t), \qquad \text{for } t \geq 0. \tag{5.2}$$

This transformation leads to

$$z'' + \mathfrak{f}(z)z' + \mathfrak{h}(z) = p(t). \tag{5.3}$$

Here, the above functions are defined as follows:

$$\begin{aligned} \mathfrak{f} &: \mathbb{R} \to \mathbb{R}, \qquad \mathfrak{f}(z) = \alpha + e^z, \\ \mathfrak{h} &: \mathbb{R} \to \mathbb{R}, \qquad \mathfrak{h}(z) = \rho\widetilde{g}(-e^z) - e^z, \\ p &: \mathbb{R} \to \mathbb{R}, \qquad p(t) = \alpha - \gamma\theta(\beta t). \end{aligned}$$

The first observation is that p is a $T-$periodic function which satisfies

$$\overline{p} := \frac{1}{T}\int_0^T p(s)ds = \alpha - \gamma\overline{\theta}.$$

Moreover, the notation is consistent with (2.4) if we rewrite p in terms of the parameters involved in (1.3). On the other hand, taking into account that $g : [0, +\infty) \to \mathbb{R}$ is a decreasing function, $\mathfrak{h} : \mathbb{R} \to \mathbb{R}$ is decreasing too, and

$$\lim_{z \to +\infty} \mathfrak{h}(z) = -\infty, \qquad \lim_{z \to -\infty} \mathfrak{h}(z) = \rho. \tag{5.4}$$

We also underline that

$$\mathfrak{f}(z) > \alpha > 0, \qquad \text{for } z \in \mathbb{R}.$$

As a final remark, we point out that if $(X, Y) : [0, +\infty) \to \mathbb{R}^2$ is a solution of (1.3) defined in the first quadrant of the plane, then by (5.1) the function z is a solution of (5.3) such that, in view of (5.2), satisfies

$$z'(t) \leq 1 \qquad \text{for } t \in [0, +\infty). \tag{5.5}$$

Conversely, if z is a solution of (5.3) with $z'(0) \leq 1$, then (5.5) holds. Moreover, the function $(X, Y) : [0, +\infty) \to \mathbb{R}^2$, obtained after doing the change of variables (5.1)–(5.2) and (3.3), is a solution of (1.3) defined in the first quadrant of the plane. Consequently, there exists a strength connection between the solutions of (1.3) with biological meaning and the solutions of (5.3) satisfying (5.5). This property is crucial and will be used throughout this work.

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5.1 Setting some sets with relevant dynamical role

From the biological point of view, the interest is focused in studying the dynamical behaviour of a certain growth tumour. In connection with this problem, we introduce the following sets:

$$D_X^0 := \left\{ (X_0, Y_0) \in \mathbb{R}^+ \times \mathbb{R}_+ : \lim_{\tau \to +\infty} X(\tau, X_0, Y_0) = 0 \right\},$$

$$D_X^\infty := \left\{ (X_0, Y_0) \in \mathbb{R}^+ \times \mathbb{R}_+ : \lim_{\tau \to +\infty} X(\tau, X_0, Y_0) = +\infty \right\},$$

$$V_X := \left\{ (X_0, Y_0) \in \mathbb{R}^+ \times \mathbb{R}_+ : \lim_{\tau \to +\infty} |X(\tau) - X_T(\tau)| + |Y(\tau) - Y_T(\tau)| = 0 \right\}.$$

To simplify, in the last set, we put $X(\tau) := X(\tau, X_0, Y_0)$, $Y(\tau) := Y(\tau, X_0, Y_0)$ and (X_T, Y_T) any possible $\tau_*/\omega-$periodic solution of (1.3). Hence, if (X_T, Y_T) would not exist, then $V_X = \emptyset$.

Following the standard notation, we rewrite the above sets using the transformations (3.3) and (5.1)–(5.2):

$$D_x^0 = \left\{ (x_0, y_0) \in \mathbb{R}^- \times \mathbb{R}_+ : \lim_{t \to +\infty} x(t, x_0, y_0) = 0 \right\},$$

$$D_x^{+\infty} = \left\{ (x_0, y_0) \in \mathbb{R}^- \times \mathbb{R}_+ : \lim_{t \to +\infty} x(t, x_0, y_0) = -\infty \right\},$$

$$V_x = \left\{ (x_0, y_0) \in \mathbb{R}^- \times \mathbb{R}_+ : \lim_{t \to +\infty} |x(t) - x_T(t)| + |y(t) - y_T(t)| = 0 \right\},$$

and

$$D^- := \left\{ (z_0, \dot{z}_0) \in \mathbb{R} \times (-\infty, 1] : \lim_{t \to +\infty} z(t, z_0, \dot{z}_0) = -\infty \right\},$$

$$D^+ := \left\{ (z_0, \dot{z}_0) \in \mathbb{R} \times (-\infty, 1] : \lim_{t \to +\infty} z(t, z_0, \dot{z}_0) = +\infty \right\},$$

$$V := \left\{ (z_0, \dot{z}_0) \in \mathbb{R} \times (-\infty, 1] : \lim_{t \to +\infty} |z(t) - z_T(t)| + |\dot{z}(t) - \dot{z}_T(t)| = 0 \right\}.$$

We set $x(t) := x(t, x_0, y_0)$, $y(t) := y(t, x_0, y_0)$ and (x_T, y_T) any possible $a\tau_*/\omega-$periodic solution of (3.4). Hence, if (x_T, y_T) would not exist, then $V_x = \emptyset$. As usual $z(t, z_0, \dot{z}_0)$ denotes the solution of (5.3) satisfying $z(0, z_0, \dot{z}_0) = z_0$ and $z'(0, z_0, \dot{z}_0) = \dot{z}_0$.

5.2 Auxiliary propositions

In this part, we will introduce some results dealing with equation (5.3). One may easily observe that many of them have a very nice interpretation when the biological variables are involved. Please keep in mind that we are referring to the biological variables that are denoted by capital letters X and Y, being these obtained by going back through the change of variables (5.1), (5.2) and after (3.3).

Lemma 5 *Assume that* $(z_0, \dot{z}_0), (z_1, \dot{z}_1) \in \mathbb{R} \times (-\infty, 1]$. *Then,*

$$z_0 \le z_1,\ \dot{z}_0 \le \dot{z}_1 \implies z(t, z_0, \dot{z}_0) \le z(t, z_1, \dot{z}_1), \qquad \text{for } t \ge 0.$$

Moreover, the strict inequality holds for $t > 0$ *if and only if either* $z_0 \ne z_1$ *or* $\dot{z}_0 \ne \dot{z}_1$.

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Proof We assume, on the contrary, that there exist $z_0 \leq z_1$, $\dot{z}_0 \leq \dot{z}_1$ such that $|z_0| + |\dot{z}_0| < |z_1| + |\dot{z}_1|$ but

$$\hat{z}_0(t_1) = \hat{z}_1(t_1), \qquad \hat{z}_0(t) < \hat{z}_1(t), \quad \text{for } t \in (0, t_1), \tag{5.6}$$

for some $t_1 > 0$. Here, $\hat{z}_i := z(\cdot, z_i, \dot{z}_i)$ $(i = 0, 1)$. We set $w(t) := \hat{z}_1(t) - \hat{z}_0(t)$, then direct computations show

$$\begin{aligned}
&w''(t) + \mathfrak{f}(\hat{z}_1(t))\hat{z}_1'(t) - \mathfrak{f}(\hat{z}_0(t))\hat{z}_0'(t) > 0, \qquad \forall \quad t \in (0, t_1)\\
&w'(t_1) - w'(0) + \int_{\hat{z}_1(0)}^{\hat{z}_1(t_1)} \mathfrak{f}(s)ds - \int_{\hat{z}_0(0)}^{\hat{z}_0(t_1)} \mathfrak{f}(s)ds > 0\\
&w'(t_1) - w'(0) > \int_{\hat{z}_0(0)}^{\hat{z}_0(t_1)} \mathfrak{f}(s)ds - \int_{\hat{z}_1(0)}^{\hat{z}_1(t_1)} \mathfrak{f}(s)ds = \int_{\hat{z}_0(0)}^{\hat{z}_0(t_1)} \mathfrak{f}(s)ds + \int_{\hat{z}_1(t_1)}^{\hat{z}_1(0)} \mathfrak{f}(s)ds \geq 0.
\end{aligned}$$

Hence, $w'(t_1) > w'(0)$. This contradicts (5.6). □

By a similar argument, one can easily prove the following statement:

Corollary 4 *Any couple of different solutions of the equation* (5.3) *with initial conditions in* $\mathbb{R} \times (-\infty, 1]$ *have at most one point in common.*

Lemma 6 *The following assertions are equivalent.*

(i) $\overline{p} < \rho$.
(ii) *There exists* $z_T : \mathbb{R} \to \mathbb{R}$ *a* $T-$*periodic solution of* (5.3).

Moreover, this is the unique solution with this property.

Proof The proof that (ii) implies (i) is immediate. Indeed, denoting by $z_T : \mathbb{R} \to \mathbb{R}$ a $T-$periodic solution of (5.3), it suffices to integrate in both sides of the equation over the interval $[0, T]$ (with $z = z_T$) to obtain (i).

The converse is also true. To prove this issue, from now on we assume (i). It is easily to check that the constant function $\hat{\beta} := \mathfrak{h}^{-1}(-\|p\|_\infty) + 1$ is an upper solution for the periodic problem associated with the equation (5.3). The remaining of the proof is devoted to check that there exists $\hat{\alpha} : [0, T] \to \mathbb{R}$ a lower solution for this problem such that

$$\hat{\alpha}(t) < \hat{\beta} \qquad \text{for } [0, T], \tag{5.7}$$

and consequently, the existence of a $T-$periodic solution of (5.3) is guaranteed by applying the classical theory of lower and upper solutions to the periodic problem.

The construction of such a lower solution is done as follows. Our starting point is considering the Dirichlet problem:

$$w'' + \mathfrak{f}(\mathcal{T}[w])w' = q(t), \quad w(0) = 0 = w(T), \tag{5.8}$$

where $q \in C$ and, for $\eta \in \mathbb{R}$, the operator $\mathcal{T}_\eta$ is defined by:

$$\mathcal{T} : C \to C, \qquad \mathcal{T}[w](t) = \eta + w(t) - m_w.$$

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Now, we can rewrite (5.8) as a fixed point problem:

$$w = F[w], \qquad w \in C^1. \tag{5.9}$$

Here,

$$F[w](t) = -\frac{1}{T}\left[(T-t)\int_0^t sN[w]ds + t\int_t^T (T-s)N[w]ds\right],$$

and $N[w](t) := -\mathfrak{f}(\mathcal{T}[w])w' + q(t)$. Thus, with the proposal of computing the topological degree of the $I - F$, we embedded the problem (5.9) into a family of homotopic problems, that is, we consider

$$w = F_\lambda[w], \qquad \lambda \in [0,1], \qquad F_\lambda :\equiv \lambda F. \tag{5.10}$$

We claim that the above homotopy is admissible. Indeed, by construction one may easily see that any solution w of (5.10) is also a solution of the problem:

$$w'' + \lambda\mathfrak{f}(\mathcal{T}[w])w' = \lambda q(t), \quad w(0) = 0 = w(T). \tag{5.11}$$

Thus, multiplying in (5.11) by w and integrating by parts over $[0, T]$, one gets

$$\int_0^T w'^2 = -\lambda\int_0^T qw = \lambda\int_0^T q^- w - \lambda\int_0^T q^+ w \le Q_*(M_w - m_w),$$

(recall that Q_* was defined in the introduction). Since $w(0) = w(T)$, the latter inequality combined with the estimation proved in [30, Lemma 2.4] yields

$$M_w - m_w \le \frac{TQ_*}{4}. \tag{5.12}$$

Since $w(0) = 0$ one has $\|w\|_\infty \le TQ_*/4$. This proves that (5.10) is admissible on any ball with centre in the origin and sufficient large radius, that is,

$$d_{LS}(I - F_1, B(0,R), 0) = d_{LS}(I - F_0, B(0,R), 0) = 1.$$

Notice that the above-mentioned ball is in C^1 endowed with its norm. However, because we know that any solution of (5.11) verifies (5.12), doing direct computations in (5.11) we deduce that

$$\|w'\|_\infty \le 2\|w\|_\infty \max_{z\in\left[\eta,\eta+\frac{TQ_*}{4}\right]} |\mathfrak{f}(z)| + \|q\|_1.$$

