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Dynamical analysis of chemotherapy models with time-dependent infusion

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ABSTRACT

Classical mathematical models for chemotherapy assume a constant infusion rate of the chemotherapy agent. However in reality the infusion rate usually varies with respect to time, due to the natural (temporal or random) fluctuation of environments or clinical needs. In this work we study a non-autonomous chemotherapy model where the injection rate and injection concentration of the chemotherapy agent are time-dependent. In particular, we prove that the non-autonomous dynamical system generated by solutions to the non-autonomous chemotherapy system possesses a pullback attractor. In addition, we investigate the detailed interior structures of the pullback attractor to provide crucial information on the effectiveness of the treatment. The main analytical tool used is the theory of non-autonomous dynamical systems. Numerical experiments are carried out to supplement the analysis and illustrate the effectiveness of different types of infusions.

1. Introduction

As the most common and fundamental form of cancer treatment, the chemotherapy is done by injecting an agent into the body to attack the cancer cells. It is well known that the chemotherapy agent attacks not only the cancer cells, but also the normal cells, and causes non-negligible side effects. In order to design a chemotherapy agent that maximizes the effect on cancer and minimizes the side effects, it is important to investigate the mechanism of chemotherapy systems by various clinical and theoretical approaches. To this end, mathematical modeling, analysis and computing have been used widely to study chemotherapy systems from different points of view (see [1–7] and references therein).

This work is based on dynamical models that describe the interactions among the chemotherapy agent, the normal cells and the cancer cells, at a single site for treatment in the body (see, e.g., [7]). Let $x(t)$ be the concentration of the chemotherapy agent, and let $y_1(t)$ and $y_2(t)$ be the concentration of the normal and

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cancer cells at the treatment site, respectively. The (autonomous) chemotherapy model reads

$$\frac{\mathrm{d}x}{\mathrm{d}t} = D(I - x(t)) - \gamma_1 x(t) U_1(y_1(t)) - \gamma_2 x(t) U_2(y_2(t)), \tag{1}$$

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = \beta_1 y_1(t)\left(1 - \frac{y_1(t)}{\kappa_1}\right) - \delta_1 y_1(t) y_2(t) - \alpha_1 x(t) U_1(y_1(t)), \tag{2}$$

$$\frac{\mathrm{d}y_2}{\mathrm{d}t} = \beta_2 y_2(t)\left(1 - \frac{y_2(t)}{\kappa_2}\right) - \delta_2 y_1(t) y_2(t) - \alpha_2 x(t) U_2(y_2(t)), \tag{3}$$

where D and I are the rates at which the chemotherapy agent is injected and washout, respectively. The product of D and I then gives the infusion rate of the chemotherapy agent to the treatment site.

Classical chemotherapy models assume that the infusion rate DI is constant. However in reality the injection rate D and injection concentration I of the chemotherapy agent are barely constant; they rather vary with respective time due to either clinical needs or the natural fluctuation of environments. This motivates the study of the chemotherapy model with time-varying input, i.e., with $I = I(t)$ and $D = D(t)$ in equation (1). More precisely, we are interested in studying the long term dynamics of the following nonautonomous chemotherapy system

$$\frac{\mathrm{d}x}{\mathrm{d}t} = D(t)(I(t) - x(t)) - c_1\alpha_1 \frac{x(t)y_1(t)}{\lambda_1 + y_1(t)} - c_2\alpha_2 \frac{x(t)y_2(t)}{\lambda_2 + y_2(t)}, \tag{4}$$

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = \beta_1 y_1(t)\left(1 - \frac{y_1(t)}{\kappa_1}\right) - \delta_1 y_1(t) y_2(t) - \alpha_1 \frac{x(t)y_1(t)}{\lambda_1 + y_1(t)}, \tag{5}$$

$$\frac{\mathrm{d}y_2}{\mathrm{d}t} = \beta_2 y_2(t)\left(1 - \frac{y_2(t)}{\kappa_2}\right) - \delta_2 y_1(t) y_2(t) - \alpha_2 \frac{x(t)y_2(t)}{\lambda_2 + y_2(t)}. \tag{6}$$

Here the normal and cancer cells are assumed to follow a logistic growth model, with β_1 and β_2 being the specific birth rates for small concentrations, and κ_1 and κ_2 being the carrying capacities of the normal and cancer cells at the treatment site, respectively. The carrying capacity has been widely used to study the cancer cells' adaptive responses (see, e.g., [8,9]). More precisely, cancer cells grow rapidly initially, but with a decelerating rate as they grow (see e.g., [10]). Therefore the per capita growth rate of cancer cells cannot be constant that yields an exponential growth. The logistic model used in (6) is a classical example of a per capita growth rate of cancer cells depending on the host carrying capacity κ_2 (see e.g., [11]). When the population size of cancer cells $y_2 \ll \kappa_2, 1 - y_2/\kappa_2 \approx 1$ and the per capita growth is approximately exponential. On the other hand when the population size of cancer cells grows and approaches the carrying capacity $\kappa_2, 1 - y_2/\kappa_2 \to 0$ and the cancer population is impeded.

Competition (for available resources) exists between the normal and cancer cells, and is assumed to be a Lotka–Volterra model (see [12–14] and references therein). Let δ_1 and δ_2 be the competition coefficients that represent the effect of cancer cells on normal cells, and normal cells on cancer cells, respectively. Note that when $\delta_1 < 1$, the effect of cancer cells on normal cells is less than the effect of normal cells on their own. On the other hand when $\delta_2 > 1$, the effect of cancer cells on normal cells is greater than the effect of normal cells on their own. The product $\delta_1 y_2$ then represents the effect of an equivalent number of cancer cells and is included in the competition term. The term $\delta_1 y_1$ is interpreted in the same manner.

The interactions between the chemotherapy agent and the cells can be described by a predator–prey model, in the sense that the chemotherapy agent acts like a predator and "preys" on both the normal and cancer cells at the treatment site. However different from the predator–prey model, the chemotherapy agent will be consumed instead of growing due to the "predation". Let α_1 and α_2 be the predation coefficients of the chemotherapy agent on normal and cancer cells, and let γ_1 and γ_2 be the combination rates of the chemotherapy with the normal and cancer cells, respectively.

For $i = 1, 2, U_i$ is the uptake function (or consumption function), that describes how the normal or cancer cells are killed by the chemotherapy agent. Basis assumptions on the uptake function $U_j : \mathbb{R}^+ \to \mathbb{R}^+$ $(j = 1, 2)$

include

(i) $U_j(0) = 0$ and $U_j(y) > 0$ for all $y > 0$.
(ii) $\lim_{y\to\infty} U_j(y) = L_j$, where $L_j < \infty$.
(iii) U_j is continuously differentiable and satisfies $U_j' > 0$.

Note that conditions (i) and (ii) of the uptake function U_j ensure the existence of a positive constant $L > 0$ such that

$$U_j(y) \le L \quad \text{for all } y \in [0, \infty).$$

In this work we assume that the uptake function follows the Michaelis–Menten (Holling type-II) form (see e.g. [15]) :

$$U_j(y) = \frac{y}{\lambda_j + y}, \quad j = 1, 2$$

where λ_j is the half-saturation constant that determines the speeds at which the normal or cancer cell reaches carrying capacity in the absence of competition and predation. In addition, notice that the combination rates γ_j $(j = 1, 2)$ are proportional to the predation coefficients α_j, i.e., $\gamma_j = c_j \cdot \alpha_j$ for $j = 1, 2$.

The major tool used to analyze the above system is the novel theory of pullback attractors for nonautonomous dynamical systems [16], and in particular for nonautonomous dynamical systems in the applied sciences [17]. Basic terminology and theory of nonautonomous dynamical systems related to this work will be introduced in the next section. In Section 3 we will study the existence and uniqueness of a non-negative and bounded solution to the system (4)–(6). In Section 4 we will study the long term dynamics of system (4)–(6), including the existence of a nonautonomous attractor and detailed interior structures of the attractor under two different scenarios: variable injection rate, and variable injection concentration. Numerical simulations will be presented in Section 5 to supplement the analysis done in Section 4, and in particular, to illustrate effectiveness of different infusion strategies. Some closing remarks will be given in Section 6.

2. Preliminaries on nonautonomous dynamical systems

In this section we provide some preliminary knowledge on nonautonomous dynamical systems (see, e.g., [16]) that is required in the sequel.

Consider an initial value problem for a nonautonomous ordinary differential equation in $\mathbb{R}^d$,

$$\frac{\mathrm{d}u(t)}{\mathrm{d}t} = g(u, t), \quad u(t_0) = u_0. \tag{7}$$

The solution of (7) usually depends on both the actual time t and the initial time t_0 rather than just on the elapsed time $t - t_0$ as in an autonomous system. The solution mapping $u(t; t_0, u_0)$ of the initial value problem (7) for which an existence and uniqueness theorem holds then satisfies

(i) the initial value property $u(t_0, t_0, u_0) = u_0$;
(ii) the two-parameter semigroup evolution property

$$u(t_2, t_0, u_0) = u\left(t_2, t_1, u(t_1, t_0, u_0)\right), \quad t_0 \le t_1 \le t_2;$$

(iii) the continuity property that $(t, t_0, u_0) \mapsto u(t, t_0, u_0)$ is continuous on $\mathbb{R}^2_{\ge} \times \mathbb{R}^d$ where $\mathbb{R}^2_{\ge} := \{(t, t_0) \in \mathbb{R}^2 : t \ge t_0\}$.

These properties of the solution mapping of nonautonomous ordinary differential equations motivate the *process* formulation of a nonautonomous dynamical system on a state space $\mathbb{R}^d$ (or, more generally, a metric space (X, dist_X)) and time set $\mathbb{R}$ for a continuous-time process.

Definition 2.1. A process φ on space $\mathbb{R}^d$ is a family of mappings

$$\varphi(t, t_0, \cdot) : \mathbb{R}^d \to \mathbb{R}^d, \quad t \geq t_0$$

which satisfies

(i) initial value property: $\varphi(t_0, t_0, u) = u$ for all $u \in \mathbb{R}^d$ and any $t_0 \in \mathbb{R}$;
(ii) two-parameter semigroup property: for all $u \in \mathbb{R}^d$ it holds

$$\varphi(t_2, t_0, u) = \varphi\left(t_2, t_1, \phi(t_1, t_0, u)\right), \quad \forall t_2 \geq t_1, t_1 \geq t_0;$$

(iii) continuity property: the mapping $(t, t_0, u) \mapsto \varphi(t, t_0, u)$ is continuous on $\mathbb{R}^2_{\geq} \times \mathbb{R}^d$.

