A MATHEMATICAL MODEL OF CHEMOTHERAPY WITH VARIABLE INFUSION

Dedicated to Prof. Dr. Tomás Caraballo’s 60th birthday

Ismail Abdulrashid and Xiaoying Han∗

Department of Mathematics and Statistics
Auburn University, Auburn, AL 36849, USA

Abstract. A nonautonomous mathematical model of chemotherapy cancer treatment with time-dependent infusion concentration of the chemotherapy agent is developed and studied. In particular, a mutual inhibition type model is adopted to describe the interactions between the chemotherapy agent and cells, in which the chemotherapy agent is modeled as the prey being consumed by both cancer and normal cells, thereby reducing the population of both. Properties of solutions and detailed dynamics of the nonautonomous system are investigated, and conditions under which the treatment is successful or unsuccessful are established. It can be shown both theoretically and numerically that with the same amount of chemotherapy agent infused during the same period of time, a treatment with variable infusion may over perform a treatment with constant infusion.

1. Introduction. Cancer is still one of the leading causes of death worldwide (see, e.g., [3, 5, 18]). Conventional methods used in cancer treatment include chemotherapy, immunotherapy, radiotherapy and surgery, etc. Chemotherapy is a well-known and commonly used method of cancer treatment, that involves the application of a chemotherapy agent to the body of the infected individual thereby attacking the cancerous cells. While being easily applicable, most of the chemotherapy agents attack not only the cancer cells but also other fast-renewing tissues such as skin, bone-marrow, gut, and other digestive epithelia (see, e.g., [1, 10, 22, 23]). This motivates both theoretical and experimental studies to better understand the trade-offs between reducing cancer cells and impacting healthy cells.

In particular, mathematical models have been used extensively to study the effectiveness of chemotherapy treatments, from dynamical point of view, optimization point of view, and compartmental point of view (see, e.g., [1, 2, 6, 11, 13, 16, 19, 20, 21, 22, 26]). Since the chemotherapy agents and cells have negative effects on each others’ growth rates, their interactions are of the mutual inhibition type [24]. In the context of chemotherapy treatments, such interactions can be understood as a “predator-prey” type relation that the “predator” has a negative growth rate by

2000 Mathematics Subject Classification. Primary: 34D45, 35B41, 37B55; Secondary: 92C50, 97M60.

Key words and phrases. Chemotherapy, mutual inhibition, nonautonomous dynamical systems, pullback attractor.

This work was partially supported by Simons Foundation, USA (Collaboration Grants for Mathematicians No. 429717).

∗Corresponding author.
consuming the “prey”, as if the prey is poisoned. Thus, among various mathematical models, the predator-prey type of systems with mutual negative affects have been adopted to describe the interaction between the chemotherapy agent and cells. There are two perspectives in modeling the chemotherapy treatment as a predator-prey system: the first type is to model the chemotherapy agent as the “predator” that kills both normal and cancer cells (see, e.g., [13, 22]), and the second type is to model the chemotherapy agent as the “prey” that is consumed by both normal and cancer cells (see, e.g., [1, 25]).

For the first type where the chemotherapy agent is considered as the predator, an autonomous model of the interaction between the normal cells and tumor cells with metastasis and time delays was studied in [22], and a nonautonomous model of interactions among tumor cells, normal cells and the chemotherapy agent under time varying environmental conditions was later developed and studied in [13]. It was demonstrated in [13] that treatments with time-dependent infusion of the chemotherapy agent can be more effective than treatments with constant infusion. The goal of this work is to investigate dynamics of a nonautonomous chemotherapy model of the second type, in which the chemotherapy agent is modeled as a prey, and infused into the treatment site with time-dependent infusion. The autonomous counterpart of this model with or without delay was recently studied by Abdulrashi et al. in [2], in which both types of autonomous models were analyzed and compared. Yet no result on the second type nonautonomous system is available up to date. This is the focus of this work.

The paper is organized as follows. In Section 2 we first formulate the underlying nonautonomous dynamical system with parameters of physical meanings and then simplify it to a dimensionless system. In Section 3 we first study the existence and uniqueness of a non-negative and bounded solution of the model and then introduce the basic terminology and theory of nonautonomous dynamical system related to this work. In Section 4 we investigate detailed dynamics of the nonautonomous model, in terms of the existence of a pullback attractor, as well as detailed dynamics within the attractor. Biological interpretations of the resulting mathematical results are also provided. In the end numerical simulations are presented to illustrate the theoretical results.

2. Mathematical model. The model to be developed and studied is based on the idea introduced in [25] and later studied in [1, 2], but with time-dependent infusion due to the natural (temporal or random) fluctuation of environments or human control.

2.1. Model formulation. Consider a single site where the cells are treated, e.g., a tumor, with fixed volume $V$. It is assumed that all cells, as well as the chemotherapy agent, are spatially uniform within the site, i.e., their concentrations do not depend on the location. At any time $t$ denote by $N_1(t)$, $N_2(t)$ and $C(t)$ be the concentration of cancer cells, normal cells, and the chemotherapy agent at the treatment site, respectively. Let $F_{in} = F_{out} = F$ be the blood flows brought into and coming out from the tumor site at any time. The novelty and focus of this work is that the chemotherapy is assumed to be infused with blood flow at time-dependent concentration. More precisely, denote by $I(t)$ the concentration of the chemotherapy agent in the blood flowing into the site, where $I(t)$ is a continuous, positive and bounded function that varies with time deterministically or randomly.
Using the idea of [25], the negative effect of the chemotherapy agent on the growth of cells is modeled by a “kill rate” \( K_j(C) \) \((j = 1, 2\) for cancer and normal cells, respectively), and the chemotherapy agent is regarded as the “prey” being consumed by both types of cells at rates proportional to the kill rates. In addition, assume that the normal and cancer cells both follow a logistic growth [9, 13, 17, 22] and have Lotka-Volterra type intra-specific competitions between them [8]. These leads to the following nonautonomous system of ODEs describing dynamics of chemotherapy

\[
\begin{align*}
\frac{dN_1(t)}{dt} &= -K_1(C)N_1 + b_1 N_1 \left( 1 - \frac{N_1}{\kappa_1} \right) - d_1 N_1 N_2, \\
\frac{dN_2(t)}{dt} &= -K_2(C)N_2 + b_2 N_2 \left( 1 - \frac{N_2}{\kappa_2} \right) - d_2 N_1 N_2, \\
\frac{dC(t)}{dt} &= -r_1 K_1(C)N_1 - r_2 K_2(C)N_2 - \frac{CF}{V} + \frac{I(t)F}{V}.
\end{align*}
\]

Note that the key difference between the model above and autonomous models in the literature is that the input concentration \( I \) is time-dependent. In addition, the difference between the model above and the nonautonomous model studied in [13] lies in that the killing rates \( K_1 \) and \( K_2 \) are functions of \( C \) instead of functions of \( N_1 \) and \( N_2 \). More precisely, the functions \(-r_1 K_1(C)N_1\) and \(-r_2 K_2(C)N_2\) can be regarded as the interactions that create a positive feedback on both variables in the mutual inhibition relation between the chemotherapy agents and the cells.

Meanings and units of parameters\( b_1, b_2, \kappa_1, \kappa_2, r_1, r_2, d_1 \) and \( d_2 \) are listed in Table 1 below.