On the other hand, since $\mathfrak{h}$ is a decreasing function and satisfies (5.4), in view of (i) we can choose $\widetilde{\beta} < \hat{\beta}$ such that

$$\mathfrak{h}(z) > \overline{p} \qquad \text{for } z < \widetilde{\beta}. \tag{5.13}$$

We set now the problem (5.8) with $q(t) := p(t) - \overline{p}$ and $\eta := \widetilde{\beta} - TQ_*/4$. We have already proved that there exists a solution w which satisfies (5.12). Moreover, by definition of q, w is $T-$periodic. Hence, the function

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$$\hat{\alpha} : [0, T] \to \mathbb{R}, \qquad \hat{\alpha}(t) := \eta + w(t) - m_w,$$

is $T-$periodic and satisfies

$$\eta \leq \hat{\alpha}(t) \leq \eta + \frac{TQ_*}{4} = \widetilde{\beta}.$$

By combining the latter inequality with (5.13), one has

$$\mathfrak{h}(\hat{\alpha}(t)) > \overline{p} \qquad \text{for } t \in [0, T],$$

and, consequently,

$$\hat{\alpha}'' = -\mathfrak{f}(\hat{\alpha})\hat{\alpha}' + p(t) - \overline{p} > -\mathfrak{f}(\hat{\alpha})\hat{\alpha}' + p(t) - \mathfrak{h}(\hat{\alpha}).$$

This proves that $\hat{\alpha}$ is a lower function for the periodic problem associated with (5.3) which satisfies (5.7) (recall that $\widetilde{\beta} < \hat{\beta}$).

Proof of the uniqueness. Using a contradiction argument, assume that there are two $T-$periodic solutions of (5.3). Denoting these solutions by z_1 and z_2, and setting $z = z_1 - z_2$, we have

$$z'' = \mathfrak{f}(z_2)z_2' - \mathfrak{f}(z_1)z_1' + \mathfrak{h}(z_2) - \mathfrak{h}(z_1). \tag{5.14}$$

There is no loss of generality in assuming that $z(t) > 0$ for every $t \in [0, T]$ (see Corollary 4). Hence, by integrating in (5.14) over $[0, T]$, one obtains a contradiction. The proof is complete. □

Remark 2 *Notice that Lemma 6 does not depend essentially on the definition of* $\mathfrak{h}$*, it only depends on its properties. This means that if one changes* $\mathfrak{h}$ *by another decreasing function satisfying* (5.4)*, the result remains true.*

Remark 3 *Although it is not true that any solution of* (5.3) *is connected with a solution of* (1.3) *with biological interpretation, this relation holds if one deals with periodic solutions. Indeed, let* z_T *be a* $T-$*periodic solution of* (5.3)*. Thus, there exists* $t_0 \in [0, T]$ *such that* $z_T'(t_0) = 0$*. By making the corresponding change of variables, first* (5.1)-(5.2) *and then* (3.3)*, we observe that the resulting function* $(X_T, Y_T) : \mathbb{R} \to \mathbb{R}^2$ *is a* $\tau_*/\omega-$*periodic solution of* (1.3) *such that*

$$(X_T, Y_T)(t_0/a) \in \mathbb{R}^+ \times \mathbb{R}^+.$$

By using Remark 1,

$$(X_T, Y_T)(\tau) \in \mathbb{R}^+ \times \mathbb{R}^+, \qquad \textit{for } \tau \geq \frac{t_0}{a}.$$

Hence, from the periodicity of (X_T, Y_T)*, one deduces that the above inclusion holds for any* $\tau \geq 0$*. So that,* (X_T, Y_T) *has biological sense.*

To establish the last results of this section, it will be convenient to introduce the following set:

$$B := \{(z_0, \dot{z}_0) \in \mathbb{R} \times (-\infty, 1] : \text{there exists } K > 0 \text{ such that } |z(t, z_0, \dot{z}_0)| < K,\ t \geq 0\}.$$

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Lemma 7 *Assume $\overline{p} < \rho$. Then, any $(z_0, \dot{z}_0) \in B$ verifies*

$$\lim_{t\to+\infty} |z(t, z_0, \dot{z}_0) - z_T(t)| + |z'(t, z_0, \dot{z}_0) - z_T'(t)| = 0.$$

Here, z_T is the unique solution which appears in Lemma 6. In other words, $B = V$.

Proof Let $(z_0, \dot{z}_0) \in \mathbb{R} \times (-\infty, 1]$ be a point lying in B. Then, there exists $K > 0$ such that

$$|\hat{z}(t)| < K \qquad \text{for } t \in [0, +\infty). \tag{5.15}$$

Here, $\hat{z}(t) := z(t, z_0, \dot{z}_0)$. Let us now modify the non-linearities of the equation (5.3) in such a way that the resulting functions are continuously defined on $\mathbb{R}$, bounded and strictly monotone; and for any $z \le K + \|z_T\|_\infty + |\mathfrak{h}^{-1}(-\|p\|_\infty)|$, these coincide with the previous ones. Denoting by $\hat{\mathfrak{f}}, \hat{\mathfrak{h}} : \mathbb{R} \to \mathbb{R}$ such functions, we have a modified equation:

$$z'' + \hat{\mathfrak{f}}(z)z' + \hat{\mathfrak{h}}(z) = p(t), \tag{5.16}$$

whose Poincaré map $\hat{P} : \mathbb{R}^2 \to \mathbb{R}^2$ is an homeomorphism. Furthermore, by virtue of Lemma 6 and Remark 2, (5.16) has a unique $T-$periodic solution, which is necessarily z_T. Since this solution was obtained by finding a pair of strict lower and upper solutions, it is well known (see, e.g., [57, Proposition 2.1]) that

$$d_B(I - \hat{P}, \Omega, 0) = -1,$$

for any open set of $\mathbb{R}^2$ such that the point $(z_T, \dot{z}_T) := (z_T(0), z_T'(0)) \in \Omega$. Thus, according to [9, Lemma 3.3] (see also, e.g., [7]), we can conclude that $\hat{P}$ is a free-homeomorphism which preserves its orientation, and consequently, it possesses nice dynamical properties. In particular, the following dichotomy:

Possibility A. There exists an unbounded subsequence of $\{\hat{P}^n(z_0, \dot{z}_0)\}_{n\in\mathbb{N}}$ (after possibly passing to the subsequence, $\|\hat{P}^n(z_0, \dot{z}_0)\| \to +\infty$ as n tends to $+\infty$).

Possibility B. $\hat{P}^n(z_0, \dot{z}_0) \to (z_T, \dot{z}_T)$ as n tends to $+\infty$.

Here $\hat{P}^n := \hat{P} \overbrace{\circ \cdots \circ}^{n} \hat{P}$. If we can prove that Possibility A does not occur, the assertion of the lemma will follow from Possibility B. Before jumping into the mathematical details of this issue, it is worthy to notice that according to (5.15), the solution $\hat{z}$ always remains at the unmodified region. Hence, $\hat{P}^n(z_0, \dot{z}_0) = P^n(z_0, \dot{z}_0)$ for every $n \in \mathbb{N}$, where P is the Poincaré map associated with the equation (5.3).

Possibility A cannot happen. Using a contradiction argument, in view of (5.15) we assume that $|\hat{z}'(nT)| \to +\infty$. Because we know that $\hat{z}'(t) \le 1$ for $t \in [0, +\infty)$,

$$\lim_{n\to+\infty} \hat{z}'(nT) = -\infty. \tag{5.17}$$

Let, on the other hand, $R > 0$ be a constant defined sufficiently large in such a way that

$$R > 2(K + \|z_T\|_\infty) + \frac{\|p\|_\infty + M_h}{\alpha}.$$

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Here,

$$M_h := \max_{|z|\le K+\|z_T\|_\infty} |\mathfrak{h}(z)|.$$

In view of (5.17), we distinguish two cases:

Case 1. There exists $t_0 > 0$ such that $\hat{z}'(t) < -R$ for $t \ge t_0$. In this case, the contradiction follows below:

$$-2(K + \|z_T\|_\infty) < \hat{z}(t_0 + 1) - \hat{z}(t_0) = \int_{t_0}^{t_0+1} \hat{z}'(s)ds < -R.$$

This is impossible and concludes this case.

Case 2. There exists a sequence $\{t_n\}_n \subseteq (0, +\infty)$ such that $\hat{z}''(t_n) = 0$ and $\hat{z}'(t_n) < -R$. Since $\hat{z}$ is solution of (5.3), we have

$$\mathfrak{h}(\hat{z}(t_n)) + \mathfrak{f}(\hat{z}(t_n))\hat{z}'(t_n) = p(t_n),$$

and consequently,

$$\begin{aligned} p(t_n) &= \left(\alpha + e^{\hat{z}(t_n)}\right)\hat{z}'(t_n) + \mathfrak{h}(\hat{z}(t_n)) \\ &= \alpha\hat{z}'(t_n) + e^{\hat{z}(t_n)}\hat{z}'(t_n) + \mathfrak{h}(\hat{z}(t_n)) \\ &< \alpha\hat{z}'(t_n) + \mathfrak{h}(\hat{z}(t_n)). \end{aligned}$$

Hence,

$$-R > \hat{z}'(t_n) > -\frac{M_h + \|p\|_\infty}{\alpha}.$$

But this contradicts the definition of R. □

Lemma 8 *Assume $\overline{p} < \rho$. Let $(z_1, \dot{z}_1), (z_2, \dot{z}_2) \in B$, then*

$$\dot{z}_1 \le \dot{z}_2 \implies z_2 \le z_1.$$

Moreover, if $\dot{z}_1 < \dot{z}_2$ then $z_2 < z_1$.

Proof Denoting by $\hat{z}_1(t) := z(t, z_1, \dot{z}_1)$ and $\hat{z}_2(t) := z(t, z_2, \dot{z}_2)$, and by $K > 0$ a constant such that

$$\sup_{t\in[0,+\infty)} \left[|\hat{z}_1(t)| + |\hat{z}_2(t)|\right] < K;$$

if we assume that $z_1 < z_2$ (or $z_1 = z_2$ if $\dot{z}_1 < \dot{z}_2$), by Lemma 5 we have

$$\hat{z}_1(t) < \hat{z}_2(t) \qquad \text{for } t > 0.$$

Furthermore, by applying Lemma 7, we know that

$$\lim_{t\to+\infty} |\hat{z}_2'(t) - \hat{z}_1'(t)| + |\hat{z}_2(t) - \hat{z}_1(t)| = 0. \tag{5.18}$$

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Direct computations yield

$$\hat{z}_2'' - \hat{z}_1'' \geq -\mathfrak{f}(\hat{z}_2)\hat{z}_2' + \mathfrak{f}(\hat{z}_1)\hat{z}_1'.$$

Hence, by integrating the latter inequality from 0 to t, we get

$$\hat{z}_2' - \hat{z}_1' \geq \dot{z}_2 - \dot{z}_1 + \int_{z_1}^{z_2} \mathfrak{f}(s)ds - \int_{\hat{z}_1(t)}^{\hat{z}_2(t)} \mathfrak{f}(s)ds.$$

Passing to the limit as $t \to +\infty$, with respect to (5.18) one obtains that $\dot{z}_2 = \dot{z}_1$ and $z_1 = z_2$. This is impossible and concludes the proof. □

5.3 Proofs of the main results

Throughout this subsection, we will assume that $\overline{p} < \rho$. Before proving the main results, we need to study some topological properties of the sets D^+, D^- and V, as for example:

Lemma 9 *The sets D^+ and D^- are open in $\mathbb{R} \times (-\infty, 1]$, and*

$$\mathbb{R} \times (-\infty, 1] = D^+ \cup D^- \cup V. \tag{5.19}$$

Proof Lemma 7 immediately proves (5.19). So that it is sufficient to prove that D^+ and D^- are open sets in $\mathbb{R} \times (-\infty, 1]$ with its relative topology. We will only prove the case D^+, because the proof for the case D^- is similar.