Definition 2.2. Let φ be a process on $\mathbb{R}^d$. A family $\mathscr{K} = \{K(t) : t \in \mathbb{R}\}$ of nonempty subsets of $\mathbb{R}^d$ is said to be φ-invariant if $\varphi\left(t, t_0, K(t_0)\right) = K(t)$ for all $t \geq t_0$, and is said to be φ-positively invariant if $\varphi\left(t, t_0, K(t_0)\right) \subseteq K(t)$ for all $t \geq t_0$.

Definition 2.3. Let φ be a process on $\mathbb{R}^d$. A φ-invariant family $\mathscr{A} = \{A(t) : t \in \mathbb{R}\}$ of nonempty compact subsets of $\mathbb{R}^d$ is called a forward attractor of φ if it forward attracts all families $\mathscr{B} = \{B(t) : t \in \mathbb{R}\}$ of nonempty bounded subsets of $\mathbb{R}^d$, i.e.,

$$\mathrm{dist}\left(\varphi(t, t_0, B(t_0)), A(t)\right) \to 0 \quad \text{as } t \to \infty \ (t_0 \text{ fixed}),$$

and is called a pullback attractor of φ if it pullback attracts all families $\mathscr{B} = \{B(t) : t \in \mathbb{R}\}$ of nonempty bounded subsets of $\mathbb{R}^d$, i.e.,

$$\mathrm{dist}\left(\varphi(t, t_0, B(t_0)), A(t)\right) \to 0 \quad \text{as } t_0 \to -\infty \ (t \text{ fixed}).$$

The existence of a pullback attractor follows from that of a pullback absorbing family, which is usually more easily determined.

Definition 2.4. A family $\mathscr{K} = \{K(t) : t \in \mathbb{R}\}$ of nonempty compact subsets of $\mathbb{R}^d$ is called a pullback absorbing family for a process φ if for each $\tau \in \mathbb{R}$ and every family $\mathscr{B} = \{B(t) : t \in \mathbb{R}\}$ of nonempty bounded subsets of $\mathbb{R}^d$ there exists some $T = T(\tau, \mathscr{B}) \geq 0$ such that

$$\varphi\left(\tau, t_0, B(t_0)\right) \subseteq K(\tau) \quad \text{for all } t_0 \in \mathbb{R} \text{ with } t_0 \leq \tau - T.$$

The proof of the following theorem is well known, see e.g., [16].

Theorem 2.1. *Suppose that a process φ on $\mathbb{R}^d$ has a φ-positively invariant pullback absorbing family $\mathscr{K} = \{K(t) : t \in \mathbb{R}\}$ of nonempty compact subsets of $\mathbb{R}^d$. Then φ has a unique global pullback attractor $\mathscr{A} = \{A(t) : t \in \mathbb{R}\}$ with its component sets determined by*

$$A(t) = \bigcap_{t_0 \leq t} \varphi\left(t, t_0, K(t_0)\right) \quad \textit{for each } t \in \mathbb{R}.$$

If $\mathscr{K}$ is not φ-positively invariant, then

$$A(t) = \bigcap_{s \geq 0} \overline{\bigcup_{t_0 \leq t-s} \varphi\left(t, t_0, K(t_0)\right)} \quad \textit{for each } t \in \mathbb{R}.$$

A pullback attractor consists of *entire solutions*, i.e., functions $\xi : \mathbb{R} \to \mathbb{R}$ such that $\xi(t) = \varphi(t, t_0, \xi(t_0))$ for all $t \geq t_0$. In special cases it consists of a single entire solution.

Definition 2.5. A nonautonomous dynamical system φ is said to satisfy a *uniform strictly contracting property* if for each $r > 0$, there exist positive constants a and b such that

$$\|\varphi(t, t_0, u_0) - \varphi(t, t_0, v_0)\|^2 \, r \leq a e^{-b(t-t_0)} \cdot \|u_0 - v_0\|^2$$

for all $t \geq t_0$ and $u_0, v_0 \in \mathbb{B}(0, r)$, where $\mathbb{B}(0, r)$ is the closed ball in $\mathbb{R}^d$ centered at the origin with radius $r > 0$.

This property suffices in combination with a pullback absorbing set to ensure the existence of an attractor in both the forward and pullback sense that consists of singleton sets, i.e., a single entire solution. The proof of the following result involves the construction of an appropriate Cauchy sequence which converges to a unique limit, see [18,19].

Theorem 2.2. *Suppose that a process φ on $\mathbb{R}^d$ is uniform strictly contracting on a φ-positively invariant pullback absorbing family $\mathscr{K} = \{K(t) : t \in \mathbb{R}\}$ of nonempty compact subsets of $\mathbb{R}^d$. Then the process φ has a unique global forward and pullback attractor $\mathscr{A} = \{A(t) : t \in \mathbb{R}\}$ with component sets consisting of singleton sets, i.e., $A(t) = \{\xi^*(t)\}$ for each $t \in \mathbb{R}$, where ξ^* is an entire solution of the process.*

Remark 2.1. Note that pullback and forward attractions do not imply each other, and hence a pullback attractor is not necessarily a forward attractor and vice versa. However Theorem 2.2 ensures the existence of an attractor in both the pullback and the forward senses that consists of singleton sets, while a process satisfies Definition 2.5.

3. Properties of solutions

Throughout this study, all parameters in the model, $\alpha_j, \beta_j, \delta_j, \kappa_j, c_j (j = 1, 2)$ are assumed to be strictly positive. In addition, several more inequalities can be imposed among the parameters to make the model more realistic. It is well known that cancer cells usually out compete the normal cells (independent of initial conditions) when no treatment is offered. The governing biological mechanism is very complicated and does not simply depend on the growth and division of cancer cells (see e.g., [20,21]). Most forms of chemotherapy are designed on the simplified assumption that cancer cells grow faster [7], i.e.,

$$\beta_2 > \beta_1. \tag{8}$$

Second, the chemotherapy agent must be considerably more effective in killing cancer cells than in killing normal cells in order for the treatment to be effective, which leads to the assumption [7]

$$\alpha_2 \gg \alpha_1. \tag{9}$$

Furthermore, we assume that the injection rate and the injection concentration of the chemotherapy agent are varying continuously in time (e.g., periodically or randomly), in bounded positive intervals:

$$D(t) \in [d_m, d_M], \qquad I(t) \in [i_m, i_M], \quad t \in \mathbb{R}. \tag{10}$$

At last we assume that the initial concentrations of the normal cells and cancer cells are strictly positive (to start the treatment), while the initial concentration of the chemotherapy agent is nonnegative, i.e.,

$$x_0 = x(t_0) \geq 0, \qquad y_{1_0} = y_1(t_0) > 0, \qquad y_{2_0} = y_2(t_0) > 0. \tag{11}$$

For simplicity, denote

$$u(t) = (x(t), y_1(t), y_2(t)), \qquad u_0 = (x_0, y_{1_0}, y_{2_0}).$$

Then system (4)–(6) can be written in a compact form

$$\frac{\mathrm{d}u}{\mathrm{d}t} = L(t)u + f(u,t), \quad u(t_0) = u_0, \tag{12}$$

where

$$L(t) = \begin{pmatrix} -D(t) & 0 & 0 \\ 0 & \beta_1 & 0 \\ 0 & 0 & \beta_2 - \nu \end{pmatrix},$$

and $f : \mathbb{R}^3 \times [t_0, \infty) \to \mathbb{R}^3$ is given by

$$f(u,t) = \begin{pmatrix} D(t)I(t) - c_1\alpha_1 \dfrac{xy_1}{\lambda_1 + y_1} - c_2\alpha_2 \dfrac{xy_2}{\lambda_2 + y_2} \\ -\beta_1 \dfrac{y_1^2}{\kappa_1} - \delta_1 y_1 y_2 - \alpha_1 \dfrac{xy_1}{\lambda_1 + y_1} \\ -\beta_2 \dfrac{y_2^2}{\kappa_2} - \delta_2 y_1 y_2 - \alpha_2 \dfrac{xy_2}{\lambda_2 + y_2} \end{pmatrix}.$$

Denote

$$\mathbb{R}^3_+ := \{(x, y_1, y_2) : x \geq 0, y_1 \geq 0, y_2 \geq 0\},$$

we have the following lemma on existence and uniqueness of bounded nonnegative solutions for system (12).

Lemma 3.1. *For any initial time $t_0 \in \mathbb{R}$ and initial conditions $u_0 \in \mathbb{R}^3_+$, system (12) has a unique bounded solution $u(\cdot, t_0, u_0) \in \mathcal{C}^1([t_0, \infty), \mathbb{R}^3_+)$.*

Proof. First since $D(t)$ is bounded, the operator L generates an evolution system on $\mathbb{R}^3$. Second, since $D(t)$ and $I(t)$ are both continuous, function f is continuous in t and locally Lipschitz in u. Then by the classical results from the theory of ordinary differential equations system (12) possesses a unique local solution.

Notice that the planes $y_1 = 0$ and $y_2 = 0$ are invariant, in the sense that

$$\left.\frac{\mathrm{d}y_1}{\mathrm{d}t}\right|_{y_1=0} = 0 \quad \text{and} \quad \left.\frac{\mathrm{d}y_2}{\mathrm{d}t}\right|_{y_2=0} = 0.$$

Moreover,

$$\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=0} = D(t)I(t) \geq d_m i_m > 0.$$

Thus by the continuity of solutions, any solution trajectory that starts from $\mathbb{R}^3_+$ will stay there forever, i.e., $\mathbb{R}^3_+$ is positively invariant.