**Table 1. Description of parameters in the chemotherapy model**

| Parameter | Description |
|-----------|-------------|
| \( b_1 \) (1/time) | Per capita growth rate of cancer cells |
| \( b_2 \) (1/time) | Per capita growth rate of normal cells |
| \( \kappa_1 \) (mass/vol) | Environmental carrying capacity of cancer cells |
| \( \kappa_2 \) (mass/vol) | Environmental carrying capacity of normal cells |
| \( d_1 \) (vol/time-mass) | Intraspecific competition coefficient of cancer on normal cells |
| \( d_2 \) (vol/time-mass) | Intraspecific competition coefficient of normal on cancer cells |
| \( r_1 \) (1) | Consumption effectiveness of cancer cells on the agent |
| \( r_2 \) (1) | Consumption effectiveness of normal cells on the agent |

Throughout this paper we adopt the Michaelis-Menten formulation of the killing rates [25]:

\[
K_j(C) = \frac{K_{j}^{max}C}{k_{j}^{half} + C}, \quad j = 1, 2,
\]

where \( K_{j}^{max} \) is the maximum killing rate of the chemotherapy agent on the cells, and \( k_{j}^{half} \) is the concentration of cells corresponding to \( K_j(C) = K_j^{max}/2 \), which is usually referred to as the half saturation rate. Note that \( K_j^{max} \) is a rate, and has units 1/time and \( k_{j}^{half} \) has units of concentration.

2.2. Non-dimensionalization. For the convenience of mathematical analysis, we first non-dimensionalize the system (1) – (3) by setting

\[
N_1(t) = N_1^* \cdot x(t), \quad N_2(t) = N_2^* \cdot y(t), \quad C(t) = C^* \cdot z(t), \quad t = t^* \cdot \tilde{t},
\]

where \( N_1^* \) and \( N_2^* \) are the normal and cancer cell densities, respectively, \( C^* \) is the concentration of the chemotherapy agent, \( t^* \) is the dimensionless time, and \( \tilde{t} \) is the original time. The dimensionless concentrations of the chemotherapy agent and the cell densities are then given by

\[
\begin{align*}
\frac{dN_1^*}{d\tilde{t}} &= -K_1(C^*)N_1^* + b_1 N_1^* \left( 1 - \frac{N_1^*}{\kappa_1} \right) - d_1 N_1^* N_2^*, \\
\frac{dN_2^*}{d\tilde{t}} &= -K_2(C^*)N_2^* + b_2 N_2^* \left( 1 - \frac{N_2^*}{\kappa_2} \right) - d_2 N_1^* N_2^*, \\
\frac{dC^*}{d\tilde{t}} &= -r_1 K_1(C^*)N_1^* - r_2 K_2(C^*)N_2^* - \frac{CF}{V} + \frac{I(\tilde{t})F}{V}.
\end{align*}
\]
with
\[ N_1^* = \frac{k_1^\text{half} F}{r_1 V K_1^\text{max}}, \quad N_2^* = \frac{k_2^\text{half} F}{r_2 V K_2^\text{max}}, \quad C^* = k_1^\text{half} + k_2^\text{half}, \quad t^* = \frac{V}{F}. \]

Still denoting \( t \) by \( t \), the ODEs (1) – (3) now become the following system
\[
\begin{align*}
\frac{dx(t)}{dt} &= -\alpha_1 \frac{x(t)z(t)}{\theta_1 + z(t)} + \beta_1 x(t)(1 - \gamma_1 x(t)) - \delta_1 x(t)y(t), \\
\frac{dy(t)}{dt} &= -\alpha_2 \frac{y(t)z(t)}{\theta_2 + z(t)} + \beta_2 y(t)(1 - \gamma_2 y(t)) - \delta_2 x(t)y(t), \\
\frac{dz(t)}{dt} &= -\frac{x(t)z(t)}{\theta_1 + z(t)} - \frac{y(t)z(t)}{\theta_2 + z(t)} - z(t) + \mu(t),
\end{align*}
\]
where the parameters
\[
\alpha_j = \frac{V}{F} K_j^\text{max}, \quad \beta_j = \frac{V}{F} b_j, \quad \gamma_j = \frac{k_1^\text{half} F}{V r_j K_j^\text{max}}, \quad \theta_j = \frac{k_2^\text{half}}{k_1^\text{half} + k_2^\text{half}}, \quad \text{for } j = 1, 2,
\]
\[
\delta_1 = \frac{d_1 k_1^\text{half}}{r_2 K_2^\text{max}}, \quad \delta_2 = \frac{d_2 k_1^\text{half}}{r_1 K_1^\text{max}}, \quad \mu(t) = \frac{I(t)}{k_1^\text{half} + k_2^\text{half}}.
\]
are all dimensionless. Moreover, notice that \( C^* \) has the unit of concentration, and both \( N_1^* \) and \( N_2^* \) have the unit of \((\text{concentration} \cdot \frac{\text{volume}}{\text{time}})/(\text{volume} \cdot \frac{1}{\text{time}}) = \text{concentration}\). Thus the new unknowns \( x(t), y(t), z(t) \) are all dimensionless.

2.3. Assumptions. By the physical meanings of parameters listed in Table 1, all dimensionless parameters defined in (7) are positive. The parameters \( \delta_1 \) and \( \delta_2 \) defined in (8) are non-negative and in the special case of no intra-specific competition they can take the value zero. In addition, by the definitions of \( \theta_1 \) and \( \theta_2 \), \( \theta_1 + \theta_2 = 1 \). Moreover, the cancer cells are assumed to grow faster than normal cells, i.e., \( \beta_1 > \beta_2 \) and thus \( \beta_1 > \beta_2 \). Furthermore, since the chemotherapy agent should be more effective killing cancer cells than killing normal cells, \( K_1^\text{max} > K_2^\text{max} \) and consequently, \( \alpha_1 > \alpha_2 \). In summary, it is assumed throughout this paper that
\[(A0) \quad \alpha_1 > \alpha_2 > 0, \quad \beta_1 > \beta_2 > 0, \quad \gamma_1, \gamma_2 > 0, \quad \theta_1, \theta_2 > 0 \quad \text{with } \theta_1 + \theta_2 = 1, \delta_1, \delta_2 \geq 0; \]
\[(A1) \quad \text{the input concentration is bounded and varies continuously with respect to time, i.e., } \mu(t) \text{ is a continuous and bounded function with}
\]
\[0 < \mu_m \leq \mu(t) \leq \mu_M \quad \text{for all } t \in \mathbb{R}.
\]

3. Properties of solutions. In this section, we first investigate basic properties of solutions to the system (4) – (6) including existence, uniqueness, boundedness and non-negativeness of the solution. We then provide a basic introduction on concept and theory of nonautonomous dynamical systems required in the sequel.

3.1. Basic properties of solutions. In this subsection we prove that system (4) – (6) has a unique global solution under the initial condition
\[ x(t_0) = x_0 > 0, \quad y(t_0) = y_0 > 0, \quad z(t_0) = z_0 \geq 0. \]
Moreover, we will prove that the solution is non-negative and bounded for all time \( t \geq t_0 \). For convenience, write \( u(t) := (x(t), y(t), z(t)) \) and \( u_0 = (x_0, y_0, z_0) \).

Lemma 3.1. The ODE system (4) – (6) with initial condition (9) has a unique bounded solution \( u(t; t_0, u_0) \in C^1([t_0, \infty], \mathbb{R}_+^3) \).
Definition 3.2. A process \( \varphi \) on space \( \mathbb{R}^d \) is a family of mappings \( \varphi(t,t_0,\cdot) : \mathbb{R}^d \to \mathbb{R}^d, \quad (t,t_0) \in \mathbb{R}_+^2, \) which satisfies

Proof. First it is straightforward to rewrite (4) – (6) as the following ODE on \( \mathbb{R}^3 \),

\[
\frac{du(t)}{dt} = Lu(t) + g(u(t), t),
\]

with

\[
L = \begin{bmatrix}
\beta_1 \\
\beta_2 \\
-1
\end{bmatrix}, \quad g = \begin{pmatrix}
-\alpha_1 x(t)/\beta_1 y(t) - \beta_1 \gamma_1 x^2(t) - \delta_1 x(t)y(t) \\
-\alpha_2 y(t)/\beta_2 y(t) - \beta_2 \gamma_2 y^2(t) - \delta_2 x(t)y(t) \\
-x(t)/\theta_1 + y(t)/\theta_2 + \mu(t)
\end{pmatrix}.
\]

Since \( \mu(t) \) is both continuous and bounded, function \( g \) is continuous in \( t \) and locally Lipschitz in \( u \). It then follows immediately from the classical theory of ODEs (see, e.g., \cite{12}), that equation (10) has a unique local solution \( u(t; t_0, u_0) \in C^1([t_0, T], \mathbb{R}^3) \).