D^+ is open. Let $(z_0, \dot{z}_0) \in D^+$ be arbitrary. Then, denoting by $\hat{z}_0(t) := z(t, z_0, \dot{z}_0)$,

$$\lim_{t \to +\infty} \hat{z}_0(t) = +\infty. \tag{5.20}$$

Let us now define $\hat{\gamma} > 0$ such that

$$\hat{\gamma} > 1 + \|(z_0, \dot{z}_0)\|_2 + |\mathfrak{h}^{-1}(-\|p\|_\infty)| + \|z_T\|_\infty.$$

Here, we denote by z_T the unique $T-$periodic solution to (5.3) provided by Lemma 6. Because we know (5.20), there exists $t_1 > 0$ such that $\hat{z}_0(t) > \hat{\gamma}$ for every $t \geq t_1$. Thus, the usual continuous dependence theorems state that for $0 < \varepsilon < 1$ sufficiently small, if $(z, \dot{z}) \in B_{\|\cdot\|_2}((z_0, \dot{z}_0), \varepsilon) \cap (\mathbb{R} \times (-\infty, 1])$ then $\hat{z}(t_1) > \hat{\gamma}$, where $\hat{z}(t) := z(t, z, \dot{z})$. We shall prove that $(z, \dot{z}) \in D^+$. Indeed, if we assume false the claim, in view of (5.19) we have

$$(z, \dot{z}) \in V \cup D^-.$$

Therefore, since $\hat{z}(t_1) > \hat{\gamma}$, by the definition of $\hat{\gamma}$, we can assure that there exists $t_M \in [t_1, +\infty)$ such that the function $\hat{z}$ attains a local maximum at such point and its value is greater than $\hat{\gamma}$, that is,

$$\hat{z}(t_M) > \hat{\gamma}, \qquad \hat{z}'(t_M) = 0, \qquad \hat{z}''(t_M) \leq 0.$$

Finally, since $\hat{z}$ is a solution of (5.3),

$$\mathfrak{h}(\hat{z}(t_M)) \geq p(t_M) \geq -\|p\|_\infty.$$

However, this contradicts the definition of $\hat{\gamma}$. □

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Lemma 10 *There exist* $-\infty \leq \widetilde{a} < \widetilde{b} \leq +\infty$ *and a continuous function* $\varphi : (\widetilde{a}, \widetilde{b}) \to \mathbb{R}$ *which is decreasing such that*

$$\{(z, \varphi(z)) : \widetilde{a} < z < \widetilde{b}\} = V \cap \mathbb{R} \times (-\infty, 1). \tag{5.21}$$

Moreover,

- *if* $-\infty < \widetilde{a}$, *then* $\varphi(\widetilde{a}^+) = 1$;
- *if* $\widetilde{b} < +\infty$, *then* $\varphi(\widetilde{b}^-) = -\infty$.

Proof By Lemma 5, D^+ has the following property:

(P_1) If $(z_0, \dot{z}_0) \in D^+$ and $z_1 \geq z_0$, $\dot{z}_1 \geq \dot{z}_0$, then $(z_1, \dot{z}_1) \in D^+$.

As a consequence D^+ is connected. Also, the symmetrical property holds for D^-:

(P_2) If $(z_0, \dot{z}_0) \in D^-$ and $z_1 \leq z_0$, $\dot{z}_1 \leq \dot{z}_0$, then $(z_1, \dot{z}_1) \in D^-$.

By a similar argument, it follows that D^- is connected too. By using Lemma 8 and these properties, it is easy to prove that

$$\widetilde{I} = \{z \in \mathbb{R} : \text{ there exist } \dot{z}_0 < \dot{z}_1 \leq 1 \text{ such that } (z, \dot{z}_0) \in D^-, (z, \dot{z}_1) \in D^+ \},$$

is an open interval $(\widetilde{a}, \widetilde{b})$ with $-\infty \leq \widetilde{a} < \widetilde{b} \leq +\infty$, that is, $\emptyset \neq \widetilde{I} \subseteq \mathbb{R}$ is a connected open set.

On the other hand, for any $z \in \widetilde{I}$, since D^+ and D^- are open sets in $\mathbb{R} \times (-\infty, 1]$, we know from (5.19) that there exists $\dot{z} \in (-\infty, 1)$ such that $(z, \dot{z}) \in V$ and, in addition, by Lemma 8, $\dot{z}$ is unique. Hence, we can define the function

$$\varphi : (\widetilde{a}, \widetilde{b}) \to (-\infty, 1), \qquad \varphi(z) := \dot{z}.$$

By construction,

$$\{(z, \varphi(z)) : \widetilde{a} < z < \widetilde{b}\} \subseteq V \cap \mathbb{R} \times (-\infty, 1).$$

Now, we shall prove the remaining inclusion. Suppose that $(z, \dot{z}) \in V \cap \mathbb{R} \times (-\infty, 1)$, by using again (5.19) and Lemma 8, we have that $(z, \dot{z}_1) \in D^+ \cup D^-$ for $\dot{z} \neq \dot{z}_1$. Moreover, by properties (P_1) and (P_2), $(z, \dot{z}_1) \in D^+$ if $\dot{z}_1 > \dot{z}$ and $(z, \dot{z}_1) \in D^-$ if $\dot{z}_1 < \dot{z}$. Consequently, $z \in \widetilde{I}$ and $\dot{z} = \varphi(z)$.

Finally, it is a direct consequence of Lemma 8 that φ is a decreasing function, and by virtue of Lemma 9, on account of (5.21), we know that its graph is closed in $\mathbb{R} \times (-\infty, 1)$. Hence, φ is also continue.

To end the proof, it now remains to show that if $-\infty < \widetilde{a}$ then $\varphi(\widetilde{a}^+) = 1$. The case when $\widetilde{b} < +\infty$ can be treated analogously and therefore its proof is omitted. Indeed, by using a contradiction argument, we assume now that $\varphi(\widetilde{a}^+) < 1$. Thus, by using property (P_2) one deduces that $\{\widetilde{a}\} \times (-\infty, 1] \subseteq D^-$, and consequently, since D^- is open in $\mathbb{R} \times (-\infty, 1]$, there exists an open set $U \subseteq \mathbb{R} \times (-\infty, 1]$ such that

$$\big(\widetilde{a}, \varphi(\widetilde{a}^+)\big) \in U \subseteq D^-.$$

However, this is impossible because in such a case $U \cap V \neq \emptyset$. □

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Remark 4 *According to the last part of Lemma 10, we can extend by continuity the function φ by setting*

$$\hat{\varphi} : [\widetilde{a}, \widetilde{b}) \to \mathbb{R}, \qquad \hat{\varphi}(\widetilde{a}) = 1,$$

whenever $-\infty < \widetilde{a}$. Hence, without loss of generality, we can assume that

$$\{(z, \hat{\varphi}(z)) : z \in \hat{I}\} = V, \tag{5.22}$$

where either $\hat{I} = [\widetilde{a}, \widetilde{b})$ if $-\infty < \widetilde{a}$ or $\hat{I} = (\widetilde{a}, \widetilde{b})$ (and hence $\hat{\varphi} \equiv \varphi$) if $\widetilde{a} = -\infty$.

We undertake now the proofs of Theorems 2 and 3 established in the introduction.

Proof of Theorem 2 Assume first that there exists $(X_T, Y_T) : \mathbb{R} \to \mathbb{R}^2$ a $\tau_*/\omega-$ periodic solution of (1.3) such that $\min_{\tau\in\mathbb{R}} X_T(\tau) > 0$. By applying first the change of variables given by (3.3) and next, by using the transformation (5.1) and (5.2), one obtains the existence of a function $z_T : \mathbb{R} \to \mathbb{R}$ which is a $T-$periodic solution to the equation (5.3). Thus, by virtue of Lemma 6, we know that $\overline{p} < \rho$. But this means that (2.1) holds.

Conversely, the latter inequality implies that there exists $z_T : \mathbb{R} \to \mathbb{R}$ a $T-$periodic solution of (5.3), see Lemma 6. Thus, by applying the above-mentioned transformations, one may observe that $(X_T, Y_T) : \mathbb{R} \to \mathbb{R}^2$ is a $\tau_*/\omega-$periodic solution of (1.3). Here, in view of Remark 3,

$$Y_T(\tau) := \frac{a(1 - z_T'(a\tau))}{b} \geq 0, \quad X_T(\tau) := \frac{ae^{z_T(a\tau)}}{|\ell|} > 0, \qquad \text{for } \tau \geq 0,$$

and consequently (2.3) holds.

Finally, the proof of the uniqueness follows from the last part of Lemma 6. The proof is now complete. □

Proof of Theorem 3 According to Lemma 10 and Remark 4, we can define a continuous decreasing function:

$$\hat{\varphi} : \hat{I} \to \mathbb{R}, \qquad \hat{I} = \begin{cases} [\widetilde{a}, \widetilde{b}), & \text{if } \widetilde{a} > -\infty \\ (-\infty, \widetilde{b}), & \text{if } \widetilde{a} = -\infty \end{cases},$$

satisfying (5.22). Thus, we define now the function:

$$\hat{\Phi} : J \to \mathbb{R}, \qquad \hat{\Phi}(X) := \frac{a\left(1 - \hat{\varphi}\left(\ln\left(\frac{|\ell|X}{a}\right)\right)\right)}{b},$$

where either $J = [Z_0, Z_1)$ if $Z_0 > 0$ or $J = (0, Z_1)$ if $Z_0 = 0$. Here,

$$Z_0 := \lim_{x\to\widetilde{a}} \frac{ae^x}{|\ell|}, \qquad Z_1 := \lim_{x\to\widetilde{b}} \frac{ae^x}{|\ell|}.$$

It is immediate to note that $\hat{\Phi}$ is a continuous increasing function such that $W = V_X$, see Lemma 7 and (5.22). Here we have also used the transformations (5.1)–(5.2). Moreover, according to the last part of Lemma 10 and using (5.19), one proves that

$$D_- = D_X^0, \qquad D_X^\infty = D_+, \qquad \mathbb{R}^+ \times [0, +\infty) = D_- \cup D_+ \cup W,$$

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(the sets D_X^0, D_X^∞ and W were defined in Section 5.1). Hence, the proof follows directly from these identities and from Lemma 8. □

6 Analysis of the tumoural growth submitted to particular therapies

So far our model has exhibited four significant dynamical cases of tumour growth with different expectancies of cure for a patient who has been diagnosed by a cancer. The objective of this section is to study what type of treatment has to be applied in the affected region in order to better understand the dynamics of the tumour growth. The worst-case scenario would be $Z_0 = 0$, because only in this case the smallest population size of tumour cells before starting with the treatment may lead to an uncontrollable growth of this population. In order to control this growth, the population size of immune cells should be greater than $\hat{\Phi}(0)$. In this setting, we can obtain a theoretical conclusion based on Theorems 1 and 3 for general therapies.

Corollary 5 *Under the hypotheses of Theorem 3. Assume that $Z_0 = 0$, then*

$$\hat{\Phi}(0) < \frac{1}{\omega\left(e^{\frac{f\tau_*}{\omega}} - 1\right)} \int_0^{\tau_*} (\nu + \theta(t)) e^{\frac{ft}{\omega}} dt.$$

In particular,

$$\hat{\Phi}(0) < \frac{\nu + \|\theta\|_\infty}{f}.$$

In consequence, it is shown that if a patient, who is diagnosed with a cancer of type $\ell < 0$ in its initial stage of formation, presents a sufficient number of immune cells (this is greater than $\frac{\nu+\|\theta\|_\infty}{f}$), then the tumour cells will disappear during the treatment period.

The question here is *what 'initial stage of formation' means*. The rest of the paper is somewhat devoted to solve this question. In particular, we will study in more detail the graph to the function $\varphi : (\widetilde{a}, \widetilde{b}) \to \mathbb{R}$ (appearing in Lemma 10) and we will interpret the results obtained in the biological model (1.3) by using the transformations (5.1)–(5.2) and (3.3).