By Eq. (4), and assumption (10), we have for any $u \in \mathbb{R}^3_+$,

$$\frac{\mathrm{d}x}{\mathrm{d}t} \leq D(t)(I(t) - x(t)) \leq d_M i_M - d_m x(t).$$

Thus by a standard comparison argument,

$$0 \leq x(t) \leq \max\left\{x_0, \frac{d_M i_M}{d_m}\right\}, \quad t \in [t_0, \infty). \tag{13}$$

By Eqs. (5), (6), for any $u \in \mathbb{R}^3_+$,

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} \leq \beta_1 y_1 \left(1 - \frac{y_1}{\kappa_1}\right), \qquad \frac{\mathrm{d}y_2}{\mathrm{d}t} \leq \beta_2 y_2 \left(1 - \frac{y_2}{\kappa_2}\right).$$

Thus by similar comparison arguments,

$$0 \le y_1(t) \le \max\{y_{1_0}, \kappa_1\}, \qquad 0 \le y_2(t) \le \max\{y_{2_0}, \kappa_2\}, \quad t \in [t_0, \infty). \tag{14}$$

By (13) and (14) and the existence of local solutions, for any initial condition $u_0 = (x_0, y_{1_0}, y_{2_0}) \in \mathbb{R}^3_+$ system (12) has a unique solution defined for all $t \ge t_0$ and remains in the bounded region

$$\mathcal{R} := \left\{ (x, y_1, y_2) \in \mathbb{R}^3_+ : \begin{array}{l} x \le \max\{x_0, d_M i_M/d_m\}, \\ y_1 \le \max\{y_{1_0}, \kappa_1\}, y_2 \le \max\{y_{2_0}, \kappa_2\} \end{array} \right\}.$$

This completes the proof.

Lemma 3.1 allows us to define a continuous process $\{\varphi(t, t_0)\}_{t \ge t_0}$ on $\mathbb{R}^3_+$ via

$$\varphi(t, t_0, u_0) = u(t; t_0, u_0), \quad \forall u_0 \in \mathbb{R}^3_+. \tag{15}$$

In the next section we will investigate the long term dynamics, in particular the existence and geometric details of the pullback attractor for the process $\{\varphi(t, t_0)\}_{t \ge t_0}$.

4. Long term dynamics of chemotherapy

In this section we will construct conditions under which the process $\{\varphi(t, t_0)\}_{t \ge t_0}$ defined by (15) has a pullback attractor. Moreover we will study the interior geometric structures of the attractor, and how the injection rate and injection concentration of the chemotherapy agent affects the structures of the attractor.

Theorem 4.1. *Let $0 < d_m < d_M < \infty, 0 < i_m < i_M < \infty$ and assume that $D : \mathbb{R} \to [d_m, d_M]$ and $I : \mathbb{R} \to [i_m, i_M]$ are continuous. Then the process defined by (15) has a pullback attractor $\mathscr{A} = \{A(t) : t \in \mathbb{R}\}$ inside the nonnegative quadrant $\mathbb{R}^3_+$.*

Proof. Recall from the proof of Lemma 3.1 that

$$\frac{\mathrm{d}x}{\mathrm{d}t} \le d_M i_M - d_m x(t).$$

It is then straightforward to obtain

$$x(t) \le \frac{d_M i_M}{d_m}\left(1 - e^{d_m(t_0 - t)}\right) + x_0 e^{d_m(t_0 - t)}, \quad \forall t \ge t_0,$$

which implies that

$$\lim_{\substack{t_0 \to -\infty \\ t \text{ fixed}}} x(t) \le \frac{d_M i_M}{d_m} \quad \text{and} \lim_{\substack{t \to \infty \\ t_0 \text{ fixed}}} x(t) \le \frac{d_M i_M}{d_m}.$$

Similarly by solving the Riccati equations

$$\frac{\mathrm{d}y_j}{\mathrm{d}t} = \beta_j y_j \left(1 - \frac{y_j}{\kappa_j}\right), \quad j = 1, 2,$$

and using standard comparison theory we obtain that

$$\lim_{\substack{t_0 \to -\infty \\ t \text{ fixed}}} y_j(t) \le \kappa_j \quad \text{and} \lim_{\substack{t \to \infty \\ t_0 \text{ fixed}}} y_j(t) \le \kappa_j, \quad j = 1, 2.$$

For any $\varepsilon > 0$, define the nonempty compact set

$$K_\varepsilon := \left\{ (x, y_1, y_2) \in \mathbb{R}^3_+ : x \le \frac{d_M i_M}{d_m} + \varepsilon,\ y_1 \le \kappa_1 + \varepsilon,\ y_2 \le \kappa_2 + \varepsilon \right\}.$$

Then K_ε is a positively invariant absorbing set for $\{\varphi(t,t_0)\}_{t\geq t_0}$. It follows immediately from Theorem 2.1 that the process defined by (15) has a pullback attractor $\mathscr{A} = \{A(t) : t \in \mathbb{R}\}$ consisting of non-empty compact subsets of $\mathbb{R}^3_+$. This completes the proof.

4.1. Constant injection rate and concentration

For the special autonomous case where $D(t) \equiv D$ and $I(t) \equiv I$, possible steady states of Eqs. (4)–(6) and their local stability properties were studied in [7] by analyzing eigenvalues of the Jacobian matrix around each steady state. The attractor thus consists of single or multiple singleton points under different conditions. For comparison purpose, here we summarize the stability results obtained in [7] in the context of attractors.

Denote by x^*, y_1^* and y_2^* the generic steady state of $x(t), y_1(t)$, and $y_2(t)$, respectively. Then there are the four different joint steady states between the normal and the cancer cells: the "axial steady state" $y_1^* = y_2^* = 0$, the "preferred steady state" with $y_1^* > 0$ and $y_2^* = 0$, the "persistence steady state" with $y_1^* > 0$ and $y_2^* > 0$, and the "failure steady state" with $y_1^* = 0$ and $y_2^* > 0$.

Lemma 4.1. *There exists a unique preferred steady state if*

$$\alpha_1 I < \beta_1 \lambda_1, \tag{16}$$

and there exist two distinct preferred steady states if

$$D\lambda_1 < \kappa_1(D + c_1\alpha_1) \quad \textit{and} \quad D\lambda_1 < \frac{\alpha_1 DI}{\beta_1} < \frac{[D\lambda_1 + \kappa_1(D + c_1\alpha_1)]^2}{4\kappa_1(D + c_1\alpha_1)}. \tag{17}$$

Lemma 4.2. *There exists a unique failure steady state if*

$$\alpha_2 I < \beta_2 \lambda_2, \tag{18}$$

and there exist two distinct failure steady states if

$$D\lambda_2 < \kappa_2(D + c_2\alpha_2) \quad \textit{and} \quad D\lambda_2 < \frac{\alpha_2 DI}{\beta_2} < \frac{[D\lambda_2 + \kappa_2(D + c_2\alpha_2)]^2}{4\kappa_2(D + c_2\alpha_2)}. \tag{19}$$

The axial steady state $(I, 0, 0)$ always exists, but becomes unstable if there exists a unique preferred or a unique failure steady state. In fact, the eigenvalues associated with the axial steady state $(I, 0, 0)$ are $-D, \beta_1 - \alpha_1 I/\lambda_1$ and $\beta_2 - \alpha_2 I/\lambda_2$, and hence $(I, 0, 0)$ is a hyperbolic saddle point if the assumption (16) or (18) is satisfied. The existence and stability of the persistence steady states were not discussed in [7] due to the complexity of the calculations of eigenvalues associated with (x^*, y_1^*, y_2^*) for $y_1^* > 0$ and $y_2^* > 0$.

Remark 4.1. A different approach will be used to investigate the persistence states (not necessarily steady states) for the nonautonomous system (4)–(6), which can also be used here to analyze the persistence steady states for the special autonomous case with constant D and I. But to avoid repeated calculations, we will skip the analysis here.

According to [7], a preferred steady state $(x^*, y_1^*, 0)$ is locally asymptotically stable if

$$\beta_2 < \delta_2 y_1^* + \frac{\alpha_2}{\lambda_2} x^*, \tag{20}$$

and a failure steady state $(x^*, 0, y_2^*)$ is locally asymptotically stable if

$$\beta_1 < \delta_1 y_2^* + \frac{\alpha_1}{\lambda_1} x^*. \tag{21}$$

In summary we have the following Theorem, conditional on all preferred steady states satisfying (20) and all failure steady states satisfying (21).

Theorem 4.2. *When $D(t) \equiv D$ and $I(t) \equiv I$, the (autonomous) attractor $\mathscr{A}$ of system (4)–(6) consists of the axial steady state $\{(I, 0, 0)\}$, possible persistence steady states $\{(x^*, y_1^*, y_2^*)\}$ and*

(i) *one unique preferred steady state and one unique failure steady state if (16) and (18) hold;*
(ii) *one unique preferred steady state and two distinct failure steady states if (16) and (19) hold;*
(iii) *two distinct preferred steady state and one unique failure steady state if (17) and (18) hold;*
(iv) *two distinct preferred steady states and two distinct failure steady states if (17) and (19) hold.*

Remark 4.2. Without assuming assumptions (20) and (21), a Theorem similar to Theorem 4.2 could still be established to include more information on possible joint steady states, but with long and tedious statements. Since our main focus of this work is the nonautonomous chemotherapy system (4)–(6), to avoid redundant calculations, the reader is referred to [7] for detailed stability analysis on the special case of autonomous system.

We will next investigate the interior structures of the pullback attractor $\mathscr{A} = \{A(t) : t \in \mathbb{R}\}$ for the nonautonomous chemotherapy system (4)–(6) and the role of injection rate and injection concentration. In particular, we consider two different scenarios:

1. Variable injection rate and constant injection concentration of the chemotherapy agent:

$$D(t) \in \mathcal{C}\left(\mathbb{R}, [d_m, d_M]\right), \quad I(t) \equiv I.$$

2. Constant injection rate and variable injection concentration of the chemotherapy agent:

$$D(t) \equiv D, \quad I(t) \in \mathcal{C}\left(\mathbb{R}, [i_m, i_M]\right).$$

4.2. Variable injection rate

In this subsection we consider system (4)–(6) with $I(t) \equiv I$. For the reader's convenience, we restate the system:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = D(t)(I - x(t)) - c_1\alpha_1\frac{x(t)y_1(t)}{\lambda_1 + y_1(t)} - c_2\alpha_2\frac{x(t)y_2(t)}{\lambda_2 + y_2(t)}, \tag{22}$$

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = \beta_1 y_1(t)\left(1 - \frac{y_1(t)}{\kappa_1}\right) - \delta_1 y_1(t)y_2(t) - \alpha_1\frac{x(t)y_1(t)}{\lambda_1 + y_1(t)}, \tag{23}$$

$$\frac{\mathrm{d}y_2}{\mathrm{d}t} = \beta_2 y_2(t)\left(1 - \frac{y_2(t)}{\kappa_2}\right) - \delta_2 y_1(t)y_2(t) - \alpha_2\frac{x(t)y_2(t)}{\lambda_2 + y_2(t)}, \tag{24}$$

where $D : \mathbb{R} \to [d_m, d_M]$ with $0 < d_m < d_M < \infty$ is continuous.