Notice that

\[
\frac{dx}{dt} \bigg|_{x=0} = 0, \quad \frac{dy}{dt} \bigg|_{y=0} = 0, \quad \frac{dz}{dt} \bigg|_{z=0} = \mu(t) \geq \mu_m > 0,
\]

i.e., the positive quadrant \( \mathbb{R}^3_+ \) is positively invariant for \( u \). Therefore by continuity of solutions, any solution trajectory that starts from \( u_0 \in \mathbb{R}^3_+ \) at \( t_0 \) will stay nonnegative for all \( t \geq t_0 \), i.e., \( u(t; t_0, u_0) \in C^1([t_0, T], \mathbb{R}^3_+) \).

As a direct consequence, components of the solution \( u(t; t_0, u_0) \) satisfy

\[
\frac{dx}{dt} \leq \beta_1 x(1 - \gamma_1 x), \quad \frac{dy}{dt} \leq \beta_2 y(1 - \gamma_2 y), \quad \frac{dz}{dt} \leq \mu(t) - z(t). \tag{11}
\]

It then follows immediately that

\[
0 \leq x(t) \leq \max \{x_0, 1/\gamma_1\}, \quad 0 \leq y(t) \leq \max \{y_0, 1/\gamma_2\}, \quad \forall t \geq t_0. \tag{12}
\]

Moreover, by using Assumption (A1) we have

\[
\frac{dz}{dt} \leq \mu_M - z(t),
\]

which implies that

\[
0 \leq z(t) \leq \max \{z_0, \mu_M\}, \quad t \in [t_0, \infty). \tag{13}
\]

The inequalities (12) and (13) and the existence of local solutions, together imply that given any initial condition \( u_0 = (x_0, y_0, z_0) \in \mathbb{R}^3_+ \) the equation (10) has a unique solution defined for all \( t \geq t_0 \) and remains in the bounded region

\[
\Omega := \{(x, y, z) \in \mathbb{R}^3_+ : x \leq \max \{x_0, 1/\gamma_1\}, y \leq \max \{y_0, 1/\gamma_2\}, z \leq \max \{z_0, \mu_M\}\}.
\]

The proof is complete. \( \square \)

3.2. Preliminaries on nonautonomous dynamical systems. In this subsection we provide introductory material of nonautonomous dynamical systems (see, e.g., \cite{4, 7, 14, 15}) required in the sequel. In particular, we will introduce the process formulation of nonautonomous dynamical systems and concepts and theory on pullback and forward attractors. Denote by

\[
\mathbb{R}_+^2 := \{(t, t_0) \in \mathbb{R}^2 : t \geq t_0\}.
\]

Definition 3.2. A process \( \varphi \) on space \( \mathbb{R}^d \) is a family of mappings

\[
\varphi(t,t_0,\cdot) : \mathbb{R}^d \to \mathbb{R}^d, \quad (t,t_0) \in \mathbb{R}_+^2,
\]

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 \( x \in \mathbb{R}^d \) and \((t_2, t_1), (t_1, t_0) \in \mathbb{R}_+^2 \)

it holds \( \varphi(t_2, t_0, u) = \varphi(t_2, t_1, \varphi(t_1, t_0, u)) \),

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

**Definition 3.3.** Let \( \varphi \) be a process on \( \mathbb{R}^d \). A family \( D = \{D(t) : t \in \mathbb{R}\} \) of nonempty subsets of \( \mathbb{R}^d \) is said to \( \varphi \)-positively invariant if \( \varphi(t, t_0, D(t_0)) \subseteq D(t) \) for all \( (t, t_0) \in \mathbb{R}_+^2 \).

**Definition 3.4.** Let \( \varphi \) be a process on \( \mathbb{R}^d \). A \( \varphi \)-invariant family \( A = \{A(t) : t \in \mathbb{R}\} \) of nonempty compact subsets of \( \mathbb{R}^d \) is called a forward attractor of \( \varphi \) if it forward attracts all families \( B = \{B(t) : t \in \mathbb{R}\} \) of nonempty bounded subsets of \( \mathbb{R}^d \), i.e.,

\[
\text{dist}(\varphi(t_0, B(t_0)), A(t)) \to 0 \quad \text{as} \quad t \to \infty \quad (t_0 \text{ fixed}),
\]

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

\[
\text{dist}(\varphi(t, t_0, B(t_0)), A(t)) \to 0 \quad \text{as} \quad t_0 \to -\infty \quad (t \text{ fixed}).
\]

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

**Definition 3.5.** A family \( \Lambda = \{\Lambda(t) : t \in \mathbb{R}\} \) of nonempty compact subsets of \( \mathbb{R}^d \) is called a pullback absorbing family for a process \( \varphi \) if for each \( \tau \in \mathbb{R} \) and every family \( B = \{B(t) : t \in \mathbb{R}\} \) of nonempty bounded subsets of \( \mathbb{R}^d \) there exists some \( T = T(\tau, B) \in \mathbb{R}^+ \) such that

\[
\varphi(\tau, t_0, B(t_0)) \subseteq \Lambda(\tau) \quad \text{for all} \quad t_0 \in \mathbb{R} \quad \text{with} \quad t_0 \leq \tau - T.
\]

The proof of the following proposition is well known, see e.g., [15].

**Proposition 1.** Suppose that a process \( \varphi \) on \( \mathbb{R}^d \) has a \( \varphi \)-positively invariant pullback absorbing family \( \Lambda = \{\Lambda(t) : t \in \mathbb{R}\} \) of nonempty compact subsets of \( \mathbb{R}^d \). Then \( \varphi \) has a unique global pullback attractor \( A = \{A(t) : t \in \mathbb{R}\} \) with its component sets determined by

\[
A(t) = \bigcap_{t_0 \leq t} \varphi(t, t_0, \Lambda(t_0)) \quad \text{for each} \quad t \in \mathbb{R}.
\]

If \( \Lambda \) is not \( \varphi \)-positively invariant, then

\[
A(t) = \bigcup_{s \geq 0} \bigcup_{t_0 \leq t-s} \varphi(t, t_0, \Lambda(t_0)) \quad \text{for each} \quad t \in \mathbb{R}.
\]

4. Dynamics of the nonautonomous chemotherapy model. First of all, due to the existence and uniqueness of a global solution to the system (4) – (6), we can define a process \( \{\varphi(t, t_0)\}_{(t, t_0) \in \mathbb{R}_+^2} \) by

\[
\varphi(t, t_0, u_0) = u(t; t_0, u_0), \quad \forall \ u_0 \in \mathbb{R}^3,
\]

where \( u(t; t_0, u_0) \) is the solution of (4) – (6) with the initial condition \( u(t_0) = u_0 \).

Moreover, it is straightforward to check that the process defined above is continuous and hence all concepts and theory introduced in the subsection 3.2 can be applied. In what follows, we first establish the existence of a pullback attractor, and then investigate detailed structures of the attractor and provide their biological insights.
4.1. **Existence of pullback attractors.** In this subsection we first construct a positive invariant absorbing set for the process \( \{ \varphi(t,t_0) \}_{t \geq t_0} \) defined in (14), stated in the Lemma below.