Proposition 1 *Assume $\|p^+\|_\infty < \rho$ and (2.5). Then the following estimate holds*

$$\widetilde{a} \geq -\frac{2(1+p^*)}{\alpha} + \mathfrak{h}^{-1}(\|p^+\|_\infty),$$

where p^* was defined in Theorem 4.

To prove this result, we shall need two auxiliary lemmas. We henceforth assume that $\|p^+\|_\infty < \rho$, $y_1 := \mathfrak{h}^{-1}(\|p^+\|_\infty)$. Moreover, we shall fix a $z_0 < y_1$ satisfying that

$$z(t, z_0) < y_1 \quad \text{for } t \in (0, t_0(z_0)), \qquad z(t_0(z_0), z_0) = y_1, \tag{6.1}$$

for some $t_0(z_0) > 0$. Here, $z(\cdot, z_0)$ denotes a solution of the Cauchy problem associated with (5.3) satisfying that $z(0) = z_0$ and $z'(0) > 0$.

Lemma 11 $z'(t, z_0) \geq 0$ *for* $t \in [0, t_0(z_0)]$.

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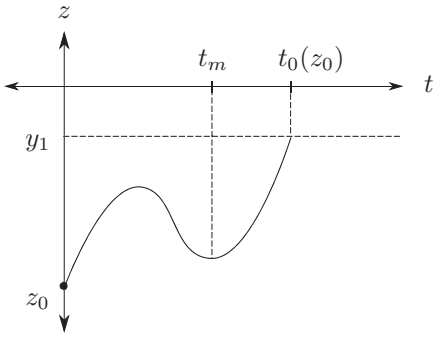

FIGURE 3. Shows the graph of the function $z(t)$ in the plane with the usual coordinate axes, assuming that the function reaches a local minimum at the point $t = t_m$.

Proof Using a contradiction argument, by (6.1) assume that there exists $t_m \in [0, t_0(z_0)]$ such that $z(t_m) < y_1$, $z'(t_m) = 0$ and $z''(t_m) \geq 0$ (see Figure 3). Here for simplicity, we denote $z(t) := z(t, z_0)$.

Since z is solution of (5.3), we have

$$z''(t_m) + \mathfrak{f}(z(t_m))z'(t_m) + \mathfrak{h}(z(t_m)) = p(t_m).$$

Consequently,

$$\begin{aligned}\mathfrak{h}(z(t_m)) &\leq z''(t_m) + \mathfrak{h}(z(t_m)) = p(t_m)\\ &\leq p^+(t_m) \leq \|p^+\|_\infty.\end{aligned}$$

Hence,

$$z(t_m) \geq \mathfrak{h}^{-1}(\|p^+\|_\infty) = y_1.$$

But this is a contradiction. □

Lemma 12 *$z''(t, z_0) \leq 0$ for $t \in [0, t_0(z_0)]$.*

Proof Since $z := z(\cdot, z_0)$ is solution of (5.3),

$$\begin{aligned}z'' &\leq -\mathfrak{f}(z)z' - \mathfrak{h}(z) + p^+(t)\\ &\leq -\mathfrak{f}(z)z' - \mathfrak{h}(z) + \|p^+\|_\infty\\ &\leq -\mathfrak{f}(z)z' - \mathfrak{h}(y_1) + \|p^+\|_\infty = -\mathfrak{f}(z)z' \leq 0.\end{aligned}$$

□

Now we are in position to prove the main result of this section.

Proof of Proposition 1 Using a contradiction argument, assume that

$$\widetilde{a} < -\frac{2(1+p^*)}{\alpha} + y_1.$$

Then, we can choose $(z_0, \dot{z}_0) \in D^+$ such that

$$\widetilde{a} < z_0 < -\frac{2(1+p^*)}{\alpha} + y_1. \tag{6.2}$$

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Since $(z_0, \dot{z}_0) \in D^+$ with $\dot{z}_0 > 0$, then (6.1) holds; where $z(t, z_0) := z(t, z_0, \dot{z}_0)$. As usual, we denote by $z(t) := z(t, z_0)$, by using Lemmas 11 and 12 we get

$$z(t) \geq z_0 + \frac{y_1 - z_0}{t_0(z_0)} t, \qquad \text{for } t \in [0, t_0(z_0)]. \tag{6.3}$$

On the other hand, if we integrate in (5.3) from 0 to t we obtain

$$\begin{aligned} z'(t) &= \dot{z}_0 - \int_{z_0}^{z(t)} \mathfrak{f}(s)ds - \int_0^t \mathfrak{h}(z(s))ds + \int_0^t p(s)ds \\ &\leq \dot{z_0} - \int_{z_0}^{z(t)} \mathfrak{f}(s)ds - \int_{z_0}^{z(t)} \mathfrak{h}(s)ds + \int_0^t p(s)ds \\ &= \dot{z}_0 - \int_{z_0}^{z(t)} [\mathfrak{f}(s) + \mathfrak{h}(s)]ds + \int_0^t p(s)ds. \end{aligned}$$

Setting

$$G(z, z_0) := \int_{z_0}^{z} [\mathfrak{f}(s) + \mathfrak{h}(s)]ds,$$

by integrating over $[0, t_0(z_0)]$ in the latter inequality one arrives at

$$\begin{aligned} y_1 &\leq z_0 + \dot{z}_0\, t_0(z_0) - \int_0^{t_0(z_0)} G(z(s, z_0), z_0)ds + \int_0^{t_0(z_0)} \int_0^s p(r)drds \\ &= z_0 + t_0(z_0) \left[\dot{z}_0 - \frac{\int_0^{t_0(z_0)} G(z(s, z_0), z_0)ds}{t_0(z_0)} + \frac{1}{t_0(z_0)} \int_0^{t_0(z_0)} \int_0^s p(r)drds \right]. \end{aligned} \tag{6.4}$$

From the definition of the function $\mathfrak{f}$ and by using (6.3),

$$G(z(s, z_0), z_0) = \int_{z_0}^{z(s,z_0)} [\mathfrak{f}(s) + \mathfrak{h}(s)]ds \geq \alpha(z(s, z_0) - z_0) \geq \alpha \left(\frac{y_1 - z_0}{t_0(z_0)} s \right),$$

whence

$$\frac{\int_0^{t_0(z_0)} G(z(s, z_0), z_0)ds}{t_0(z_0)} \geq \frac{\alpha(y_1 - z_0)}{2}.$$

Then by (6.4),

$$y_1 \leq z_0 + t_0(z_0) \left[\dot{z}_0 - \frac{\alpha(y_1 - z_0)}{2} + \frac{1}{t_0(z_0)} \int_0^{t_0(z_0)} \int_0^s p(r)drds \right].$$

However, since $\dot{z}_0 < 1$, in view of (6.2),

$$\dot{z}_0 - \frac{\alpha(y_1 - z_0)}{2} + \frac{1}{t_0(z_0)} \int_0^{t_0(z_0)} \int_0^s p(r)drds < 0.$$

But this contradicts $z_0 < y_1$. □

Remark 5 *Note that Theorem 4 is nothing more than writing Proposition 1 in the biological variables, that is, one has to use the change of variables* (5.1) *and* (5.2) *and finally* (3.3) *to rewrite Proposition 1 in terms of the variables X and Y.*

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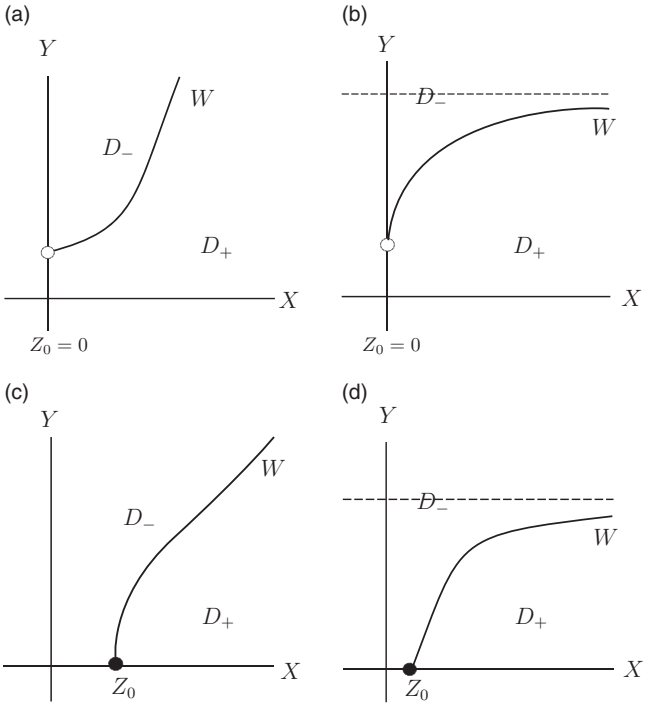

FIGURE 4. It shows the different dynamic cases to our model in relation to Theorem 3. As in Figure 1, the x- and y-axes are connected with the variables X and Y, that is, they indicate the number of initial tumour and immune cells coexisting in the affected region before starting with the therapy.

Finally, we finish the section with a result on the behaviour of the function $\varphi : (\widetilde{a}, \widetilde{b}) \to \mathbb{R}$ in at neighbourhood of $\widetilde{b}$. In this direction, we analyse if either

$$\varphi(\widetilde{b}) = -\infty, \text{ or } \quad \varphi(\widetilde{b}) > -\infty.$$

In other words, in the framework of Theorem 3, we shall study when it is possible to discard the cases (b) and (d) in Figure 4.

Proposition 2 *Assume* (2.1) *and* (2.8)*. Then either*

$$\widetilde{b} \leq y_2 + \frac{2|p_*|}{\alpha},$$

or

$$\varphi(z_0) \leq -\left(p_* + \frac{\alpha(z_0 - y_2)}{2}\right) \qquad \text{for } z_0 \in \left(y_2 + \frac{2|p_*|}{\alpha}, \widetilde{b}\right), \tag{6.5}$$

where $y_2 := \mathfrak{h}^{-1}(-\|p^-\|_\infty)$ *and* p_* *was defined in Theorem 5.*

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Proof Assume that $\widetilde{b} > y_2 + \dfrac{2|p_*|}{\alpha}$, then we will prove that (6.5) is fulfilled. Indeed, using a contradiction argument, assume that there exists $z_0 \in (y_2 + \dfrac{2|p_*|}{\alpha}, \widetilde{b})$ such that

$$\varphi(z_0) > -\left(p_* + \frac{\alpha(z_0 - y_2)}{2}\right).$$

Setting

$$\dot{z}_0 = -\left(p_* + \frac{\alpha(z_0 - y_2)}{2}\right),$$

we have that $(z_0, \dot{z}_0) \in D^-$ and moreover $\dot{z}_0 < 0$. Denoting by $z(t, z_0) := z(t, z_0, \dot{z}_0)$, there exists $t_1(z_0) > 0$ such that $z(t, z_0) > y_2$, for $t \in (0, t_1(z_0))$ and $z(t_1(z_0), z_0) = y_2$. It is easy to prove that

$$z'(t, z_0) \leq 0, \quad z''(t, z_0) \geq 0, \qquad \text{for } t \in [0, t_1(z_0)].$$

Thus,

$$z(t, z_0) \leq z_0 - \frac{z_0 - y_2}{t_1(z_0)} t \qquad \text{for } t \in [0, t_1(z_0)].$$

By similar steps to those done in the proof of Proposition 1, we obtain

$$y_2 \geq z_0 + t_1(z_0)\left(\dot{z}_0 + \frac{\alpha(z_0 - y_2)}{2} + p_*\right) = z_0,$$

which is a contradiction. □

Remark 6 *Note that Theorem 5 is nothing more than writing Proposition 2 in the biological variables, that is, one has to use the change of variables* (5.1) *and* (5.2) *and finally* (3.3) *in order to rewrite Proposition 2 in terms of the variables X and Y.*

6.1 Examples. Particular therapies

Just as a way of an example, let's choose some therapies to illustrate Theorems 4 and 5. In this section, it will be essential to understand that when we talk about the effectiveness (resp. inefficacy) of the treatment in terms of μ_* (resp. μ^*), it is in the sense of analytically estimating its magnitude. However, a numerical analysis in any specific case may show a higher level of effectiveness μ_*^{num} (resp. lower level of inefficacy μ^{*num}) in the treatment, but at the same time its reliability may be more questionable.