First of all, by Eq. (22) and the assumption that $d_m \le D(t) \le d_M$ we obtain

$$d_m I - (d_M + c_1\alpha_1 + c_2\alpha_2)x(t) \le \frac{\mathrm{d}x}{\mathrm{d}t} \le d_M I - d_m x(t),$$

which implies that for any $\varepsilon > 0$ and t large enough,

$$x_m =: \frac{d_m I}{d_M + c_1\alpha_1 + c_2\alpha_2} - \varepsilon \le x(t) \le \frac{d_M I}{d_m} + \varepsilon := x_M. \tag{25}$$

Lemma 4.3. *For $j = 1, 2$, the trivial state $y_j = 0$ is asymptotically stable provided that*

$$\beta_j(\kappa_j + \lambda_j)^2 < 4\alpha_j\kappa_j \cdot \frac{d_m I}{d_M + c_1\alpha_1 + c_2\alpha_2}. \tag{26}$$

Proof. Note that $\frac{\mathrm{d}y_j(t)}{\mathrm{d}t}\Big|_{y_j=0} = 0$ and for any $y_j > 0 (j = 1 \text{or} 2)$ and ε small enough, we have

$$\begin{aligned}\frac{\mathrm{d}y_j(t)}{\mathrm{d}t} &\leq \frac{y_j}{\kappa_j(\lambda_j + y_j)} \cdot [\beta_j(\kappa_j - y_j)(\lambda_j + y_j) - \alpha_j\kappa_j x(t)] \\ &\leq \frac{y_j}{\kappa_j(\lambda_j + y_j)} \cdot \left[-\beta_j y_j^2 + \beta_j(\kappa_j - \lambda_j)y_j + \beta_j\lambda_j\kappa_j - \alpha_j\kappa_j x_m\right] \\ &= \frac{y_j}{\kappa_j(\lambda_j + y_j)} \cdot \left[-\beta_j\left(y_j - \frac{\kappa_j - \lambda_j}{2}\right)^2 + \frac{\beta_j}{4}(\kappa_j + \lambda_j)^2 - \alpha_j x_m\kappa_j\right] \\ &< 0,\end{aligned}$$

i.e., $\frac{\mathrm{d}y_j(t)}{\mathrm{d}t}$ is negative definite. This implies that the y_j component of all trajectories in the nonnegative quadrant approach 0 asymptotically if the assumption (26) holds, which completes the proof.

Remark 4.3. Lemma 4.3 implies that the normal (or cancer) cells will eventually die out if the ratio between the product of their per capita growth rate and carrying capacity and the maximum treatment effect of the chemotherapy agent on them, $\beta_j\kappa_j/\alpha_j$, is less than a certain threshold determined by magnitude of the variation of the injection rate (d_m and d_M) and the injection concentration I of the chemotherapy agent.

It then follows immediately that the axial steady state $(I, 0, 0)$ for system (22)–(24) is asymptotically stable provided that (26) is fulfilled for both $j = 1$ and $j = 2$. Let $j' = 1$ when $j = 2$ and $j' = 2$ when $j = 1$, We next investigate the subsystems of (22)–(24) with one of the y_j's vanishing. Without loss of generality, assume $y_{j'}$ is vanishing as $t \to \infty$, which results in the subsystem

$$\frac{\mathrm{d}x}{\mathrm{d}t} = D(t)(I - x(t)) - c_j\alpha_j\frac{x(t)y_j(t)}{\lambda_j + y_j(t)}, \tag{27}$$

$$\frac{\mathrm{d}y_j}{\mathrm{d}t} = \beta_j y_j(t)\left(1 - \frac{y_j(t)}{\kappa_j}\right) - \alpha_j\frac{x(t)y_j(t)}{\lambda_j + y_j(t)}. \tag{28}$$

Let $\left\{\varphi_j^s(t, t_0)\right\}_{t\geq t_0}$ be the continuous process on $\mathbb{R}^2_+$ defined by solutions to the subsystem (27)–(28), i.e.,

$$\varphi_j^s(t; t_0, x_0, y_{j_0}) = \left(x(t; t_0, x_0, y_{j_0}), y_j(t; t_0, x_0, y_{j_0})\right), \quad \forall\, (x_0, y_{j_0}) \in \mathbb{R}^2_+.$$

Theorem 4.3. *Assume (26) holds for j'. For $j = 1$ or 2, the continuous process $\left\{\varphi_j^s(t, t_0)\right\}_{t\geq t_0}$ has a pullback attractor $\mathscr{A}_j^s = \{A_j^s(t) : t \in \mathbb{R}\}$ inside the nonnegative quadrant $\mathbb{R}^2_+ := \{(x, y_j) \in \mathbb{R}^2 : x \geq 0, y_j \geq 0\}$. Moreover,*

(i) *the pullback attractor $\mathscr{A}_j^s$ has a singleton component subset $A_j^s(t) = \{(I, 0)\}$ for all $t \in \mathbb{R}$, provided (26) holds for j;*

(ii) *the pullback attractor $\mathscr{A}_j^s$ contains also points inside the strictly positive quadrant in addition to the axial state $\{(I, 0)\}$, provided that*

$$\beta_j\lambda_j > \alpha_j I; \tag{29}$$

(iii) *the pullback attractor $\mathscr{A}_j^s$ consists of the axial state $\{(I, 0)\}$ and a single entire solution $\xi_j^*(t) = (x^*(t), y_j^*(t))$ that is uniformly bounded away from the axes, as well as heteroclinic entire solutions between them, provided that*

$$d_m^2 > \frac{c_j\alpha_j d_M I}{2\lambda_j} \quad \text{and} \quad \beta_j + \frac{\alpha_j}{2c_j} > \frac{\alpha_j\lambda_j}{2(\lambda_j + \kappa_j)^2} \cdot \frac{d_m I}{d_M + c_1\alpha_1 + c_2\alpha_2}. \tag{30}$$

Proof. Similar to the proof of Theorem 4.1, for any $\varepsilon > 0$ the nonempty compact set

$$K_\varepsilon := \left\{(x, y_j) \in \mathbb{R}^2_+ : x \le \frac{d_M I}{d_m} + \varepsilon,\ y_j \le \kappa_j + \varepsilon\right\}$$

is positively invariant and absorbing for the process $\{\varphi^s_j(t, t_0)\}_{t\ge t_0}$ in $\mathbb{R}^2_+$. Thus the process $\{\varphi^s_j(t, t_0)\}_{t\ge t_0}$ has a pullback attractor $\mathscr{A}^s_j = \{A^s_j(t) : t \in \mathbb{R}\}$ consisting of non-empty compact subsets of $\mathbb{R}^2_+$.

(i) This is a direct consequence of Lemma 4.3.

(ii) Consider the nonempty compact set of $\mathbb{R}^2_+$,

$$K^s_\varepsilon := \left\{(x, y_j) \in \mathbb{R}^2_+ : \varepsilon \le x \le I, \quad \varepsilon \le y_j \le \kappa_j\right\}.$$

Then for any $(x, y_j) \in K^s_\varepsilon$ with ε small enough, by using (29) we have

$$\begin{aligned}
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=\varepsilon} &= D(t)(I-\varepsilon) - c_j\alpha_j\frac{\varepsilon y_j}{\lambda_j + y_j} \ge d_m I - d_M\varepsilon - c_j\alpha_j\varepsilon > 0,\\
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=I} &= -c_j\alpha_j\frac{I y_j}{\lambda_j + y_j} < 0,\\
\left.\frac{\mathrm{d}y_j}{\mathrm{d}t}\right|_{y_j=\varepsilon} &= \varepsilon\left(\beta_j\left(1-\frac{\varepsilon}{\kappa_j}\right) - \frac{\alpha_j x}{\lambda_j+\varepsilon}\right) \ge \varepsilon\left(\beta_j\left(1-\frac{\varepsilon}{\kappa_j}\right) - \frac{\alpha_j I}{\lambda_j}\right) > 0,\\
\left.\frac{\mathrm{d}y_j}{\mathrm{d}t}\right|_{y_j=\kappa_j} &= -\alpha_j\frac{x\kappa_j}{\lambda_j+\kappa_j} < 0.
\end{aligned}$$

Hence K^s_ε is positively invariant for the process $\{\varphi^s_j(t, t_0)\}_{t\ge t_0}$, which proves assertion (ii).