**Lemma 4.1.** The process \( \{ \varphi(t,t_0) \}_{t \geq t_0} \) has a positive invariant absorbing set

\[
\Lambda = \left\{ (x, y, z) \in \mathbb{R}^3_+ : x \leq \frac{2}{\gamma_1}, y \leq \frac{2}{\gamma_2}, \frac{\theta_1 \theta_2 \gamma_2 \mu_m}{4(\theta_1 \gamma_1 + \theta_2 \gamma_2) + 2 \theta_1 \theta_2 \gamma_2} \leq z \leq 2 \mu_M \right\},
\]

(15)

**Proof.** First, solving the differential inequalities of \( x(t) \) and \( y(t) \) in (11) with \( x(t_0) = x_0 \) and \( y(t_0) = y_0 \) gives

\[
x(t) \leq \frac{x_0}{x_0 \gamma_1 + (1 - \gamma_1 x_0) e^{-\beta_1(t-t_0)}}, \quad \forall \ t \geq t_0, \tag{16}
\]

\[
y(t) \leq \frac{y_0}{y_0 \gamma_2 + (1 - \gamma_2 y_0) e^{-\beta_2(t-t_0)}}, \quad \forall \ t \geq t_0. \tag{17}
\]

Therefore for any \( \varepsilon > 0 \) there exists \( T_1(\varepsilon) > 0 \) such that

\[
0 \leq x(t) \leq \frac{1}{\gamma_1} + \varepsilon, \quad 0 \leq y(t) \leq \frac{1}{\gamma_2} + \varepsilon, \quad \text{for } t - t_0 > T_1(\varepsilon). \tag{18}
\]

Next, solving the differential inequality of \( z(t) \) in (11) with \( z(t_0) = z_0 \) gives

\[
z(t) \leq z_0 e^{-t} + \int_{t_0}^{t} \mu(s) e^{s-t} ds \leq z_0 e^{-t} + \mu_M \left( 1 - e^{-(t-t_0)} \right), \quad \forall \ t \geq t_0, \tag{19}
\]

which implies that for any \( \varepsilon > 0 \) there exists \( T_2(\varepsilon) > 0 \) such that

\[
z(t) \leq \mu_M + \varepsilon \quad \text{for } t - t_0 > T_2(\varepsilon). \tag{20}
\]

On the other side, using (18), equation (6) and \( \frac{1}{\beta_j + \varepsilon} \leq \frac{1}{\beta_j} \) for \( j = 1, 2 \), we have for any \( \varepsilon > 0 \)

\[
\frac{dz}{dt} \geq - \left( \frac{1}{\theta_1} \left( \frac{1}{\gamma_1} + \varepsilon \right) + \frac{1}{\theta_2} \left( \frac{1}{\gamma_2} + \varepsilon \right) + 1 \right) z(t) + \mu(t), \quad \forall \ t - t_0 > T_1(\varepsilon)
\]

and consequently there exists \( T_3(\varepsilon) > T_1(\varepsilon) \) such that

\[
z(t) \geq z_0 e^{-\left( \frac{1}{\theta_1} \left( \frac{1}{\gamma_1} + \varepsilon \right) + \frac{1}{\theta_2} \left( \frac{1}{\gamma_2} + \varepsilon \right) + 1 \right)(t-t_0)} + \int_{t_0}^{t} \mu(s) e^{\left( \frac{1}{\theta_1} \left( \frac{1}{\gamma_1} + \varepsilon \right) + \frac{1}{\theta_2} \left( \frac{1}{\gamma_2} + \varepsilon \right) + 1 \right)(s-t)} ds
\]

\[
\geq \frac{\mu_m}{\theta_1} \left( \frac{1}{\gamma_1} + \varepsilon \right) + \frac{\mu_m}{\theta_2} \left( \frac{1}{\gamma_2} + \varepsilon \right) + 1 \left( 1 - e^{-t} \right), \quad \forall \ t - t_0 > T_3(\varepsilon). \tag{21}
\]

Summarizing the above, for any \( 0 < \varepsilon < 1 \) define

\[
\Lambda_{\varepsilon} = \left\{ (x, y, z) \in \mathbb{R}^3_+ : x \leq \frac{1}{\gamma_1} + \varepsilon, y \leq \frac{1}{\gamma_2} + \varepsilon, \frac{\mu_m(1-\varepsilon)}{\theta_1 \left( \frac{1}{\gamma_1} + \varepsilon \right) + \frac{\mu_m(1-\varepsilon)}{\theta_2} \left( \frac{1}{\gamma_2} + \varepsilon \right) + 1} \leq z \leq 2 \mu_M + \varepsilon \right\}
\]

Then for any bounded family \( \mathcal{B} = \{ B(t) : t \in \mathbb{R} \} \) there exists \( T(\varepsilon, \mathcal{B}) > 0 \) such that

\[
\varphi(t, t_0, B(t_0)) \subset \Lambda_{\varepsilon}, \quad \forall \ t - t_0 > T(\varepsilon),
\]

i.e., \( \Lambda_{\varepsilon} \) is an absorbing set for the process \( \{ \varphi(t, t_0) \}_{(t,t_0) \in \mathbb{R}^2_+} \). In particular, picking \( \varepsilon = \min \{ 1/\gamma_1, 1/\gamma_2, 2, \mu_M \} \), then \( \Lambda_{\varepsilon} \) can be simplified to the set \( \Lambda \) in (15).

It remains to show that \( \Lambda \) is positive invariant. In fact by using (16) we have

\[
x(t; t_0, u_0) \leq \left\{ \begin{array}{ll}
x_0 \left( \frac{1}{x_0 \gamma_1 (1 - \gamma_1 x_0)} \right) = \frac{1}{x_0 \gamma_1}, & x_0 \in \left( 0, \frac{1}{\gamma_1} \right] \\
x_0 \left( \frac{1}{x_0 \gamma_1} \right) & x_0 \in \left( \frac{1}{\gamma_1}, \frac{1}{\gamma_2} \right]
\end{array} \right., \quad \forall \ t \geq t_0.
\]
Thus
\[ x(t; t_0, u_0) \leq \frac{2}{\gamma_1} \quad \text{for all } u_0 \in \Lambda, \quad \forall \ t \geq t_0. \] (22)

Similarly it follows from (17) that
\[ y(t; t_0, u_0) \leq \frac{2}{\gamma_2} \quad \text{for all } u_0 \in \Lambda, \quad \forall \ t \geq t_0. \] (23)

Next, by using (19), for any \( z_0 \leq 2\mu_M \),
\[ z(t; t_0, u_0) \leq \mu_M + (z_0 - \mu_M)e^{-(t-t_0)} \leq 2\mu_M. \] (24)

Then using (22), (23) and the ODE (6) we obtain
\[
\frac{dz(t)}{dt} \geq -\frac{2}{\gamma_1} \frac{z}{\theta_1 + z} - \frac{2}{\gamma_2} \frac{z}{\theta_2 + z} - z(t) + \mu(t)
\geq -\left( \frac{2}{\gamma_1} \frac{1}{\theta_1} + \frac{2}{\gamma_2} \frac{1}{\theta_2} + 1 \right) z(t) + \mu_m.
\]

Then for any \( z_0 \geq \frac{\theta_1 \gamma_1 \theta_2 \gamma_2 \mu_m}{4(\theta_1 \gamma_1 + \theta_2 \gamma_2 + 2\theta_1 \theta_2 \gamma_1 \gamma_2)} \),
\[
z(t; t_0, u_0) \geq \left( z_0 - \frac{\mu_m}{\gamma_1 \theta_1 + \frac{\mu_m}{\gamma_2 \theta_2} + 1} \right) e^{-\left( \frac{\gamma_1 \theta_1}{\gamma_2 \theta_2} + \frac{\gamma_2 \theta_2}{\gamma_1 \theta_1} + 1 \right)(t-t_0)} + \frac{\mu_m}{\gamma_1 \theta_1 + \frac{\mu_m}{\gamma_2 \theta_2} + 1}
\geq \frac{1}{\theta_1 \gamma_1 \theta_2 \gamma_2 \mu_m}
\frac{\theta_1 \gamma_1 \theta_2 \gamma_2 \mu_m}{4(\theta_1 \gamma_1 + \theta_2 \gamma_2 + 2\theta_1 \theta_2 \gamma_1 \gamma_2)}, \quad \text{for all } u_0 \in \Lambda, \quad \forall \ t \geq t_0. \] (25)

Summarizing (22)–(25), \( u(t; t_0, u_0) \in \Lambda \) for any \( u_0 \in \Lambda \), i.e., \( \Lambda \) is positively invariant. The proof is complete. \( \square \)

The following theorem follows directly from Proposition 1.