Example 1 Consider $\theta : \mathbb{R} \to \mathbb{R}$ a high-power therapy without interruption (this means that there is no break in the treatment regime) such that (2.7) holds. In this setting, $\mu_* = \widetilde{x} e^{-\frac{2a}{f}}$, where $\widetilde{x}$ is implicitly defined by:

$$g(\widetilde{x}) - \frac{a|\ell|}{\nu b}\widetilde{x} = 0. \tag{6.6}$$

Consequently, if a patient who has been diagnosed by a cancer of type $\ell < 0$, initially possesses a density of tumour cells less than μ_*, is submitted to a therapy of this kind, then the tumour cells

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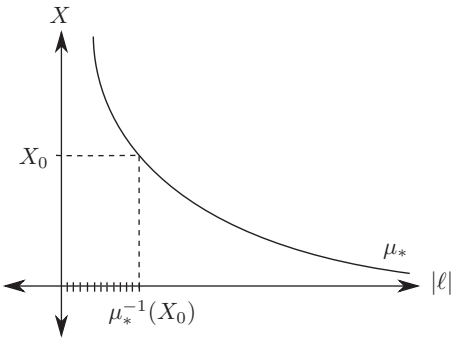

FIGURE 5. It shows the graphic of the function $\mu_*(|\ell|)$. Here, the independent variable indicates the level of aggressiveness of the cancer under consideration, whereas the other variable is connected with the number of tumour cells coexisting in the affected region before starting with the therapy. In consequence, the value $\mu_*^{-1}(X_0)$ reveals the maximum level of aggressiveness of a cancer which can be successfully treated, when the population size of tumour cells just before starting with the treatment is X_0.

will disappear during the treatment period. In this framework, we can also express analytically the effectiveness of the treatment in terms of the degree of aggressiveness of the cancer, as follows:

$$\mu_*(|\ell|) := \Psi_{|\ell|}^{-1}(0)e^{-\frac{2a}{f}},$$

where $\Psi_{|\ell|} : \mathbb{R}^+ \to \mathbb{R}$ is a decreasing function defined by $\Psi_{|\ell|}(x) := g(x) - \frac{a|\ell|}{\nu b}x$. Now μ_* is an explicit decreasing function and satisfies

$$\lim_{|\ell|\to 0^+} \mu_*(|\ell|) = +\infty, \qquad \lim_{|\ell|\to+\infty} \mu_*(|\ell|) = 0.$$

An interesting question comes up in the following terms: knowing the size of the tumour just before starting with the treatment, computing the maximum level of aggressiveness of a cancer which can be successfully treated by this therapy. In this setting, if X_0 is the initial number of tumour cells, an estimation of this level is given by $\mu_*^{-1}(X_0)$ (see Figure 5), that is, if $|\ell| < \mu_*^{-1}(X_0)$ then the cancer can be successfully treated with the therapy.

For instance, if we assume the case when $a = 1/10$, $b = 1/2$, $f = 1/5$, $\nu = 1$, $g(x) = e^{-x}$ and $\theta = \frac{af}{b} (= \frac{1}{25})$, it follows that

$$\mu_*(|\ell|) = W\left(\frac{5}{|\ell|}\right)e^{-1},$$

where W denotes the Lambert function (implicitly defined for $y > 0$ by $W(y)\exp(W(y)) = y$). In this context, from the analytical point of view, the maximum level of aggressiveness of a cancer which can be successfully treated with this therapy, when the population size of tumour cells before starting with the treatment is $X_0 = 1$, is equal to $\mu_*^{-1}(1) \approx 0.121378$. Consequently, for any $\ell < 0$ with $|\ell| < 0.121378$, we can assure that the treatment will be effective independently of the initial number of immune cells (see Figure 6).

We close this example by noting that, a stationary therapy with a constant dose $\sigma = \frac{af}{b}$ minimises the intensity between all the admissible therapies (i.e., therapies satisfying (2.7)).

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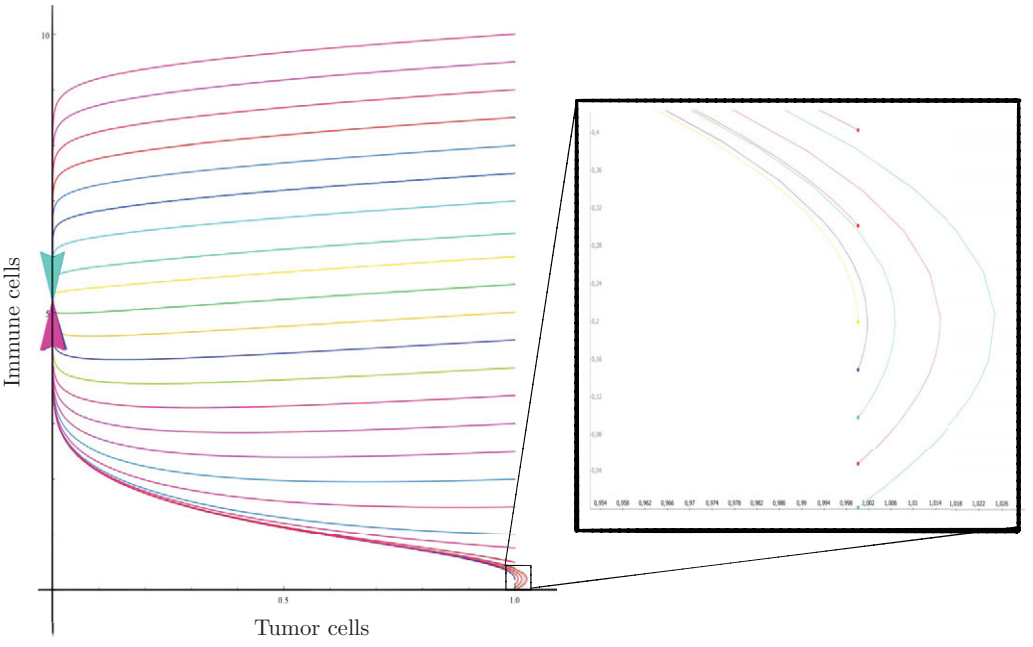

FIGURE 6. Several orbits in the phase portrait of the equation (1.3) with initial conditions of the form $X_0 = 1$ and $Y_0 > 0$ arbitrary. Here, $a = 1/10$, $b = 1/2$, $\ell = -0.1213$, $f = 1/5$, $\nu = 1$, $g(x) = e^{-x}$ and $\theta = \frac{af}{b} = 1/25$. This picture has been performed with Mathematica © software.

When $\theta_{min} = 0$, the main difficulty to apply Theorems 4 and 5 may be in computing the numbers $p^* \geq 0$ and $p_* \leq 0$. However, this task is simplified when

$$\frac{af}{2b} \leq \inf_{t\in[0,+\infty)} \frac{1}{t^2} \int_0^t (t-s)\theta\left(\frac{\omega s}{a}\right) ds,$$

resp.

$$\frac{af}{2b} \geq \sup_{t\in[0,+\infty)} \frac{1}{t^2} \int_0^t (t-s)\theta\left(\frac{\omega s}{a}\right) ds.$$

Because in this setting $p^* = 0$, resp. $p_* = 0$. Now we can easily establish some examples where it is shown which properties have the treatments with rest (i.e., $\theta_{min} = 0$).

Example 2 Consider $\theta : \mathbb{R} \to \mathbb{R}$ a continuous treatment with an instantaneous rest period. In this setting, we include a basic model of therapy of the form:

$$\sigma \cos^2 t, \qquad \frac{\sigma(1+\cos t)}{2}, \qquad \sigma|\sin t|, \qquad \ldots$$

To fix ideas, let us consider $\theta(t) := \sigma \cos^2 t$ with $\sigma > 0$ satisfying

$$\frac{af}{\nu b} < 1, \qquad \sigma \geq \frac{2af}{b}. \tag{6.7}$$

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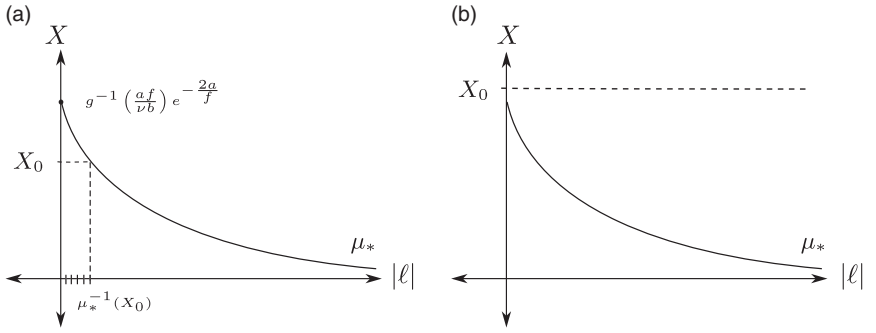

FIGURE 7. It shows the graphic of the function $\mu_*(|\ell|)$. As Figure 7(b) illustrates, our criterion for deciding whether or not the treatment is suitable could not be useful if $X_0 \geq g^{-1}\left(\frac{af}{\nu b}\right)e^{-\frac{2a}{f}}$.[2]

Under this framework, all the conditions of Theorem 4 are fulfilled, obtaining $p^* = 0$ and $\mu_* = \widetilde{x}e^{-\frac{2a}{f}}$, where $\widetilde{x}$ is implicitly defined by

$$g(\widetilde{x}) - \frac{a|\ell|}{\nu b}\widetilde{x} = \frac{af}{\nu b}. \tag{6.8}$$

Again we can express the effectiveness of the treatment in terms of the degree of the aggressiveness of the cancer:

$$\mu_*(|\ell|) = \Psi_{|\ell|}^{-1}\left(\frac{af}{\nu b}\right)e^{-\frac{2a}{f}}, \tag{6.9}$$

where $\Psi_{|\ell|}$ was already defined in Example 1. In contrast with the treatments without interruption analysed in Example 1, the rest period substantially changes its effectiveness. Indeed, in view of (6.9),

$$\lim_{|\ell|\to 0^+}\mu_*(|\ell|) = g^{-1}\left(\frac{af}{\nu b}\right)e^{-\frac{2a}{f}}, \qquad \lim_{|\ell|\to+\infty}\mu_*(|\ell|) = 0.$$

Consequently, the treatment is unable to provide a global cure for cancers not too aggressive. In this setting (see Figure 7):

- We cannot guarantee the efficacy of the treatment when $X_0 \geq g^{-1}\left(\frac{af}{\nu b}\right)e^{-\frac{2a}{f}}$;
- The treatment will be effective for any type of cancer with a degree of aggressiveness no higher than $\mu_*^{-1}(X_0)$, when $X_0 < g^{-1}\left(\frac{af}{\nu b}\right)e^{-\frac{2a}{f}}$.

For instance, if we assume the case when $a = 1/10$, $b = 1/2$, $f = 1/5$, $\nu = 1$, $g(x) = e^{-x}$ and $\theta = \frac{2af}{b}\cos^2\tau$, it follows that

$$\mu_*(|\ell|) = \frac{W\left(\frac{5e^{\frac{1}{5|\ell|}}}{|\ell|}\right) - \frac{1}{5|\ell|}}{e}, \tag{6.10}$$

[2]This figure departs from Figure 5, hence we adopt its elements and terminology for convenience.