(iii) For any two solutions $(x(t), y_j(t))$ and $(\tilde{x}(t), \tilde{y}_j(t))$ to the subsystem (27)–(28), denote

$$\Delta_x(t) := x(t) - \tilde{x}(t), \qquad \Delta_{y_j}(t) := y_j(t) - \tilde{y}_j(t).$$

Then Δ_x and Δ_{y_j} satisfy the ODE system

$$\frac{\mathrm{d}\Delta_x}{\mathrm{d}t} = -D(t)\Delta_x - \frac{c_j\alpha_j y_j}{\lambda_j + y_j}\Delta_x - \frac{c_j\alpha_j\lambda_j\tilde{x}}{(\lambda_j+y_j)(\lambda_j+\tilde{y}_j)}\Delta_{y_j}, \tag{31}$$

$$\frac{\mathrm{d}\Delta_{y_j}}{\mathrm{d}t} = \beta_j\Delta_{y_j} - \frac{\beta_j}{\kappa_j}(y_j+\tilde{y}_j)\Delta_{y_j} - \frac{\alpha_j y_j}{\lambda_j+y_j}\Delta_x - \frac{\alpha_j\lambda_j\tilde{x}}{(\lambda_j+y_j)(\lambda_j+\tilde{y}_j)}\Delta_{y_j}. \tag{32}$$

Note that $\Delta_x = \Delta_{y_j} = 0$ is a steady state for the system (31)–(32). We next prove that $(0, 0)$ is an asymptotically stable steady state for system (31)–(32). To this end, define the Lyapunov functional

$$V(\Delta_x, \Delta_{y_j}) = \frac{1}{2}(\Delta_x^2 + \Delta_{y_j}^2).$$

Then $V > 0$ for $\Delta_x, \Delta_{y_j} \ne 0$ and the time derivative of V along solutions to (31)–(32) satisfies

$$\begin{aligned}
\dot{V} = &-D(t)\Delta_x^2 - \frac{c_j\alpha_j y_j}{\lambda_j+y_j}\Delta_x^2 - \frac{c_j\alpha_j\lambda_j\tilde{x}}{(\lambda_j+y_j)(\lambda_j+\tilde{y}_j)}\Delta_x\Delta_{y_j} + \beta_j\Delta_{y_j}^2\\
&- \frac{\beta_j}{\kappa_j}(y_j+\tilde{y}_j)\Delta_{y_j}^2 - \frac{\alpha_j y_j}{\lambda_j+y_j}\Delta_x\Delta_{y_j} - \frac{\alpha_j\lambda_j\tilde{x}}{(\lambda_j+y_j)(\lambda_j+\tilde{y}_j)}\Delta_{y_j}^2.
\end{aligned} \tag{33}$$

Using

$$-\Delta_x\Delta_{y_j} \le \frac{c_j}{2}\Delta_x^2 + \frac{1}{2c_j}\Delta_{y_j}^2$$

and simplifying (33) gives

$$\begin{aligned}\dot{V} &\leq \left(-D(t) - \frac{c_j\alpha_j y_j}{2(\lambda_j + y_j)} + \frac{c_j^2\alpha_j\lambda_j\tilde{x}}{2(\lambda_j + y_j)(\lambda_j + \tilde{y}_j)}\right)\Delta_x^2 \\ &\quad + \left(\beta_j - \frac{\beta_j}{\kappa_j}(y_j + \tilde{y}_j) + \frac{\alpha_j y_j}{2c_j(\lambda_j + y_j)} - \frac{\alpha_j\lambda_j\tilde{x}}{2(\lambda_j + y_j)(\lambda_j + \tilde{y}_j)}\right)\Delta_{y_j}^2 \\ &\leq \left(-d_m + \frac{c_j^2\alpha_j x_M}{2\lambda_j}\right)\Delta_x^2 + \left(\beta_j + \frac{\alpha_j}{2c_j} - \frac{\alpha_j\lambda_j x_m}{2(\lambda_j + \kappa_j + \varepsilon)^2}\right)\Delta_{y_j}^2.\end{aligned}$$

Therefore pick ε small enough and use (30) we obtain immediately that

$$\dot{V} < 0,$$

which implies that $\Delta_x = \Delta_y = 0$ is asymptotically stable.

As a direct consequence, the pullback limit for strictly positive initial conditions of subsystem (27)–(28) is uniformly strictly contractive on $(0, I) \times (0, \kappa_j)$. Hence due to Theorem 2.2 there exists a single entire solution $\xi_j^*(t) = (x^*(t), y_j^*(t)) \in (0, I) \times (0, \kappa_j)$, which is also forward asymptotically stable in the usual forward sense. The corresponding pullback attractor $\mathscr{A}_j^s$ of the subsystem (27)–(28) includes the axial steady state solution $(I, 0)$ and has component sets $A_j^s(t) = [x^*(t), I] \times [0, y_j^*(t)]$ for all $t \in \mathbb{R}$, i.e., the pullback attractor also includes the heteroclinic trajectories joining the solution $\xi_j^*(t)$ and $(I, 0)$. In fact the pullback attractor $\mathscr{A}_j^s$ for the process $\{\varphi_j^s(t, t_0)\}_{t\geq t_0}$ has component sets

$$A_j^s(t) = \left\{(x, y_j) : x^*(t) \leq x \leq I, \quad 0 \leq y_j \leq y_j^*(t)\right\}.$$

This completes the proof.

Remark 4.4. Theorem 4.3 implies that when the cancer cells are all cleared, if (1) the ratio between the product of normal cells' per capita growth rate and carrying capacity and the maximum treatment effect of the chemotherapy agent on them, $\beta_1\kappa_1/\alpha_1$, is larger than a certain threshold determined by magnitude of the variation of the injection rate (d_m and d_M) and the injection concentration I of the chemotherapy agent, and (2) the ratio between consuming rate of chemotherapy on normal cells and the half saturation of normal cells, $c_1\alpha_1/\lambda_1$, is less than another threshold determined by magnitude of the variation of the injection rate (d_m and d_M) and the injection concentration I of the chemotherapy agent, then normal cells will survive and eventually follow a dynamic relation with the chemotherapy agent. Vise versa for the cancer cells while all normal cells are cleared.

Similar to the autonomous case, we name a time-dependent state with $y_1 = 0$ and $y_2 = 0$ as an "axial state", with $y_1 = 0$ and $y_2 > 0$ as a "failure state", with $y_1 > 0$ and $y_2 = 0$ as a "preferred state", and with $y_1 > 0$ and $y_2 > 0$ as a "persistence state". The next theorem provides descriptions on the interior structure of the pullback attractor $\mathscr{A}$ for the process $\{\varphi(t, t_0)\}_{t\geq t_0}$ defined by solutions to the full system (22)–(24).

Theorem 4.4. *The pullback attractor $\mathscr{A}$ with component subsets $\{A(t) : t \in \mathbb{R}\}$ for the process $\{\varphi(t, t_0)\}_{t\geq t_0}$ defined by solutions to the system (22)–(24) consists of*

(i) *a singleton axial state, i.e., $A(t) = \{(I, 0, 0)\}$ for all $t \in \mathbb{R}$, provided that (26) holds for both $j = 1$ and $j = 2$;*
(ii) *failure states in addition to the axial state provided that (26) holds for $j = 1$ and*

$$\beta_2\lambda_2 > \alpha_2 I;$$

(iii) *preferred states in addition to the axial state provided that (26) holds for $j = 2$ and*

$$\beta_1\lambda_1 > \alpha_1 I;$$

(iv) *persistence states in addition to the axial state provided that*

$$\beta_1\lambda_1 > \delta_1\lambda_1\kappa_2 + \alpha_1 I, \tag{34}$$
$$\beta_2\lambda_2 > \delta_2\lambda_2\kappa_1 + \alpha_2 I. \tag{35}$$

Proof. (i), (ii) and (iii) are direct consequences of Theorem 4.3. It only remains to prove (iv).

Define the nonempty compact set of $\mathbb{R}^3_+$

$$K_\varepsilon := \left\{(x, y_1, x_2) \in \mathbb{R}^3_+ : \varepsilon \le x \le I,\ \varepsilon \le y_1 \le \kappa_1,\ \varepsilon \le y_2 \le \kappa_2\right\}.$$

Then K_ε is positively invariant for the process $\{\varphi(t, t_0)\}_{t\ge t_0}$ for ε small enough. In fact, by using (34) and (35) we have for any $(x, y_1, y_2) \in K_\varepsilon$:

$$\begin{aligned}
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=\varepsilon} &= D(t)(I-\varepsilon) - c_1\alpha_1\frac{\varepsilon y_1}{\lambda_1+y_1} - c_2\alpha_2\frac{\varepsilon y_2}{\lambda_2+y_2} \ge d_m I - \varepsilon(d_M + c_1\alpha_1 + c_1\alpha_2) > 0,\\
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=I} &= -c_1\alpha_1\frac{I y_1}{\lambda_1+y_1} - c_2\alpha_2\frac{I y_2}{\lambda_2+y_2} < 0,\\
\left.\frac{\mathrm{d}y_1}{\mathrm{d}t}\right|_{y_1=\varepsilon} &= \varepsilon\left(\beta_1 - \beta_1\frac{\varepsilon}{\kappa_1} - \delta_1 y_2 - \frac{\alpha_1 x}{\lambda_1+\varepsilon}\right) > \varepsilon\left(\beta_1 - \beta_1\frac{\varepsilon}{\kappa_1} - \delta_1\kappa_2 - \frac{\alpha_1 I}{\lambda_1}\right) > 0,\\
\left.\frac{\mathrm{d}y_1}{\mathrm{d}t}\right|_{y_1=\kappa_1} &= -\kappa_1\left(\delta_1 y_2 + \frac{\alpha_1 x}{\lambda_1+\kappa_1}\right) < 0,\\
\left.\frac{\mathrm{d}y_2}{\mathrm{d}t}\right|_{y_2=\varepsilon} &= \varepsilon\left(\beta_2 - \beta_2\frac{\varepsilon}{\kappa_2} - \delta_2 y_1 - \frac{\alpha_2 x}{\lambda_2+\varepsilon}\right) > \varepsilon\left(\beta_2 - \beta_2\frac{\varepsilon}{\kappa_2} - \delta_2\kappa_1 - \frac{\alpha_2 I}{\lambda_2}\right) > 0,\\
\left.\frac{\mathrm{d}y_2}{\mathrm{d}t}\right|_{y_2=\kappa_2} &= -\kappa_2\left(\delta_2 y_1 + \frac{\alpha_2 x}{\lambda_2+\kappa_2}\right) < 0.
\end{aligned}$$

This implies that K_ε is positively invariant, and hence the assertion (iv).

Remark 4.5. Theorem 4.4 implies that when all cancer cells die out, if the ratio between the product of normal cells' per capita growth rate and half saturation and the maximum effect of chemotherapy agent on normal cells, $\beta_1\lambda_1/\alpha_1$, is greater than the input concentration of chemotherapy agent I, normal cells will definitely survive. Vice versa for the cancer cells when normal cells die out. In addition, when the per capita growth rates of cancer and normal cells are mutually controlled by the carrying capacities of their counterparts, cancer and normal cells will co-exist.