**Theorem 4.2.** Assume that assumptions (A0) and (A1) hold. Then the process \( \{\varphi(t, t_0)\}_{(t, t_0) \in \mathbb{R}^2_+} \) generated by the solution of system (4) - (6) has a pullback attractor \( \mathcal{A} = \{A(t) : t \in \mathbb{R}\} \) inside the nonnegative quadrant \( \mathbb{R}^3_+ \).

**Remark 4.3.** Notice that the estimations (18) - (25) hold both forwardly and pullback, i.e., for \( t_0 \) fixed with \( t \to \infty \), as well as for \( t \) fixed with \( t_0 \to -\infty \). The set \( \Lambda \) is both a pullback absorbing set and a forward absorbing set. Although this does not necessarily ensure the existence of a forward attractor (see, e.g., [7]), it can still be used to investigate forward dynamics of the system.

**4.2. Detailed dynamics within the attractor.** Theorem 4.2 provides the existence of a pullback attractor for the process \( \{\varphi(t, t_0)\}_{(t, t_0) \in \mathbb{R}^2_+} \) defined by the solution of system (4) - (6). In fact, since \( \Lambda \) is \( \varphi \)-positively invariant, the component subsets of the attractor \( \mathcal{A} \) are defined by
\[ A(t) = \bigcap_{t_0 \leq t} \varphi(t, t_0, \Lambda), \quad \text{for each } t \in \mathbb{R}. \]

In this subsection we investigate detailed structure of \( \mathcal{A} \), with both mathematical and biological interpretations.
Theorem 4.4. Assume that
\[ \beta_1 < \alpha_1 \frac{z_m}{\theta_1 + z_m}, \]  
\[ \beta_2 < \alpha_2 \frac{z_m}{\theta_2 + z_m}. \]  
with
\[ z_m := \frac{\mu_m}{\gamma_1 \theta_1 + \gamma_2 \theta_2 + 2}. \]

Then the pullback attractor \( A(t) = \{(0,0,z^*(t))\} \) for all \( t \in \mathbb{R} \), where
\[ z^*(t) = \int_{-\infty}^{t} \mu(s)e^{-(t-s)}ds. \]

Proof. First note that \( \frac{dz}{dt} \big|_{x=0} = 0 \). Then for any \( x > 0 \), using the lower bound of \( z \) in (25), we have
\[ \frac{z}{\theta_1 + z} \geq \frac{z_m}{\theta_1 + z_m}. \]
It then follows immediately from the assumption (26) that
\[ \frac{dx(t)}{dt} < x(-\alpha_1 \frac{z_m}{\theta_1 + z_m} + \beta_1) < 0, \]
i.e., \( \frac{dx(t)}{dt} \) is negative definite. Thus the \( x \) component of all trajectories in the nonnegative quadrant \( \mathbb{R}^3_+ \) approaches 0 asymptotically. Similarly, the \( y \) component of all trajectories in the nonnegative quadrant \( \mathbb{R}^3_+ \) all approaches 0 asymptotically provided \( \alpha_2 z_m > \beta_2 \), which is equivalent to the assumption (27).

With \( x(t) = 0 \) and \( y(t) = 0 \), the equation (6) becomes
\[ \frac{dz(t)}{dt} = -z(t) + \mu(t), \]
which can be solved to get
\[ z(t; t_0, u_0) = z_0 e^{-(t-s)} + \int_{t_0}^{t} \mu(s)e^{-(t-s)}ds \]
\[ \quad \rightarrow \int_{-\infty}^{t} \mu(s)e^{-(t-s)}ds \quad \text{as} \ t_0 \to -\infty. \]
The proof is complete. \( \square \)

Remark 4.5. The singleton trajectory \( z^*(t) \) is obtained by fixing \( z_0 \) and letting \( t_0 \) approach \( -\infty \). Notice that the chemotherapy agent does not exists until the treatment starts, thus \( z_0 = 0 \) for \( t_0 < 0 \) and \( \mu(t) = 0 \) for \( t < t_0 \). While it seems that \( z^*(t) \) then depends on the starting time \( t_0 \), it is in fact a function of \( t \) dependent on the definition of \( \mu(t) \) which is given.

Theorem 4.6. Assume that (26) holds and
\[ \beta_2 > \alpha_2 + \frac{2\delta_2}{\gamma_1}. \]  
Then the pullback attractor contains points inside the strictly positive subspace \( \{(x,y,z) \in \mathbb{R}^3_+: x = 0, y > 0, z > 0\} \).
Proof. We look at the derivative of \( y(t) \) at any \( \varepsilon < 1/\gamma_2 \). Using Lemma 4.1
\[
\frac{dy(t)}{dt} \bigg|_{y=\varepsilon} = -\alpha_2\varepsilon \frac{z}{\theta_2 + z} + \beta_2\varepsilon(1 - \gamma_2\varepsilon) - \delta_2\varepsilon x \\
> \varepsilon \left( -\alpha_2 \frac{2\mu_M}{\theta_2 + 2\mu_M} + \beta_2 - \beta_2\varepsilon\gamma_2 - \delta_2 \frac{2}{\gamma_1} \right).
\]
In particular picking \( \varepsilon \leq \frac{\alpha_2\theta_2}{\beta_2\gamma_2(\theta_2 + 2\mu_M)} \), then under the assumption (29),
\[
\beta_2(1 - \varepsilon\gamma_2) \geq \frac{2\alpha_2\mu_M}{\theta_2 + 2\mu_M} + \frac{2\delta_2}{\gamma_1},
\]
which implies that \( \frac{dy(t)}{dt} \bigg|_{y=\varepsilon} > 0 \). Thus \( y(t) \in [\varepsilon, 2/\gamma_2] \) for all \( t \geq t_0 \) and the attractor contains points inside \( \{(x, y, z) \in \mathbb{R}_+^3 : x = 0, y \geq \varepsilon, z > 0 \} \). The proof is complete.

**Theorem 4.7.** Assume that (27) holds and
\[
\beta_1 > \alpha_1 + \frac{2\delta_1}{\gamma_2}, \tag{30}
\]
Then the pullback attractor contains points inside the strictly positive subspace \( \{(x, y, z) \in \mathbb{R}_+^3 : x > 0, y = 0, z > 0 \} \).

Proof. We look at the derivative of \( x(t) \) at any \( \varepsilon < 1/\gamma_1 \). Using Lemma 4.1
\[
\frac{dx(t)}{dt} \bigg|_{x=\varepsilon} = -\alpha_1\varepsilon \frac{z}{\theta_1 + z} + \beta_1\varepsilon(1 - \gamma_1\varepsilon) - \delta_1\varepsilon y \\
> \varepsilon \left( -\alpha_1 \frac{2\mu_M}{\theta_1 + 2\mu_M} + \beta_1 - \beta_1\varepsilon\gamma_1 - \delta_1 \frac{2}{\gamma_2} \right).
\]
In particular picking \( \varepsilon \leq \frac{\alpha_1\theta_1}{\beta_1\gamma_1(\theta_1 + 2\mu_M)} \), then under the assumption (30),
\[
\beta_1(1 - \varepsilon\gamma_1) \geq \frac{2\alpha_1\mu_M}{\theta_1 + 2\mu_M} + \frac{2\delta_1}{\gamma_2},
\]
which implies that \( \frac{dx(t)}{dt} \bigg|_{x=\varepsilon} > 0 \). Thus \( x(t) \in [\varepsilon, 2/\gamma_1] \) for all \( t \geq t_0 \) and the attractor contains points inside \( \{(x, y, z) \in \mathbb{R}_+^3 : x \geq \varepsilon, y = 0, z > 0 \} \). The proof is complete.