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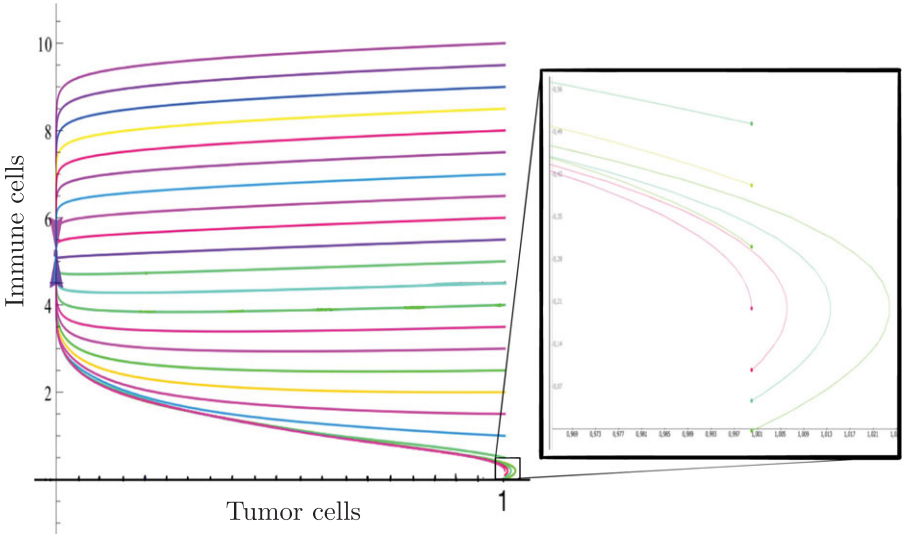

FIGURE 8. Several orbits in the phase portrait of the equation (1.3) with initial conditions of the form $X_0 = 1$ and $Y_0 > 0$ arbitrary. Here, $a = 1/10$, $b = 1/2$, $\ell = -0.047$, $f = 1/5$, $\nu = 1$, $g(x) = e^{-x}$ and $\theta(\tau) = \frac{2af}{b}\cos^2\tau$. This picture has been performed with Mathematica © software.

where W is the Lambert function. In this setting, from the analytical point of view, the maximum level of aggressiveness of a cancer which can be successfully treated with this therapy, when the population size of tumour cells before starting with the treatment is $X_0 = 1$, is equal to $\mu_*^{-1}(1) \approx 0.0478023$. In consequence, for any $\ell < 0$ with $|\ell| < 0.0478023$, we can assure that the treatment will be effective independently of the initial number of immune cells (see Figure 8).

We finish by noting that $\sigma = \frac{2af}{b}$ minimises the dose between all the admissible therapies of this kind, that is, those verifying (6.7). Hence, it seems that the best choice is to set $\theta(t) := \frac{2af}{b}\cos^2 t$.

Generally speaking, we have seen that the rest in a treatment of immunotherapy considerable may reduce its efficacy, at least from the analytical point of view. However, for obvious reasons, it seems necessary to consider it. In this setting, all the treatments behave similarly in terms of curing cancer, but the time devoted to rest opens ways for designing new therapies.

Example 3 Consider $\theta : \mathbb{R} \to \mathbb{R}$ the simplest treatment with an interruption time τ_1 during its period τ_*, that is, θ is the periodic extension of the function:

$$\theta(t) = \begin{cases} \sigma, & \text{if } t \in [0, L_{act}), \\ 0, & \text{if } t \in [L_{act}, \tau_*), \end{cases} \tag{6.11}$$

where $\sigma > 0$ and $L_{act} := \tau_* - \tau_1$ is the period of activity of the treatment. In this setting when

$$\frac{af}{\nu b} < 1, \qquad \sigma \geq \frac{af}{b}\left(\frac{\tau_*}{L_{act}}\right), \tag{6.12}$$

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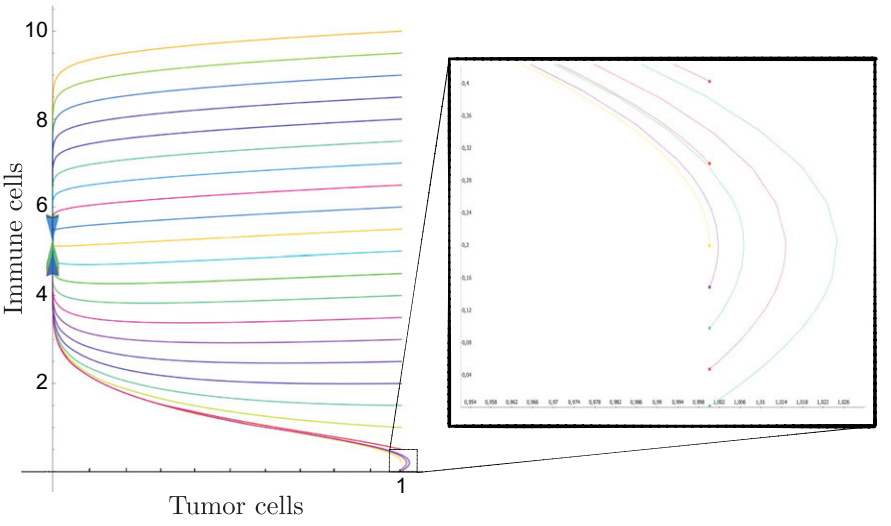

FIGURE 9. Several orbits in the phase portrait of the equation (1.3) with initial conditions of the form $X_0 = 1$ and $Y_0 > 0$ arbitrary. Here, $a = 1/10$, $b = 1/2$, $\ell = -0.047$, $f = 1/5$, $\nu = 1$, $g(x) = e^{-x}$, $L_{act} = 2.6$, $\tau_* = \pi$ and θ is defined by (6.11) with $\sigma = \frac{af}{b}\left(\frac{\tau_*}{L_{act}}\right)$. This picture has been performed with Mathematica © software.

we can apply Theorem 4 with $p^* = 0$, arriving at $\mu_* = \widetilde{x}e^{-\frac{2a}{f}}$, where $\widetilde{x}$ is implicitly defined by (6.8). As above we can express the effectiveness of the treatment in terms of the degree of aggressiveness of the cancer, by (6.9).

For instance, if we assume the case when $a = 1/10$, $b = 1/2$, $f = 1/5$, $\nu = 1$, $g(x) = e^{-x}$, $L_{act} = 2.6$, $\tau_* = \pi$ and θ is defined by (6.11) with $\sigma = \frac{af}{b}\left(\frac{\tau_*}{L_{act}}\right)$, it follows (6.10). In this setting, from the analytical point of view, the maximum level of aggressiveness of a cancer which can be successfully treated with this therapy, when the population size of tumour cells before starting with the treatment is $X_0 = 1$, is equal to $\mu_*^{-1}(1) \approx 0.0478023$. In consequence, for any $\ell < 0$ with $|\ell| < 0.0478023$, we can assure that the treatment will be effective independently of the initial number of immune cells (see Figure 9).

So far there are no substantial differences with Example 2. However, since the rest in the therapy does not play any role in terms of effectiveness in relation to the previous case, we can ask ourselves the problem of minimising L_{act} after fixing the period of the treatment τ_* and its maximum dose σ_*. As a result of applying this strategy, the best choice would be to consider a treatment with period of activity $L_{act}^{min} := \frac{af}{b}\left(\frac{\tau_*}{\sigma_*}\right)$.

■

Finally, for instance, when $\theta : \mathbb{R} \to \mathbb{R}$ satisfies

$$\frac{af}{b} - 1 < \theta(t) \leq \frac{af}{b} \qquad \text{for } t \in \mathbb{R}, \tag{6.13}$$

the situation is the following. All the conditions of Theorem 5 are fulfilled, obtaining $p_* = 0$ and $\mu^* = \Psi_{|\ell|}^{-1}(0)$. In this setting, a treatment of this type would be ineffective and even dangerous if (2.10) holds (see Corollary 2).

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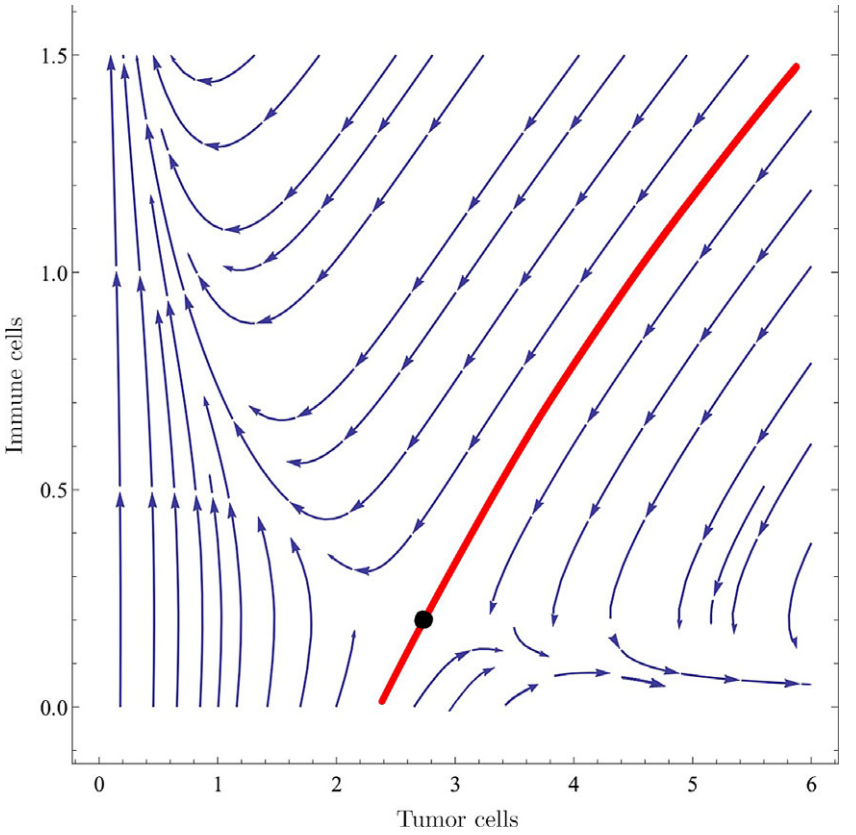

FIGURE 10. Phase portrait of the equation (1.3) when $a = 1/10$, $b = 1/2$, $\ell = -0.1213$, $f = 1/5$, $g(x) = e^{-x}$, $\nu = 1$ and $\theta(\tau) = \frac{af}{b}$. The immunology barrier curve (denoted by W in Theorem 3) is drawn in red colour. The black dot represents the unstable cancer-present state. This picture has been performed with Mathematica © software.

7 Conclusions

In this paper, we study a host-tumour model including a time-dependent source term for immunotherapy proposed in an earlier paper [19], where the interactions between immune and tumour cells are considered under the presence of an aggressive cancer ($\ell < 0$). We study in particular equation (1.3) rigorously, and find, an asymptotic stable tumour-free state and an unstable cancer-present state, both varying periodically at the time, under a relationship between the parameters of the model and the amount of dose applied to combat the tumour (see (2.1) in Theorems 1 and 2).

In this context, the model exhibits an immunological barrier below which initial conditions in terms of immune and tumour cells lead to an immunologically uncontrollable tumour growth, but above which the tumour is cleared (see Theorem 3, and Figure 10 as an example). This analytical result is consistent with the earlier prediction based on numerical results for a model describing the dynamics of growth of a BCL_1 lymphoma in the spleen of chimeric mice, see [33]. This same pattern has been reported in similar models studied in the literature, see e.g., [5, 32].