Remark 4.6. Following similar arguments to item (iii) of Theorem 4.3, we could construct conditions under which the pullback attractor $\mathscr{A} = \{A(t) : t \in \mathbb{R}\}$ for the process $\{\varphi(t, t_0)\}_{t\ge t_0}$ defined by solutions to the system (22)–(24) consists of the axial state $\{(I, 0, 0)\}$ and a single entire solution $\xi^*(t) = (x^*(t), y_1^*(t), y_2^*(t))$ that is uniformly bounded away from the axes, as well as heteroclinic entire solutions between them. The component sets are given by

$$A(t) = \left\{(x, y_1, y_2) : x^*(t) \le x \le I,\ 0 \le y_1 \le y_1^*(t),\ 0 \le y_2 \le y_2^*(t)\right\}.$$

To avoid redundant calculations, we skip the details here.

4.3. Variable injection concentration

In this subsection we consider system (4)–(6) with $D(t) \equiv D$. For the reader's convenience, we restate the system:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = D(I(t) - x(t)) - c_1\alpha_1 \frac{x(t)y_1(t)}{\lambda_1 + y_1(t)} - c_2\alpha_2 \frac{x(t)y_2(t)}{\lambda_2 + y_2(t)}, \tag{36}$$

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = \beta_1 y_1(t)\left(1 - \frac{y_1(t)}{\kappa_1}\right) - \delta_1 y_1(t)y_2(t) - \alpha_1 \frac{x(t)y_1(t)}{\lambda_1 + y_1(t)}, \tag{37}$$

$$\frac{\mathrm{d}y_2}{\mathrm{d}t} = \beta_2 y_2(t)\left(1 - \frac{y_2(t)}{\kappa_2}\right) - \delta_2 y_1(t)y_2(t) - \alpha_2 \frac{x(t)y_2(t)}{\lambda_2 + y_2(t)}. \tag{38}$$

where $I : \mathbb{R} \to [i_m, i_M]$ with $0 < i_m < i_M < \infty$ is continuous.

Note that by the assumption $i_m \le I \le i_M$, we can calculate from Eq. (36) that

$$D(i_m - x) - c_1\alpha_1 x - c_2\alpha_2 x \le \frac{\mathrm{d}x}{\mathrm{d}t} \le D(i_M - x),$$

which implies that for any $\varepsilon > 0$ and t large enough,

$$\hat{x}_m := \frac{Di_m}{D + c_1\alpha_1 + c_2\alpha_2} - \varepsilon \le x(t) \le i_M + \varepsilon. \tag{39}$$

Then we have a Lemma similar to Lemma 4.3 but with different assumptions.

Lemma 4.4. *For $j = 1, 2$, the trivial state $y_j = 0$ is asymptotically stable provided that*

$$\beta_j(\kappa_j + \lambda_j)^2 < 4\alpha_j\kappa_j \cdot \frac{Di_m}{D + c_1\alpha_1 + c_2\alpha_2}. \tag{40}$$

Proof. Note that $\left.\frac{\mathrm{d}y_j(t)}{\mathrm{d}t}\right|_{y_j=0} = 0$ and for any $y_j > 0$ ($j = 1$ or 2) and ε small enough, due to (40) we have

$$\begin{aligned}
\frac{\mathrm{d}y_j(t)}{\mathrm{d}t} &\le \frac{y_j}{\kappa_j(\lambda_j + y_j)} \cdot \left[-\beta_j y_j^2 + \beta_j(\kappa_j - \lambda_j)y_j + \beta_j\lambda_j\kappa_j - \alpha_j\kappa_j\hat{x}_m\right] \\
&= \frac{y_j}{\kappa_j(\lambda_j + y_j)} \cdot \left[-\beta_j\left(y_j - \frac{\kappa_j - \lambda_j}{2}\right)^2 + \frac{\beta_j}{4}(\kappa_j + \lambda_j)^2 - \alpha_j\hat{x}_m\kappa_j\right] \\
&< 0,
\end{aligned}$$

i.e., $\frac{\mathrm{d}y_j(t)}{\mathrm{d}t}$ is negative definite. This implies that the y_j component of all trajectories in the nonnegative quadrant approach 0 asymptotically if the assumption (40) holds, which completes the proof.

Again we first consider the subsystem with one of the y_j's vanished:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = D(I(t) - x(t)) - c_j\alpha_j \frac{x(t)y_j(t)}{\lambda_j + y_j(t)}, \tag{41}$$

$$\frac{\mathrm{d}y_j}{\mathrm{d}t} = \beta_j y_j(t)\left(1 - \frac{y_j(t)}{\kappa_j}\right) - \alpha_j \frac{x(t)y_j(t)}{\lambda_j + y_j(t)}. \tag{42}$$

Let $\left\{\hat{\varphi}_j^s(t, t_0)\right\}_{t \ge t_0}$ be the continuous process on $\mathbb{R}^2_+$ defined by solutions to the subsystem (41)–(42), i.e.,

$$\hat{\varphi}_j^s(t; t_0, x_0, y_{j_0}) = \left(x(t; t_0, x_0, y_{j_0}), y_j(t; t_0, x_0, y_{j_0})\right), \quad \forall\, (x_0, y_{j_0}) \in \mathbb{R}^2_+.$$

Theorem 4.5. *For $j = 1$ or 2, the continuous process $\left\{\hat{\varphi}_j^s(t, t_0)\right\}_{t \ge t_0}$ has a pullback attractor $\hat{\mathscr{A}}_j^s = \{\hat{A}_j^s(t) : t \in \mathbb{R}\}$ inside the nonnegative quadrant $\mathbb{R}^2_+ := \{(x, y_j) \in \mathbb{R}^2 : x \ge 0, y_j \ge 0\}$. Moreover,*

(i) *the pullback attractor* $\hat{\mathscr{A}}_j^s$ *has a singleton component subset* $\hat{A}_j^s(t) = \{(\zeta(t), 0)\}$ *where*

$$\zeta(t) = De^{-Dt}\int_{-\infty}^{t} I(s)e^{Ds}\mathrm{d}s,$$

for all $t \in \mathbb{R}$*, provided (40) holds;*

(ii) *the pullback attractor* $\hat{\mathscr{A}}_j^s$ *contains also points inside the strictly positive quadrant in addition to the axial entire solution* $\{(\zeta, 0)\}$*, provided that*

$$\beta_j\lambda_j > \alpha_j i_M; \tag{43}$$

(iii) *the pullback attractor* $\hat{\mathscr{A}}_j^s$ *contains a nontrivial entire solution* $\hat{\xi}_j^*(t) = (\hat{x}^*(t), \hat{y}_j^*(t))$ *that attracts both in the pullback and forward senses all other strictly positive entire solutions, provided that*

$$2D\lambda_j > \alpha_j c_j^2 i_M \quad \textit{and} \quad \beta_j + \frac{\alpha_j}{2c_j} < \frac{\alpha_j\lambda_j}{2(\lambda_j+\kappa_j)^2}\cdot\frac{Di_m}{D + c_1\alpha_1 + c_2\alpha_2}. \tag{44}$$

Proof. For any $\varepsilon > 0$ define the nonempty compact set

$$K_\varepsilon := \left\{(x, y_j) \in \mathbb{R}_+^2 : x \le i_M + \varepsilon, \quad y_j \le \kappa_j + \varepsilon\right\}.$$

Then by (39), K_ε is a positively invariant absorbing set for the process $\left\{\hat{\varphi}_j^s(t, t_0)\right\}_{t\ge t_0}$ in $\mathbb{R}_+^2$. Thus the process $\left\{\hat{\varphi}_j^s(t, t_0)\right\}_{t\ge t_0}$ has a pullback attractor $\hat{\mathscr{A}}_j^s := \left\{\hat{A}_j^s(t) : t \in \mathbb{R}\right\}$, consisting of non-empty compact subsets of $\mathbb{R}_+^2$.

(i) When (40) holds, $y_j \to 0$ asymptotically as $t \to \infty$. Then x satisfies the ODE

$$\frac{\mathrm{d}x}{\mathrm{d}t} = D(I(t) - x(t)). \tag{45}$$

Different from the subsystem (27)–(28), Eq. (45) does not have a steady state when $I(t)$ is not a constant. But it has a nontrivial time-dependent "stationary" solution that is both pullback and forward attracting. In fact, solution to (45) can be found explicitly to be

$$\begin{aligned} x(t) &= x_0e^{D(t-t_0)} + De^{-D(t-t_0)}\int_{t_0}^{t} I(s)e^{D(s-t_0)}\mathrm{d}s \\ &= x_0e^{-D(t-t_0)} + De^{-Dt}\int_{t_0}^{t} I(s)e^{Ds}\mathrm{d}s, \end{aligned}$$

which converges to

$$\zeta(t) = De^{-Dt}\int_{-\infty}^{t} I(s)e^{Ds}\mathrm{d}s$$

when $t_0 \to -\infty$ and t fixed, or $t \to \infty$ and t_0 fixed, i.e.,

$$\lim_{t\to\infty}|x(t) - \zeta(t)| = \lim_{t_0\to-\infty}|x(t) - \zeta(t)| = 0.$$

In addition $\zeta(t) \in [i_m, i_M]$ for all $t \in \mathbb{R}$, due to the bounds of $I(t)$.