4.3. Biological interpretations. Theorem 4.4 says that all cancer cells will die out if the assumption (26) is satisfied and all normal cells will die out if the assumption (27) is satisfied. The assumption (26) is equivalent to \( b_1 < K_1^{\max}r_1 \), and the assumption (27) is equivalent to \( b_2 < K_2^{\max}r_2 \) where \( r_1 \) and \( r_2 \) can be thought of as a portion of the maximal killing rate on the cancer and normal cells, respectively. More importantly \( r_1 \) and \( r_2 \) depend on the minimum infusion concentration \( \min_{t \geq t_0} I(t) \).

Theorem 4.6 provides sufficient conditions for a successful treatment, i.e., all cancer cells are killed but normal cells still remain. The assumption (29) is equivalent to \( b_2 > K_2^{\max} + 2d_2\gamma_1 \), which means that the per capita birth rate of normal cells has to be large enough to cover the maximal killing rate of the chemotherapy agent on the normal cells and twice the intra-specific competition created by all cancer cells carried by the environment. In the special case where \( d_2 = 0 \), this reduces to \( b_2 > K_2^{\max} \) only.
Theorem 4.7 provides sufficient condition for a failed treatment, i.e., all normal
cells are killed but cancer cells are remaining. The assumption (30) is equivalent to
\[ b_1 > K_1^{\text{max}} + 2d_1 \kappa_2, \]
which means that the per capita birth rate of cancer cells is
even larger than the maximal killing rate of the chemotherapy agent on the cancer
cells and twice the intra-specific competition created by all normal cells carried by
the environment. In the special case where \( d_1 = 0 \), this reduces to
\[ b_1 > K_1^{\text{max}} \] only.

It is implied by the theoretical results above that the success or failure of a
chemotherapy treatment is mostly determined by the relations between the per
capita growth rate of cells, the maximum killing rate, i.e., effectiveness of the
chemotherapy agent on cells. The carrying capacity of cells also affect the results,
but according to the strength of intra-specific competitions.

However, it is worth mentioning that after a closer look at the computations in
the proof of Theorem 4.6, the assumption (29) can be weakened to
\[ \beta_2 > \alpha_2 \frac{2\mu_M}{\theta_2 + 2\mu_M} + \frac{2\theta_2}{\gamma_1}, \]
which is equivalent to
\[ b_2 > K_2^{\text{max}} R_2 + 2d_2 \kappa_1 \quad \text{with} \quad R_2 = \frac{2 \max_{t \geq t_0} I(t)}{\mu_M + 2 \max_{t \geq t_0} I(t)}. \]
This means that for the normal cells to remain while all cancer cells are cleared, the
per capita growth rate of normal cells does not really need to be much larger than
the maximum killing rate of the agent on the normal cells. In fact, it only needs
to be faster than a percentage \( R_2 \) of the maximum killing rate on the normal cells,
which is determined by the relation between the maximum input concentration of
the chemotherapy agent and the half saturation concentration of the consumption
function of normal cells.

Similarly, for the cancer cells to remain while all normal cells die, the per capita
growth rate of cancer cells does not really need to be much larger than the maximum
killing rate of the agent on the cancer cells. In fact, it only needs to be faster than a
percentage \( R_1 \) of the maximum killing rate on the cancer cells, which is determined
by the relation between the maximum input concentration of the chemotherapy
agent and the half saturation concentration of the consumption function of cancer
cells.

These bring in the effect of control on the input concentration \( I(t) \), as well as a
major difference between nonautonomous and autonomous models.

4.4. Comparison to the autonomous counterpart. For comparison purpose,
we analyze the autonomous counterpart of the system (4) – (6), in which \( \mu(t) \equiv \hat{\mu} \).
In particular, we exam the sufficient conditions for a successful treatment and a fail-
ure treatment and compare to the nonautonomous results. For reader’s convenience,
we state the autonomous system below.

\[
\begin{align*}
\frac{dx(t)}{dt} &= -\alpha_1 \frac{x(t)z(t)}{\theta_1 + z(t)} + \beta_1 x(t)(1 - \gamma_1 x(t)) - \delta_1 x(t)y(t), \\
\frac{dy(t)}{dt} &= -\alpha_2 \frac{y(t)z(t)}{\theta_2 + z(t)} + \beta_2 y(t)(1 - \gamma_2 y(t)) - \delta_2 x(t)y(t), \\
\frac{dz(t)}{dt} &= -\frac{x(t)z(t)}{\theta_1 + z(t)} - \frac{y(t)z(t)}{\theta_2 + z(t)} - z(t) + \hat{\mu}.
\end{align*}
\]
Note that all computations in Lemma (4.1) still hold for the above system, and hence we can also focus our attention on the positive invariant set

\[
\tilde{\Lambda} = \left\{ (x, y, z) \in \mathbb{R}^3 : x \leq \frac{2}{\gamma_1}, y \leq \frac{2}{\gamma_2}, \frac{\theta_1 \theta_2 \gamma_1 \gamma_2 \hat{\mu}}{4(\theta_1 \gamma_1 + \theta_2 \gamma_2) + 2 \theta_1 \theta_2 \gamma_1 \gamma_2} \leq z \leq \frac{2 \hat{\mu}}{\gamma_2} \right\}.
\]  

(34)

Recall that a major difference between autonomous and nonautonomous systems is that solutions of autonomous systems depend only on the time elapsed, \( t - t_0 \), while solutions of nonautonomous systems depend on both \( t_0 \) and \( t \). In general, nonautonomous systems do not possess constant equilibria as autonomous systems do. But there may exist entire trajectories of nonautonomous systems which can be regarded as the time-dependent counterpart of equilibria for autonomous systems. For example, \((0, 0, \hat{\mu})\) is one equilibrium for the autonomous system (31) – (33) that is asymptotically stable under the assumptions (26) and (27), while \((0, 0, z^*(t))\) is an entire trajectory of the nonautonomous system (4) – (6) that attracts all other solutions under the assumptions (26) and (27).

Our main aim next is to investigate the situation that the nonautonomous system (4) – (6) approaches a successful treatment with \( \mu(t) \), while the autonomous system (31) – (33) with \( \hat{\mu} = \frac{1}{t-T_0} \int_{t_0}^{t} \mu(t) dt \) approaches a fail treatment. To that end, consider a “failure” steady state \( E_f := (x^*, 0, z^*) \) with \( x^*, z^* > 0 \), satisfying

\[
- \alpha_1 \frac{x^* z^*}{\theta_1 + x^*} + \beta_1 x^*(1 - \gamma_1 x^*) = 0, \quad - \frac{x^* z^*}{\theta_1 + z^*} - z^* + \hat{\mu} = 0.
\]  

(35)

Setting \( \hat{x}(t) = x(t) - x^* \) and \( \hat{z}(t) = z(t) - z^* \), then \( \hat{x}(t) \) and \( \hat{z}(t) \) satisfy the ODEs

\[
\frac{d\hat{x}(t)}{dt} = - \alpha_1 \frac{(\hat{x}(t) + x^*) z(t)}{\theta_1 + z(t)} + \beta_1 (\hat{x}(t) + x^*)(1 - \gamma_1 (\hat{x}(t) + x^*)),
\]  