In this scenario, we explore the effects of the immunotherapy on the model and we describe under what circumstances is possible to extract more qualitative and quantitative information

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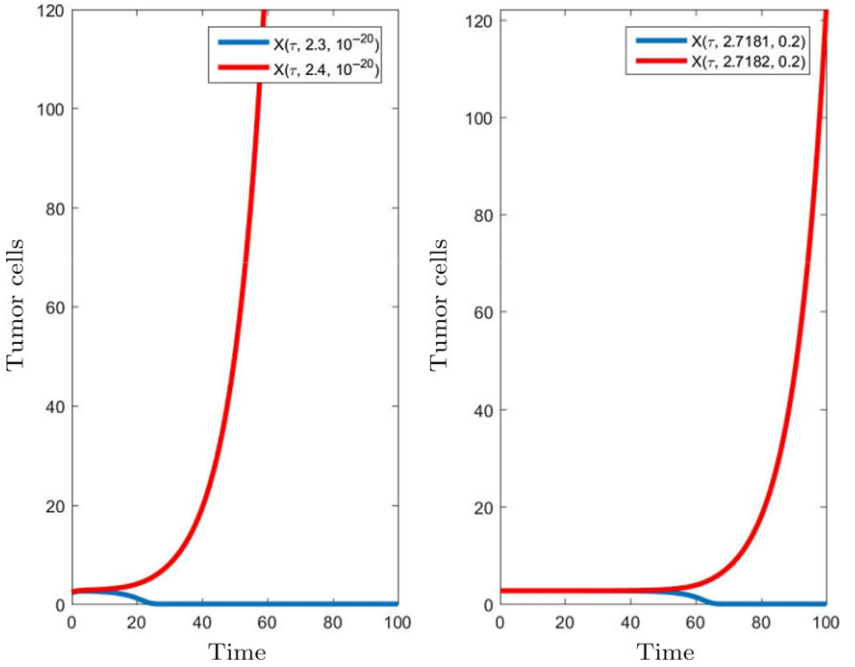

FIGURE 11. Evolution of the tumour cells within the context of the model (1.3) when $a = 1/10$, $b = 1/2$, $\ell = -0.1213$, $f = 1/5$, $g(x) = e^{-x}$, $\nu = 1$ and $\theta(\tau) = \frac{af}{b}$ ('optimal therapy'), for dimensionless time $\tau \in [0, 100]$ and different initial conditions in terms of immune and tumour cells. The plot on the left displays experimentally that $\mu_*^{num} \approx 2.351$. We have obtained analytically that $\mu_* = 1$. The plot on the right displays experimentally that $\mu^{*num} \approx 2.7182$. We have obtained analytically that $\mu^* \approx 2.7182$. Following the notation of this paper, $X(\tau, X_0, Y_0)$ denotes the first component of the unique solution $(X(\tau, X_0, Y_0), Y(\tau, X_0, Y_0))$ for the equation (1.3) verifying $X(0) = X_0$ and $Y(0) = Y_0$.

about this immunological barrier. At this point, the administration of an appropriate dose in the treatment plays a crucial role. Indeed, when we increase the dose in such a way that (2.5) holds, we can find a region of tumour clearance. In particular, our parameter μ_*, which was discussed in the introduction and analytically computed in (2.6), is connected with the mentioned region through the following property: *μ_* is an analytical threshold number of initial tumour cells below which the tumour clearance should be found (after applying the therapy) independently of the initial number of immune cells available in the host immune system to attack the cancer.*

To our surprise, in this setting we observe that, as of a certain moment, increasing the dose in the therapy does not reflect any change in the parameter μ_*. In this regard, we can choose a therapy with the lowest dose needed to eliminate the tumour, by reducing in this way its possible side effects reported in previous studies (see e.g. [32, 46]). Figures 11, 12 and 13 show particular examples of *'optimal therapies'* (in the above sense) where we have computed the parameter μ_* and compared it with its experimental estimation μ_*^{num} with the help of Matlab © software. It is also worth mentioning that, in spite of the fact that μ_*^{num} can be significantly better than μ_*, it is questionable whether it satisfies the same property as μ_*.

On the other hand, if the dose is not adequate, the application of the treatment can lead to an immunologically uncontrollable tumour growth. Indeed, in the administration of a low

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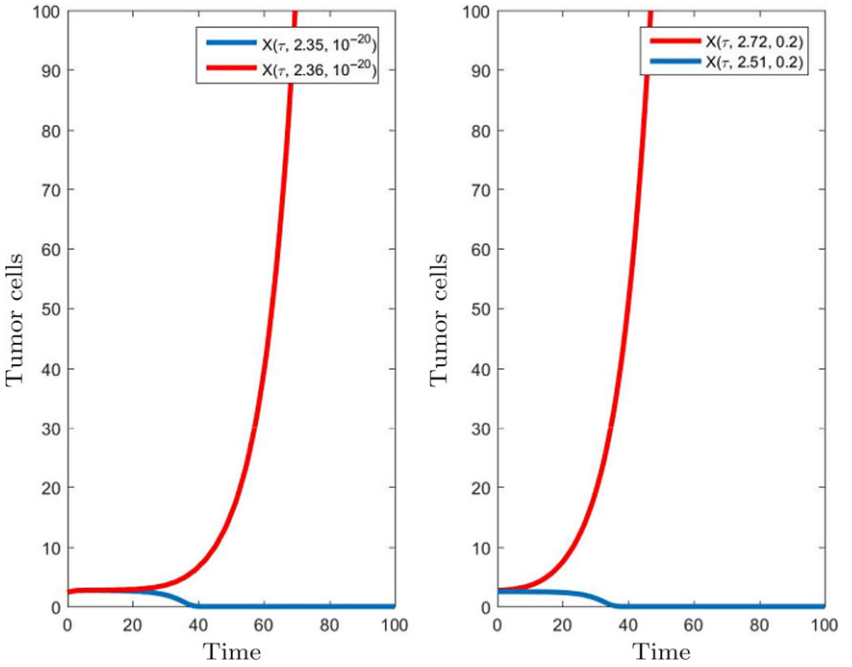

FIGURE 12. Evolution of tumour cells within the context of the model (1.3) when $a = 1/10$, $b = 1/2$, $\ell = -0.1213$, $f = 1/5$, $g(x) = e^{-x}$, $\nu = 1$ and $\theta(\tau) = \frac{2af}{b}\cos^2(\tau)$ ('optimal therapy') in the first case, whereas, in the second one, $\theta(t) = \frac{af}{b}\cos^2(\tau)$ ('low-dose therapy'); for dimensionless $\tau \in [0, 100]$ and different initial conditions in terms of immune and tumour cells. The plot on the left displays experimentally that $\mu_*^{num} \approx 2.354$. We have obtained analytically that $\mu_* \approx 0.8593$. The plot on the right shows experimentally that $\mu^{*num} \approx 2.515$. We have obtained analytically that $\mu^* \approx 2.7182$. Here, $X(\tau, X_0, Y_0)$ denotes the first component of the unique solution $(X(\tau, X_0, Y_0), Y(\tau, X_0, Y_0))$ for the equation (1.3) verifying $X(0) = X_0$ and $Y(0) = Y_0$.

dose in the treatment, for example, such that (6.13) holds, our analytical parameter μ^*, which was computed in (2.9), plays a fundamental role: *μ^* is a parameter for which a threshold number of immune cells, equivalent to a/b, is predicted below which an immunologically uncontrollable tumour growth should be found, assuming that the number of tumour cells, or the size of the tumour, before starting with the therapy is greater or equal than μ^*.* Figures 11, 12 and 13 show particular examples of low-dose therapies (in the above sense) where we have computed the parameter μ^* and compared it with its experimental estimation μ^{*num} with the help of Matlab© software. An immunologically uncontrollable tumour growth has been also reported in similar models studied in the literature, see for example, [5, 33].

Our model also reveals a curious phenomenon which can be connected with the so-called *tumour sneaking through model*, analysed in [33] (which refers to a specific process in which low amount of tumour cells can escape to the immune defences and grow into a large tumour). This fact occurs in Figures 4(a) and (b), and hence, it may only happen when the dose in the treatment is low and assuming certain biological factors so that the hypotheses of Theorem 4 do not hold. This growth of the tumour cells is of particular interest in our study since it is difficult to detect it numerically. It requires long time intervals in order to measure it, and hence,

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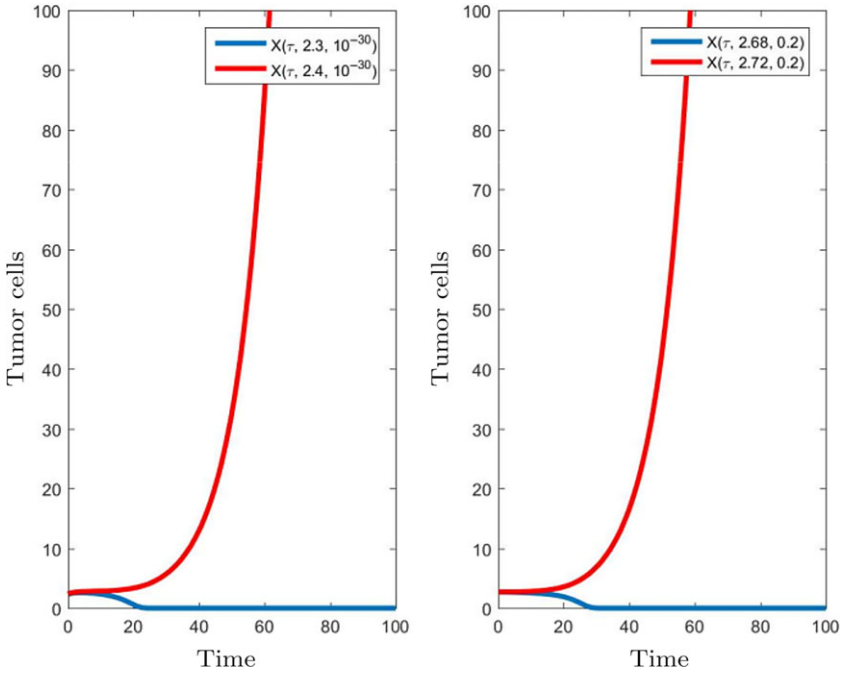

FIGURE 13. Evolution of tumour cells within the context of the model (1.3) when $a = 1/10$, $b = 1/2$, $\ell = -0.1213$, $f = 1/5$, $g(x) = e^{-x}$, $\nu = 1$, $L_{act} = 2.6$, $\tau_* = \pi$, θ is defined by (6.11), with $\sigma = \frac{af}{b}\left(\frac{\tau_*}{L_{act}}\right)$ ('optimal therapy') in the first case, whereas, in the second one, $\sigma = \frac{af}{b}$ ('low-dose therapy'); for dimensionless $\tau \in [0, 100]$ and different initial conditions in terms of immune and tumour cells. The plot on the left displays that $\mu_*^{num} \approx 2.366$. We have obtained analytically that $\mu_* \approx 0.8593$. The plot on the right displays experimentally that $\mu^{*num} \approx 2.685$. We have obtained analytically that $\mu^* \approx 2.7182$. Here, $X(\tau, X_0, Y_0)$ denotes the first component of the unique solution $(X(\tau, X_0, Y_0), Y(\tau, X_0, Y_0))$ for the equation (1.3) verifying $X(0) = X_0$ and $Y(0) = Y_0$.

it causes problems in the output of the numerical results (see Figure 14). In this context, the dynamics of this pattern needs to be more carefully studied, developing a better understanding for extracting more effective information about what circumstances lead, or not, to it. This study would complement Corollary 5 of this paper.

From the results reported here, *we arrive at the following conclusion:* among all the parameters involved in the model, the most important by far is b. Indeed, according to Theorem 4 and, in particular, to the examples given in this paper (see Examples 1, 2 and 3), as the parameter b grows, the effectiveness of the treatment increases simultaneously that its lowest doses needed to eliminate the tumour decreases. For instance, by applying the treatment of Example 2 and administering a dose $\sigma = 2af/b$, as b grows, simultaneously σ decreases and μ_* increases. In particular,

$$\sigma \to 0, \qquad \mu_* \to +\infty,$$

as $b \to +\infty$. In consequence, the model predicts that the optimal strategy would be to apply an immunotherapy treatment administering simultaneously cells immunologically modified for a more effective fight against the tumour. A similar conclusion is drawn in [45] by numerically

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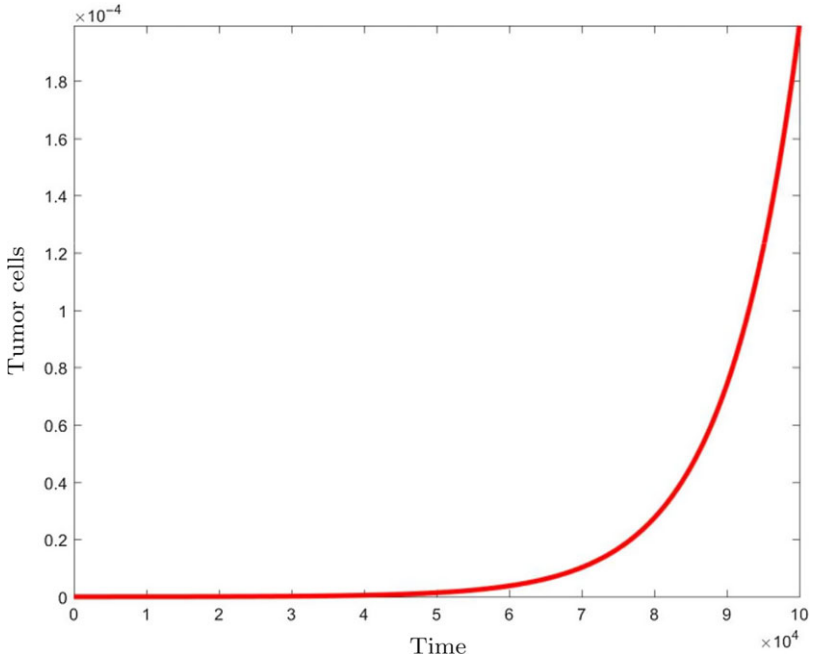

FIGURE 14. Evolution of tumour cells within the context of the model (1.3) when $a = 10^{-4}$, $b = 10^{-4}$, $\ell = -1$, $f = 100$, $g(x) = e^{-x}$, $\nu = 1$, $\theta = 0$; for dimensionless $\tau \in [0, 10^5]$ and initial conditions: $X_0 = 10^{-8}$ tumour cells and $Y_0 = 10^{-5}$ immune cells. This picture has been performed with Matlab © software.

analysing a specific model based on and validated by the experimental studies published in [17, 27].