(ii) Pick ε small enough and define

$$\hat{K}_\varepsilon^s := \left\{(x, y_j) \in \mathbb{R}_+^2 : \varepsilon \le x \le i_M, \quad \varepsilon \le y_j \le \kappa_j\right\}.$$

Then $\hat{K}_\varepsilon^s$ is a positively invariant set for the process $\left\{\hat{\varphi}_j^s(t, t_0)\right\}_{t\ge t_0}$, which implies the assertion (ii). In fact, by using (43) we have

$$\begin{aligned}
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=\varepsilon} &= D(I(t)-\varepsilon) - c_j\alpha_j\frac{\varepsilon y_j}{\lambda_j + y_j} \ge D(i_m - \varepsilon) - c_j\alpha_j\varepsilon > 0,\\
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=i_M} &= D(I(t)-i_M) - c_j\alpha_j\frac{I y_j}{\lambda_j + y_j} < 0,\\
\left.\frac{\mathrm{d}y_j}{\mathrm{d}t}\right|_{y_j=\varepsilon} &= \varepsilon\left(\beta_j\left(1-\frac{\varepsilon}{\kappa_j}\right) - \frac{\alpha_j x}{\lambda_j+\varepsilon}\right) \ge \varepsilon\left(\beta_j\left(1-\frac{\varepsilon}{\kappa_j}\right) - \frac{\alpha_j i_M}{\lambda_j}\right) > 0,\\
\left.\frac{\mathrm{d}y_j}{\mathrm{d}t}\right|_{y_j=\kappa_j} &= -\alpha_j\frac{x\kappa_j}{\lambda_j+\kappa_j} < 0.
\end{aligned}$$

(iii) Following exactly the same procedure as used in the proof of part (iii) of Theorem 4.3, and using the same Lyapunov functional V, but with $D(t)$ changed to D, x_m changed to $\hat{x}_m$, and x_M changed to $i_M + \varepsilon$ in all calculations we obtain

$$\dot{V} \le \left(-D + \frac{\alpha_j c_j^2 i_M}{2\lambda_j}\right)\Delta_x^2 + \left(\beta_j + \frac{\alpha_j}{2c_j} - \frac{\alpha_j\lambda_j\hat{x}_m}{2(\lambda_j+\kappa_j)^2}\right)\Delta_{y_j}^2 < 0.$$

This implies that the difference between any two solutions to the system (41)–(42) converges to 0 asymptotically, i.e., the system (41)–(42) is strict uniformly contracting in the positive quadrant and thus has a unique entire solution $(\hat{x}^*(t), \hat{y}_j^*(t))$ away from the axes that attracts all other positive solutions.

Remark 4.7. Theorem 4.5 implies that when the cancer cells are all cleared, if (1) the ratio between the product of normal cells' per capita growth rate and carrying capacity and the maximum treatment effect of the chemotherapy agent on them, $\beta_1\kappa_1/\alpha_1$, is larger than a certain threshold determined by the lower bound of injection concentration i_m and the injection rate of the chemotherapy agent D, and (2) the ratio between consuming rate of chemotherapy on normal cells and the half saturation of normal cells, $c_1\alpha_1/\lambda_1$ is less than a threshold determined by the upper bound of injection concentration i_M and the injection rate of the chemotherapy agent D, then normal cells will survive and eventually follow a dynamic relation with the chemotherapy agent. Vice versa for the cancer cells while all normal cells are cleared.

Theorem 4.6. *The pullback attractor $\hat{\mathscr{A}}$ with component subsets $\{\hat{A}(t) : t \in \mathbb{R}\}$ for the process $\{\hat{\varphi}(t, t_0)\}_{t\ge t_0}$ defined by solutions to the system (36)–(38) contains*

(i) *a singleton time-dependent stationary state, i.e., $\hat{A}(t) = \{(\zeta(t), 0, 0)\}$ for all $t \in \mathbb{R}$, provided that (40) holds for both $j = 1$ and $j = 2$;*

(ii) *failure states in addition to the axial state provided that (40) holds for $j = 1$ and*

$$\beta_2\lambda_2 > \alpha_2 i_M;$$

(iii) *preferred states in addition to the axial state provided that (26) holds for* $j = 2$ *and*

$$\beta_1\lambda_1 > \alpha_1 i_M;$$

(iv) *persistence states in addition to the time-dependent stationary state* $(\zeta(t), 0, 0)$ *provided that*

$$\beta_1\lambda_1 > \delta_1\lambda_1\kappa_2 + \alpha_1 i_M, \tag{46}$$
$$\beta_2\lambda_2 > \delta_2\lambda_2\kappa_1 + \alpha_2 i_M. \tag{47}$$

Proof. We only need to prove assertion (iv). Define the nonempty compact set of $\mathbb{R}^3_+$

$$K_\varepsilon := \left\{(x, y_1, x_2) \in \mathbb{R}^3_+ : \varepsilon \le x \le i_M,\ \varepsilon \le y_1 \le \kappa_1,\ \varepsilon \le y_2 \le \kappa_2\right\}.$$

Then K_ε is positively invariant for the process $\{\varphi(t, t_0)\}_{t\ge t_0}$ for ε small enough. In fact, by using (46) and (47) we have for any $(x, y_1, y_2) \in K_\varepsilon$:

$$\begin{aligned}
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=\varepsilon} &= D(I(t) - \varepsilon) - c_1\alpha_1\frac{\varepsilon y_1}{\lambda_1 + y_1} - c_2\alpha_2\frac{\varepsilon y_2}{\lambda_2 + y_2}\\
&\ge D(i_m - \varepsilon) - \varepsilon(d_M + c_1\alpha_1 + c_1\alpha_2) > 0,\\
\left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{x=i_M} &= D(I(t) - i_M) - c_1\alpha_1\frac{i_M y_1}{\lambda_1 + y_1} - c_2\alpha_2\frac{i_M y_2}{\lambda_2 + y_2} < 0,\\
\left.\frac{\mathrm{d}y_1}{\mathrm{d}t}\right|_{y_1=\varepsilon} &= \varepsilon\left(\beta_1 - \beta_1\frac{\varepsilon}{\kappa_1} - \delta_1 y_2 - \frac{\alpha_1 x}{\lambda_1 + \varepsilon}\right) > \varepsilon\left(\beta_1 - \beta_1\frac{\varepsilon}{\kappa_1} - \delta_1\kappa_2 - \frac{\alpha_1 i_M}{\lambda_1}\right) > 0,\\
\left.\frac{\mathrm{d}y_1}{\mathrm{d}t}\right|_{y_1=\kappa_1} &= -\kappa_1\left(\delta_1 y_2 + \frac{\alpha_1 x}{\lambda_1 + \kappa_1}\right) < 0,\\
\left.\frac{\mathrm{d}y_2}{\mathrm{d}t}\right|_{y_2=\varepsilon} &= \varepsilon\left(\beta_2 - \beta_2\frac{\varepsilon}{\kappa_2} - \delta_2 y_1 - \frac{\alpha_2 x}{\lambda_2 + \varepsilon}\right) > \varepsilon\left(\beta_2 - \beta_2\frac{\varepsilon}{\kappa_2} - \delta_2\kappa_1 - \frac{\alpha_2 i_M}{\lambda_2}\right) > 0,\\
\left.\frac{\mathrm{d}y_2}{\mathrm{d}t}\right|_{y_2=\kappa_2} &= -\kappa_2\left(\delta_2 y_1 + \frac{\alpha_2 x}{\lambda_2 + \kappa_2}\right) < 0.
\end{aligned}$$

The proof is complete.

Remark 4.8. Theorem 4.6 implies that when all cancer cells die out, if the ratio between the product of normal cells' per capita growth rate and half saturation coefficient, and the maximum effect of chemotherapy agent on normal cells, $\beta_1\lambda_1/\alpha_1$, is greater than upper bound of the input concentration of chemotherapy agent i_M, then normal cells will definitely survive. Vice versa for the cancer cells when normal cells die out. In addition, when the per capita growth rates of cancer and normal cells are mutually controlled by the carrying capacities of their counterparts, cancer and normal cells will co-exist.

Remark 4.9. Theorems 4.4 and 4.6 do not provide as much detailed information as Theorems 4.3 and 4.5 on interior structures of the pullback attractor, in particular the existence of attracting nontrivial entire solutions. But they provide biologically interesting and important statements on the full three dimensional system.

5. Numerical simulations

In this section we present some numerical simulations to illustrate the role of the injection concentration and injection rate on the effectiveness of the treatment. Assume the treatment starts at $t_0 = 0$ and ends at

T. We will investigate four different types of treatments with the same average infusion rate, i.e., with the same value of $\frac{1}{T}\int_0^T D(t)I(t)\mathrm{d}t$:

1. constant injection rate and constant injection concentration

$$D(t) = \frac{d_m + d_M}{2}, \qquad I(t) = \frac{i_m + i_M}{2}; \tag{48}$$

2. constant injection rate and periodic injection concentration

$$D(t) = \frac{d_m + d_M}{2}, \qquad I(t) = \frac{i_m + i_M}{2} + \frac{i_M - i_m}{2}\sin\frac{2k\pi}{T}t, \quad k \in \mathbb{Z}; \tag{49}$$

3. periodic injection rate and constant injection concentration

$$D(t) = \frac{d_m + d_M}{2} + \frac{d_M - d_m}{2}\sin\frac{2k\pi}{T}t, \qquad I(t) = \frac{i_m + i_M}{2}, \quad k \in \mathbb{Z}; \tag{50}$$

4. periodic injection rate and periodic injection concentration

$$D(t) = \frac{d_m + d_M}{2} + \frac{d_M - d_m}{2}\sin\frac{2k\pi}{T}t, \qquad I(t) = \frac{i_m + i_M}{2} + \frac{i_M - i_m}{2}\sin\frac{2k\pi}{T}t, \quad k \in \mathbb{Z}. \tag{51}$$

All parameters are chosen to be strictly positive and satisfy the biological assumptions (8) and (9). In particular, we are interested in investigating the scenarios when not all treatments result in a preferred state. Noting that 4.3 and 4.4 are not sufficient but not necessary conditions to achieve a preferred state, we pick parameters that do not satisfy 4.3 or 4.4 for $j = 2$, with $I = (i_m + i_M)/2$ and $D = (d_m + d_M)/2$:

$$\begin{aligned} &i_m = 2, \quad i_M = 6, \quad d_m = 2, \quad d_M = 6, \quad T = 10, \\ &\alpha_1 = 0.5, \quad \beta_1 = 2, \quad c_1 = 1, \quad \delta_1 = 1, \quad \kappa_1 = 5, \quad \lambda_1 = 1, \\ &\alpha_2 = 2, \quad \beta_2 = 5, \quad c_2 = 1, \quad \delta_2 = 1, \quad \kappa_2 = 5, \quad \lambda_2 = 1. \end{aligned} \tag{52}$$

The dynamics of the chemotherapy agent, normal and cancer cells with inputs (48)–(50) and periodic (51) are shown in Figs. 1–4, respectively. To better compare the difference among each type of treatment, we illustrate the dynamics of normal cells in Fig. 5 and dynamics of cancer cells in Fig. 6. It is clearly shown that treatments with constant injection concentration all fail (all normal cells die while cancer cells still exist) while treatments with periodic injection concentration are all successful (all cancer cells die while normal cells still exist). Moreover, due to extensive numerical experiments, it turns out that the effectiveness of chemotherapy relies largely on the injection concentration of the chemotherapy agent, but not as much on injection rate. This is consistent with the over-yielding phenomena discussed briefly in [22]. The supporting theory for such phenomena, i.e., periodic input out performs constant input with the same average, will be developed in future work.