(36)

\[
\frac{d\hat{z}(t)}{dt} = - \frac{y(t)(\hat{z}(t) + z^*)}{\theta_2 + z(t)} - (\hat{z}(t) + z^*) + \hat{\mu}.
\]  

(37)

Theorem 4.8. The “failure” steady state \( E_f \) for system (31) – (33) is asymptotically stable provided

\[
\beta_2 < \alpha_2 \frac{z_l}{\theta_2 + z_l},
\]  

(38)

\[
\frac{\alpha_1 z_l}{\theta_1 + z_l} - \frac{(\alpha_1 x^* + z^*)^2}{4\theta_1^2} > \beta_1 - \beta_1 \gamma_1 x^* + \frac{(\delta x^*)^2 (\theta_2 + z_l)}{4(\alpha_2 z_l - \beta_2 (\theta_2 + z_l))}.
\]  

(39)

where

\[
z_l := \frac{\theta_1 \theta_2 \gamma_1 \gamma_2 \hat{\mu}}{4(\theta_1 \gamma_1 + \theta_2 \gamma_2) + 2 \theta_1 \theta_2 \gamma_1 \gamma_2}.
\]  

(40)

Proof. First, by using (32) and the lower bound of \( z \) in (34) we have

\[
y \frac{dy}{dt} = y^2 \left( - \alpha_2 \frac{z_1}{\theta_2 + z_l} + \beta_2 - \beta_2 \gamma_2 y - \delta_2 x \right) \leq y^2 \left( - \alpha_2 \frac{z_1}{\theta_2 + z_l} + \beta_2 \right).
\]  

(41)
Then by using (35) and (36) we have
\[
\frac{\dot{x}}{dt} = -\frac{\alpha_1 z}{\theta_1 + z} (\dot{x}^2 + \dot{x} x^*) + \beta_1 \dot{x}^2 (1 - \gamma_1 x) + \beta_1 \dot{x} x^* (1 - \gamma_1 x^*) \\
- \beta_1 \gamma_1 x^* \dot{x}^2 - \delta_1 x y \dot{x} \\
\leq \left( \beta_1 - \frac{\alpha_1 z}{\theta_1 + z} - \beta_1 \gamma_1 x^* \right) \dot{x}^2 - \alpha_1 x^* \dot{x} \left( \frac{z}{\theta_1 + z} - \frac{z^*}{\theta_1 + z^*} \right) - \delta_1 x^* y \dot{x}. \tag{42}
\]

Next, by using (35) and (37) we have
\[
\frac{\dot{z}}{dt} = -\frac{x}{\theta_1 + z} z^2 - \frac{x z^*}{\theta_1 + z} \dot{z} - \ddot{z}^2 - (-z^* + \hat{\mu}) \ddot{z} \\
= -\left( \frac{x}{\theta_1 + z} + 1 \right) z^2 - \left( \frac{x}{\theta_1 + z} - \frac{x^*}{\theta_1 + z^*} \right) z^* \ddot{z} \\
\leq -\ddot{z}^2 - \left( \frac{x}{\theta_1 + z} - \frac{x^*}{\theta_1 + z^*} \right) z^* \ddot{z}. \tag{43}
\]

Now define \( V(x, \dot{x}, \ddot{z}) = \frac{1}{2} y^2 + \frac{1}{2} \dot{x}^2 + \frac{1}{2} \ddot{z}^2 \). Then \( V(\ddot{x}, \ddot{z}) > 0 \) for all \( x, \dot{x}, \ddot{z} \neq 0 \) and by (41) – (43), the derivative of \( V(x, \ddot{x}, \ddot{z}) \) along solutions of the system (31) – (36) – (37) satisfies
\[
\frac{dV}{dt} \leq \left( -\alpha_2 \frac{z_l}{\theta_2 + z_l} + \beta_2 \right) y^2 + \left( \beta_1 - \frac{\alpha_1 z_l}{\theta_1 + z_l} - \beta_1 \gamma_1 x^* \right) \dot{x}^2 - \ddot{z}^2 - \delta_1 x^* y \dot{x} \\
- \alpha_1 x^* \dot{x} \left( \frac{z}{\theta_1 + z} - \frac{z^*}{\theta_1 + z^*} \right) - \left( \frac{x}{\theta_1 + z} - \frac{x^*}{\theta_1 + z^*} \right) z^* \ddot{z}. \tag{44}
\]

Notice that
\[
-\alpha_1 x^* \dot{x} \left( \frac{z}{\theta_1 + z} - \frac{z^*}{\theta_1 + z^*} \right) - \left( \frac{x}{\theta_1 + z} - \frac{x^*}{\theta_1 + z^*} \right) z^* \ddot{z} = -\frac{\theta_1 (\alpha_1 x^* + z^*)}{(\theta_1 + z)(\theta_1 + z^*)} \ddot{x} \ddot{z},
\]
in which
\[
\frac{\theta_1 (\alpha_1 y^* + z^*)}{(\theta_1 + z)(\theta_1 + z^*)} \leq \frac{\alpha_1 x^* + z^*}{\theta_1}.
\]

Hence there exist \( p, q > 0 \) such that
\[
\frac{dV}{dt} \leq \left( -\alpha_2 \frac{z_l}{\theta_2 + z_l} + \beta_2 + \delta_1 x^* \frac{p}{2} \right) y^2 + \left( -1 + \frac{\alpha_1 x^* + z^* q}{\theta_1} \right) \ddot{z}^2 \\
+ \left( \beta_1 - \frac{\alpha_1 z_l}{\theta_1 + z_l} - \beta_1 \gamma_1 x^* + \frac{\delta_1 x^*}{2p} + \frac{\alpha_1 x^* + z^*}{2q\theta_1} \right) \dot{x}^2.
\]

In particular, pick \( p \) and \( q \) such that
\[
\delta_1 x^* \frac{p}{2} = \alpha_2 \frac{z_l}{\theta_2 + z_l} - \beta_2, \quad \frac{\alpha_1 x^* + z^* q}{\theta_1} = 1.
\]

Then it follows directly from assumptions (38) and (39) that
\[
\frac{dV}{dt} \leq \left( \beta_1 - \frac{\alpha_1 z_l}{\theta_1 + z_l} - \beta_1 \gamma_1 x^* + \frac{(\delta x^*)^2 (\theta_2 + z_l)}{4(\alpha_2 z_l - \beta_2 (\theta_2 + z_l))} + \frac{(\alpha_1 x^* + z^*)^2}{4\theta_l^2} \right) \ddot{x}^2 < 0.
\]

The proof is complete. \( \square \)

Following similar computations, we have the following stability result for a “successful” steady state \( E_s := (0, y^*, z^*) \) with \( y^*, z^* > 0 \).
Theorem 4.9. The “successful” steady state $E_s$ for system (31) – (33) is asymptotically stable provided

$$
\frac{\alpha_2 z_l}{\theta_2 + z_l} < \alpha_1 \frac{z_l}{\theta_1 + z_l},
$$

(45)

$$
\frac{\alpha_2 y^* + z^*}{4\theta_2^2} > \beta_2 - 2\gamma_2 y^* + \frac{\gamma^2 y^* (\theta_1 + z_l)}{4(\alpha_1 z_l - \beta_1 (\theta_1 + z_l))},
$$

(46)

where $z_l$ is defined as in (40).

The assumption $\beta_2 < \alpha_2 \frac{z_l}{\theta_2 + z_l}$ in Theorem 4.8 basically ensures that all normal cells die out for the autonomous system (31) – (33). Recall for the nonautonomous systems (4) – (6) that the assumption for all normal cells to die out is $\beta_2 < \alpha_2 \frac{z_m}{\theta_2 + z_m}$.