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Conflict of interest

None.

References

[1] AGARWAL, R. P. & REGAN, D. O. (1996) Singular boundary value problems for superlinear second order ordinary and delay differential equations. *J. Differential Equations* **130**, 333–355.

[2] ARABAMERI, A., ASEMANI, D. & HAJATI, J. (2018) Mathematical modeling of in-vivo tumor-immune interactions for the cancer immunotherapy using matured dendritic cells. *J. Biolog. Syst.* **26**, 167–188.

[3] BELLOMO, N., BELLOUQUID, A. & DELITALA, M. (2004) Mathematical topics on the modelling complex multicellular systems and tumor immune cells competition. *Math. Models Methods Appl. Sci.* **14**, 1683–1733.

[4] BELLOMO, N. & PREZIOSI, L. (2000) Modelling and mathematical problems related to tumor evolution and its interaction with the immune system. *Math. Comput. Model.* **32**, 413–452.

https://doi.org/10.1017/S0956792521000152 Published online by Cambridge University Press

[5] De Boer, R. J. & Boerlijst, M. C. (1994) Diversity and virulence thresholds in AIDS. *Proc. Natl. Acad. Sci.* **94**, 544–548.
[6] Bonadonna, G. & Robustelli della Cuna, G. (editors) (1994) *Medicina Oncologica*, Masson, Milano, (in Italian), pp. 259–272.
[7] Brown, M. (1985) Homeomorphisms of two-dimensional manifolds. *Houston J. Math.* **11**, 455–469.
[8] Brú, A., Albertos, S., Subiza, J. L., García-Asenjo, J. L. & Brú, I. (2003) The universal dynamics of tumor growth. *Biophys. J.* **85**, 2948–2961.
[9] Campos, J. & Torres, P. (1999) On the structure of the set of bounded solutions on a periodic Liénard equation. *Proc. Amer. Math. Soc.* **127**, 1453–1462.
[10] Campos, J., Ortega, R. & Tineo, A. (1997) Homeomorphisms of the disk with trivial dynamics and extinction of competitive systems. *J. Differential Equations* **138**, 157–170.
[11] Capietto, A., Mawhin, J. & Zanolin, F. (1990) A continuation approach to superlinear periodic boundary value problems. *J. Differential Equations* **88**, 347–395.
[12] Castelli, R. & Garrione, M. (2018) Some unexpected results on the Brillouin singular equation: fold bifurcation of periodic solutions. *J. Differential Equations* **265**(6), 1502–1543.
[13] Chouaib, S., Asselin-Paturel, C., Mami-Chouaib, F., Caignard, A. & Blay, J. (1997) The host-tumor immune conflict: from immunosuppression to resistance and destruction. *Immunol. Today* **18**, 493–497.
[14] Cid, J. A., Propst, G. & Tvrdy, M. (2014) On the pumping effect in a pipe\tank flow configuration with friction. *Physica D* **273–274**, 28–33.
[15] De Coster, C. & Habets, P. (2004) The lower and upper solutions method for boundary value problems. In: *Handbook of Differential Equations*, ODE, Elsevier, p. 69–160.
[16] DeVita, V. T., Hellman, S. & Rosenberg, S. A. (2001) *Cancer: Principles and Practice of Oncology*. Lippincott Williams and Wilkins.
[17] Diefenbach, A., Jensen, E., Jamieson, A. & Raulet, D. (2001) Rae1 and H60 ligands of the NKG2D receptor stimulate tumor immunity. *Nature* **413**, 165–171.
[18] Doban, A. L. & Lazar, M. (2017) A switching control law approach for cancer immunotherapy of an evolutionary tumor growth model. *Math. Biosci.* **284**, 40–50.
[19] d'Onofrio, A. (2005) A general framework for modeling tumor-inmune system competition and immunotherapy: mathematical analysis and biomedical inferences. *Physica D* **208**, 220–235.
[20] d'Onofrio, A. & Gandolfi, A. (2004) Tumour eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al. (1999). *Math. Biosci.* **191**, 159–184.
[21] d'Onofrio, A. (2006) Tumour-immune system interaction: modeling the tumour-stimulated proliferation of effectors and immunotherapy. *Math. Models Methods Appl. Sci.* **16**, 1375–1401.
[22] d'Onofrio, A. (2008) Metamodeling tumor-immune system interaction, tumor evasion and immunotherapy. *Math. Comput. Model.* **47**, 614–637.
[23] d'Onofrio, A. & Gandolfi, A. (2013) *Mathematical Oncology*. Birkhauser.
[24] Fabry, C. & Fonda, A. (1998) Nonlinear resonance in asymmetric oscillators. *J. Differential Equations* **147**, 58–78.
[25] Fonda, A. & Toader, R. (2008) Periodic orbits of radially symmetric Keplerian-like systems: a topological degree approach. *J. Differential Equations* **244**, 3235–3264.
[26] Fonda, A. & Ureña, A. J. (2011) Periodic, subharmonic, and quasi-periodic oscillations under the action of a central force. *Disc. Cont. Dyn. Syst. Sec. A* **29**, 169–192.
[27] Dudley, M. E., Wunderlich, J. R., Robbins, P. F. *et al*. (2002) Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. *Science* **298**, 850–854.
[28] Forys, U., Waniewski, J. & Zhivkov, P. (2006) Anti-tumor immunity and tumor anti-immunity in a mathematical model of tumor immunotherapy. *J. Biol. Syst.* **14**, 13–30.
[29] Galach, M. (2003) Dynamics of the tumor-immune system competition: the effect of time delay. *Int. J. Applied Math. Comput. Sci.* **13**(3), 395–406.
[30] Hakl, R., Torres, P. J. & Zamora, M. (2011) Periodic solutions of singular second order differential equations: upper and lower functions. *Nonlin. Anal.* **TMA 74**, 7078–7093.
[31] Hirsch, M. (1988) Systems of differential equations which are competitive or cooperative. III. Competing species. *Nonlinearity* **1**, 51–71.

[32] KIRSCHNER, D. & PANETTA, J. C. (1998) Modeling immnotherapy of the tumor-immune interaction. *J. Math. Biol.* **37**, 235–252.
[33] KUZNETSOV, V. A., MAKALKIN, I. A., TAYLOR, M. & PERELSON, A. (1994) Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bull. Math. Biol.* **56**, 295–321.
[34] LOMTATIDZE, A. (2016) Theorems on differential inequalities and periodic boundary value problem for second-order ordinary differential equations. *Memoirs Diff. Equ. Math. Phys.* **67**, 1–129.
[35] MARRAS, C., MENDOLA, C., LEGNANI, F. G. & DIMECO, F. (2003) Immunotherapy and biological modifiers for the treatment of malignant brain tumors. *Curr. Opin. Oncol.* **15**, 204–208.
[36] MAWHIN, J. (1993) Topological degree and boundary value problems for nonlinear differential equations. In: M. Furi (editor), *Topological Methods for Ordinary Differential Equations*. Lect. Notes Math., vol. 1537, Springer, Berlin, p. 73–142.
[37] MICHELSON, S. & LEITH, J. (1993) Growth factors and growth control of heterogeneous populations. *Bull. Math. Biol.* **55**, 993–1011.
[38] MICHELSON, S. & LEITH, J. T. (1994) Dormancy, regression and recurrence: towards a unifying theory of tumor growth control. *J. Teor. Biol.* **169**, 327–338.
[39] MICHELSON, S., MILLER, B., GLICKSMAN, A. & LEITH, J. (1987) Tumor micro-ecology and competitive interactions. *J. Theor. Biol.* **128**, 233–246.
[40] DE MOTTONI, P. & SCHIAFFINO, A. (1981) Competition systems with periodic coefficients: a geometric approach. *J. Math. Biol.* **11**, 319–335.
[41] MURRAY, J. D. (2001) Mathematical Biology: I. An Introduction, Springer.
[42] NANI, F. & FREEDMAN, H. I. (2000) A mathematical model of cancer treatment by immunotherapy. *Math. Biosci.* **163**, 159–199.
[43] ORTEGA, H. (1999) Un Modelo Logístico para Crecimiento Tumoral en Presencia de Células Asesinas. *Revista Mexicana de Ingeniería Biomédica* **20** (in spanish), 61–67.
[44] ORTEGA, R. & TINEO, A. (1995) On the number of positive periodic solutions for planar competing Lotka-Volterra systems. *J. Math. Anal. Appl.* **193**, 975–978.
[45] DE PILLIS, L. G., RADUNSKAYA, A. E. & WISEMAN, C. L. (2005) A validated mathematical model of cell-mediated immune response to tumor growth. *Cancer Res.* **65**, 7950–7958.
[46] PRENDERGAST, G. C. & JAFFEE, E. M. (2013) *Cancer Immunotherapy: Immune Suppression and Tumor Growth*, 2nd edn. (2013).
[47] RANCHUNKOVÁ, I., STANĚK, S., & TVRDÝ, M. (2009) *Solvability of Nonlinear Singular Problems for Ordinary Differential Equations*, Vol. 5. Hindawi Publishing Corporation.
[48] ROBERTSON-TESSI, M., EL-KAREH, A. & GORIELY, A. (2012) A mathematical model of tumor-immune interactions. *J. Teor. Biol.* 294, 56–73.
[49] SCHMIELAU, J. & FINN, O. J. (2001) Activated granulocytes and granulocyte-derived gydrogen peroxide are the underlying mechanism of suppression of $T-$cell function in advanced cancer patients. *Cancer Res.* **61**, 4756–4760.
[50] SMALE, E. (1976) On the differential equations of species in competition. *J. Math. Biol.* **3**, 5–7.
[51] SOTOLONGO-COSTA, O., MORALES-MOLINA, L., RODRÍGUEZ-PÉREZ, D. ANTONRAZ, J. C. & CHACÓN-REYES, M. (2003) Behaviour of tumors under nonstationary therapy. *Physica D* **178**, 242–253.
[52] STEPANOVA, N. V. (1980) Course of the immune reaction during the development of a malignant tumor. *Biophysics* **24**, 917–923.
[53] SZYMÁNSKA, S. (2003) Analysis of the immunotherapy models in the context of cancer dynamics. *Int. J. Appl. Math. Comput. Sci.* **13**, 407–418.
[54] TALKINGTON, A., DANTOIN, C. & DURRETT, R. (2018) Ordinary differential equation models for adoptive immunotherapy. *Bull. Math. Biol.* **80**, 1059–1083.
[55] VAYDIA, V. G. & ALEXANDRO, F. J. (1982) Evaluation of some mathematical models for tumor growth. *Int. J. Bio-Med. Comput.* **13**, 19–35.
[56] DE VLADAR, H. P. & GONZÁLEZ, J. A. (2004) Dynamic response of cancer under the influence of immunological activity and therapy. *J. Theor. Biol.* **227**, 335–348.
[57] ZITAN, A. & ORTEGA, R. (1994) Existence of asymptotically stable periodic solutions of a forced equation of Liénard type. *Nonlinear Anal.* **22**, 993–103.