6. Closing remarks

Classical stability analysis of biological systems proceeds by identifying steady states of the system and investigating conditions under which the system will converge on one of these steady states. However, most natural populations fluctuate greatly with respect to the variation of their environments, and may exhibit dynamical patterns within observable times that cannot be fully characterized by the steady states. Various

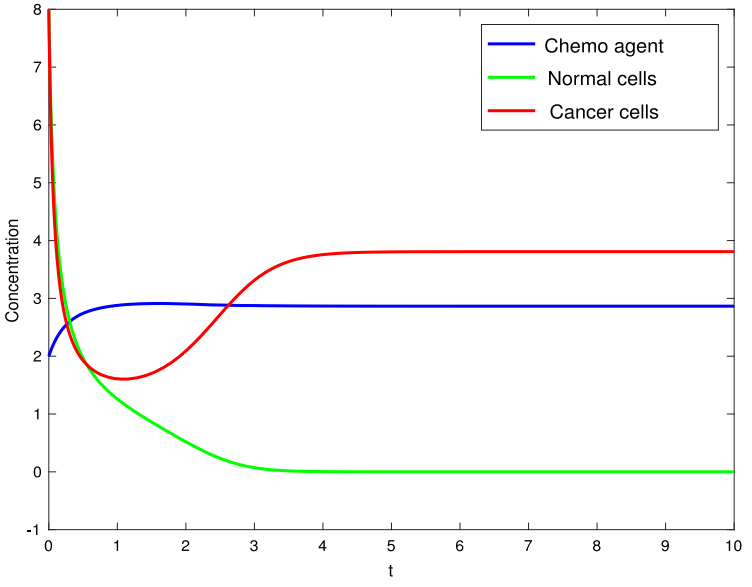

Fig. 1. Dynamics of chemotherapy with constant injection rate and constant injection concentration.

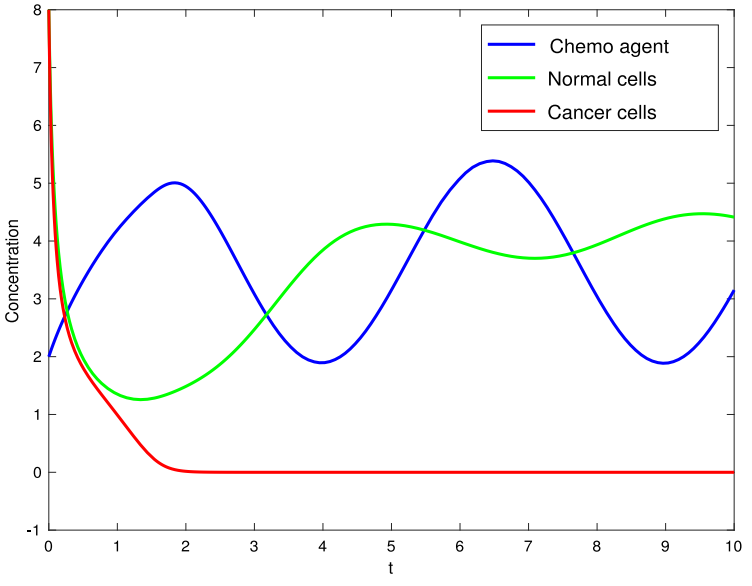

Fig. 2. Dynamics of chemotherapy with constant injection rate and periodic injection concentration.

replacements for the steady state exist, such as limit cycles, strange attractors and stationary probability distributions, but they all suffer from the complaint that they are merely steady states on different time scales [23].

The recent development of nonautonomous dynamical systems [17,16] allows us to introduce time-dependent inputs in biological systems that can reflect the interactions between cells and varying environments or the effects of varying control. Most recently Caraballo et al. studied the chemostat systems with varying inputs [24,25,22], in which the nutrients and the biomass follow a predator–prey model. The

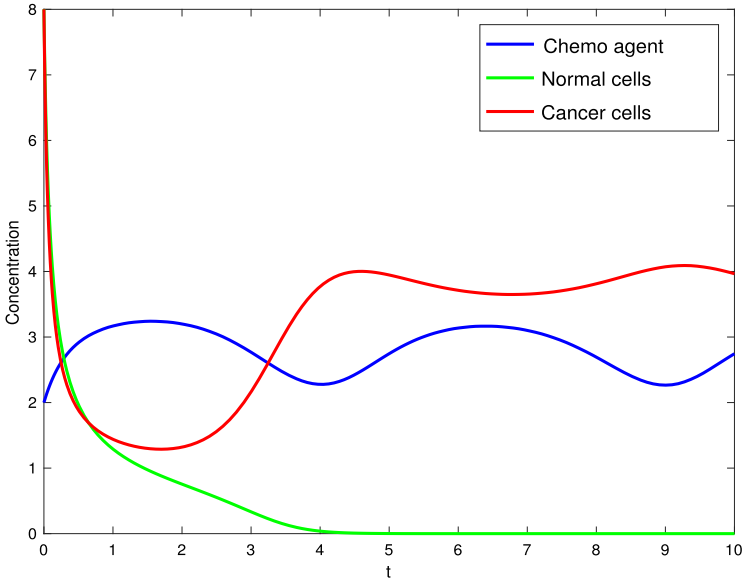

Fig. 3. Dynamics of chemotherapy with periodic injection rate and constant injection concentration.

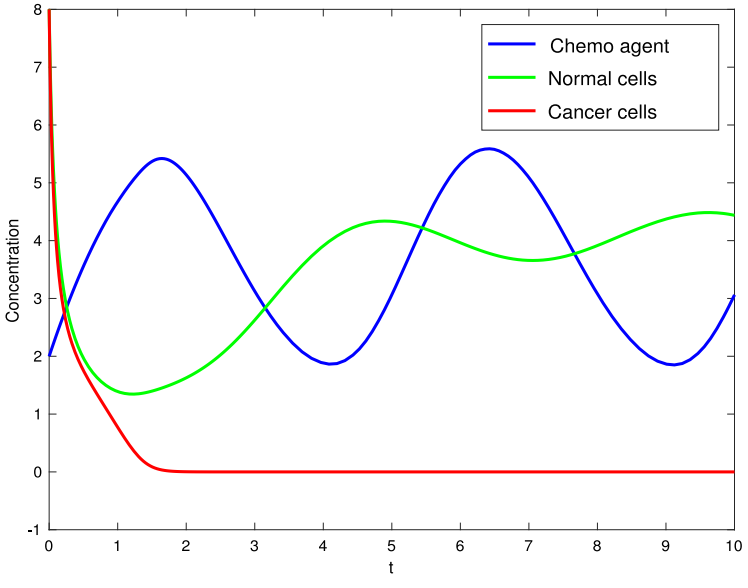

Fig. 4. Dynamics of chemotherapy with periodic injection rate and periodic injection concentration.

model studied in this work does not assume an exact predator–prey model between the chemotherapy agent and cells and considers competitions between the normal and cancer cells, and hence requires different and more sophisticated techniques to analyze. More importantly, the results on time-dependent "preferred states" and time-dependent "failure states" obtained in this work provided important insights in the effectiveness of the chemotherapy treatment that may interest biologists and medical scientists.

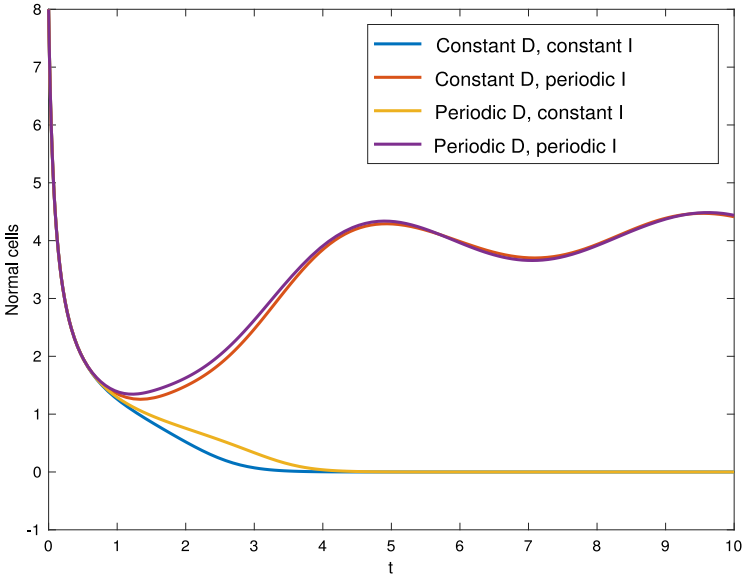

Fig. 5. Comparison of normal cells with input (48)–(51).

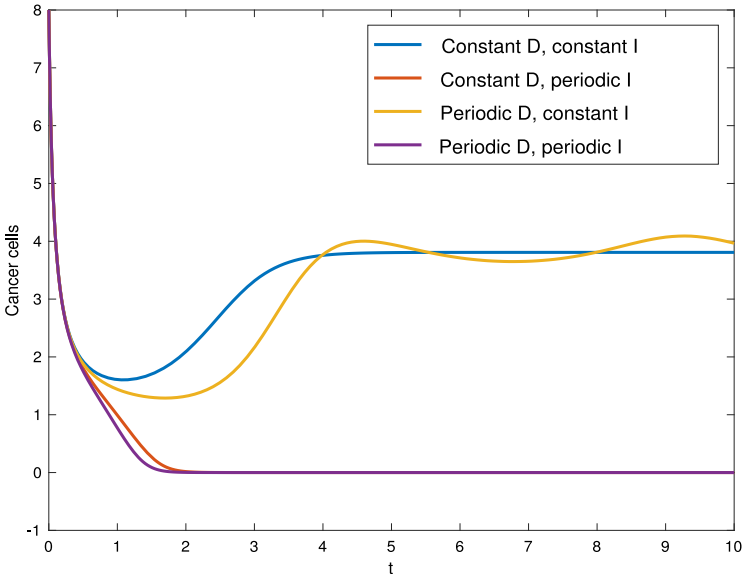

Fig. 6. Comparison of cancer cells with input (48)–(51).

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