It is important to note that $z_m \leq z_l$ as defined in (28) and (40), respectively. Therefore intuitively when $\beta_2$ belongs the interval

$$
\alpha_2 \frac{z_m}{\theta_2 + z_m} \leq \beta_2 \leq \alpha_2 \frac{z_l}{\theta_2 + z_l},
$$

the normal cells may survive for the nonautonomous case while dying out for the autonomous case. However, the sufficient condition for the cancer cells to die out in the nonautonomous system, $\beta_1 < \alpha_1 \frac{z_l}{\theta_1 + z_l}$ automatically ensures the the assumption $\beta_1 < \alpha_1 \frac{z_l}{\theta_1 + z_l}$ for the cancer cells to die out in the autonomous system. Nevertheless a successful treatment resulted from the nonautonomous system (4) – (6) and an axial steady state for the autonomous system (31) – (33) can be easily constructed. Moreover, all assumptions constructed are sufficient but not necessary conditions, so the scenarios of successful treatment in the nonautonomous case and failed treatment in the autonomous case cannot be theoretically excluded. In fact, extensive numerical simulations reveal that such cases do exist.

4.5. Numerical simulations. To illustrate the theoretical results above, we pick one set of parameters that satisfy assumptions (45) and (46) resulting a “failure” treatment in the autonomous system, and assumptions (26) and (29) resulting a “success” treatment in the nonautonomous system. In particular, we pick

$$
\hat{\mu} = \frac{\mu_m + \mu_M}{2}, \quad \mu(t) = \frac{\mu_m + \mu_M}{2} + \frac{\mu_M - \mu_m}{2} \sin \frac{2k\pi}{T} t, \quad k \in \mathbb{Z},
$$

with

$$
\mu_m = 2, \quad \mu_M = 6, \quad k = 2, \quad T = 100.
$$

All parameters are chosen to be strictly positive and satisfy the assumptions (A0) and (A1), shown in the table below.

| $\alpha_1$ | $\alpha_2$ | $\beta_1$ | $\beta_2$ | $\gamma_1$ | $\gamma_2$ | $\theta_1$ | $\theta_2$ | $\delta_1$ | $\delta_2$ |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 2          | 1.28       | 2.98       | 1.95       | 0.2        | 0.2        | 0.5        | 0.5        | 1          | 1          |

Figures 1 and 2 show the numerical simulations of chemotherapy with the same parameters shown in the above table, but with time-dependent and constant infusion, respectively. The two simulations have the same amount of chemotherapy agent infused between the starting time 0 and ending time 100. It is clearly observed that with the time-dependent infusion the amount of cancer cells approaches zero near time 20, with the amount of normal cells remain positive until time 100. On the other hand with the constant infusion the normal cells approaches zero slightly after time 30, whereas the amount of cancer cells approaches a positive constant close to 3 as time evolves. These demonstrate our conjecture that with the same
amount of chemotherapy agent, infused during the same period of time, a treatment with time-dependent infusion can over perform a treatment with constant infusion.

\[ \mu(t) = 4 + 2 \sin 0.04t, \] resulting a successful treatment where all cancer cells are removed and normal cells remain.

**Figure 1.** Chemotherapy with time-dependent infusion \( \mu(t) = 4 + 2 \sin 0.04t \), resulting a successful treatment where all cancer cells are removed and normal cells remain.

\[ \mu = 4, \] resulting a failed treatment where all normal cells are removed and cancer cells remain.

**Figure 2.** Chemotherapy with time-dependent infusion \( \mu = 4 \), resulting a failed treatment where all normal cells are removed and cancer cells remain.
REFERENCES

[1] I. Abdulrashid, A. M. A. Abdallah and X. Han, Stability analysis of a chemotherapy model with delays, 2019.
[2] I. Abdulrashid, T. Caraballo and X. Han, Effects of delays in mathematical models of cancer chemotherapy, preprint.
[3] P. Boyle and B. Levin, *The World Cancer Report*, World Health Organization, 2008.
[4] T. Caraballo and X. Han, *Applied Nonautonomous and Random Dynamical Systems*, SpringerBriefs in Mathematics, Springer, Cham, 2016.
[5] A. F. Chambers, A. C. Groom and I. C. MacDonald, Metastasis: dissemination and growth of cancer cells in metastatic sites, *Nature Rev. Cancer*, 2 (2002), 563–572.
[6] M. Costa and J. Boldrini, Chemotherapeutic treatments: A study of the interplay among drugs resistance, toxicity and recuperation from side effects, *Bull. Math. Biol.*, 59 (1997), 205–232.
[7] H. Cui, P. E. Kloeden and M. Yang, Forward omega limit sets of nonautonomous dynamical systems, *Disc. Cont. Dyn. Sys. - S*, to appear.
[8] L. de Pillis, W. Gu and A. Radunskaya, Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations, *J. Theoret. Bio.*, 238 (2006), 841–862.
[9] L. de Pillis, A. E. Radunskaya and C. L. Wiseman, A validated mathematical model of cell-mediated immune response to tumor growth, *Cancer Res.*, 65 (2005), 7950–7958.
[10] R. Dorr and D. Von Hoff, *Cancer chemotherapy Handbook*, Appleton and Lange, Connecticut, 1994.
[11] M. Eisen, Mathematical models in cell biology and cancer chemotherapy, in *Lect. Notes Biomath.*, vol. 30, Springer-Verlag, Berlin, 1979.
[12] J. K. Hale, *Ordinary Differential Equations*, Dover Publication, Mineola, NY, 1980.
[13] X. Han, Dynamical analysis of chemotherapy model with time-dependent infusion, *Nonlinear Analysis: RWA*, 14 (2017), 459–480.
[14] P. E. Kloeden and C. Potzsche, *Nonautonomous Dynamical Systems in the Life Sciences, Lecture Note in Math.*, Springer, New York, 2013.
[15] P. Kloeden and M. Rasmussen, *Nonautonomous Dynamical Systems*, in Mathematical Surveys and Monographs, Vol. 176, American Mathematical Society, Providence, RI, 2011.
[16] P. Krishnapriya and M. Pitchaimani, Optimal control of mixed immunotherapy and chemotherapy of tumors with discrete delay, *Int. J. Dynam. Control*, 5 (2017), 872–892.
[17] A. Lopez, J. Seoane and M. Sanjuan, A validated mathematical model of tumor growth including tumor host interaction, cell-mediated immune response and chemotherapy, *Bull. Math. Biol.*, 76 (2014), 2884–2906.
[18] J. Mackay and G. Mensah, *The Atlas of Disease and Stroke*, Published by the World Health Organization in Collaboration with the Centers for Disease Control and Prevention, 2004.
[19] J. Murray, Optimal drug regimens in cancer chemotherapy for single drug that block progression through the cell cycle, *Math. Biosci.*, 123 (1994), 181–213.
[20] F. Nani and H. I. Freedman, A mathematical model of cancer treatment by immunotherapy, *Math. Biosci.*, 163 (2000), 159–199.
[21] J. Panetta and J. Adam, A mathematical model of cycle-specific chemotherapy, *Math. Comput. Modeling*, 22 (1995), 67–82.
[22] S. Pinho, H. I. Freedman and F. Nani, A chemotherapy model for the treatment of cancer with metastasis, *Math. Comput. Modeling*, 36 (2002), 773–803.
[23] M. S. Rajput and P. Agrawal, Microspheres in cancer therapy, *Indian J. Cancer*, 47 (2010), 458–468.
[24] E. D. Sontag, *Lecture Notes in Mathematical Biology*, 2006.
[25] E. D. Sontag, *Lecture Notes on Mathematical Systems Biology*, Northeastern University, Boston, 2018.
[26] T. Wheldon, *Mathematical Models in Cancer Research*, Adam Hilger, Bristol, 1988.

Received June 2019; revised September 2019.

E-mail address: iza0009@auburn.edu
E-mail address: xzh0003@auburn.edu