Dynamics of Chemotherapy Models with Variable Infusion and Time Delays

by

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Abstract

Chemotherapy is a fundamental and commonly used form of cancer treatment, usually done with the application of a chemotherapy agent to the infected individual. The chemotherapy agent targets fast-growing cells including cancer cells as well as other fast-growing normal cells such as those of the skin, hair and bone marrow, and hence may cause severe side effects to the body of the patient. To better understand the trade-offs between reducing cancer cells and impacting normal cells, mathematical models have been used extensively to study the effectiveness of chemotherapy treatments. In particular, Pinho et al. proposed an autonomous dynamical system with time delays which modeled the interaction between the normal cells and cancer cells with metastasis and used to study the effect of the metastasis. Based on the idea of Pinho's work, a nonautonomous dynamical system that models the interactions among cancer cells, normal cells and the chemotherapy agent under time varying environmental conditions was developed and studied by Xiaoying Han in 2017.

It is well justified in the existing literature that time delays often exist in chemotherapy treatments, yet the effect of delays is not fully understood. For example, Pihno et al. conjectured that time delays are critical for the global stability of the tumor-free equilibrium but did not provide further evidence. To the best of our knowledge there are no solid results elaborating how time delays affect dynamics of chemotherapy models. The goal of this dissertation is to investigate both analytically and numerically the effects of time delays and time-varying environmental conditions on the stability of steady states of chemotherapy models.

To this end two mathematical models of chemotherapy cancer treatment are studied and compared, one modeling the chemotherapy agent as the predator and the other modeling the chemotherapy agent as the prey. In both models constant delay parameters are introduced to incorporate the time lapsed from the instant the chemotherapy agent is injected to the moment it starts to be effective. For each model, the existence and uniqueness of non-negative bounded solutions are first established. Then both local and Lyapunov stability for all steady states are

investigated. In particular, sufficient conditions dependent on the delay parameters under which each steady state is asymptotically stable are constructed. Numerical simulations are presented to illustrate the theoretical results.

Furthermore, another 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.

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Chapter 1

Introduction

Cancer is still one of the leading causes of death worldwide (see, e.g., [3, 6, 22]). 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, 11, 26, 29]). 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, 7, 12, 17, 20, 23, 24, 25, 26, 31]). Since the chemotherapy agents and cells have negative effects on each others' growth rates, their interactions are of the mutual inhibition type [30]. 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 consuming the "prey", as if the prey is poisoned. Thus, among various mathematical models, the predator-prey type of systems with mutual negative effects 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., [17, 26]), 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, 30]).

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 [26], 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 [17]. It was demonstrated in [17] that treatments with time-dependent infusion of the chemotherapy agent can be more effective than treatments with constant infusion. Furthermore, it is well justified in the existing literature that time delays often exist in chemotherapy treatments (see, e.g., [5], [20], [26], [27], [28]), yet the effect of delays is not fully understood. For example, in [26] Pihno *et al*. conjectured that time delays are critical for the global stability of the tumor-free equilibrium but did not provide further evidence. To the best of our knowledge there are no solid results elaborating how time delays affect dynamics of chemotherapy models.

In this dissertation, we investigate both analytically and numerically the effect of time delays on stability of steady states of chemotherapy models. Moreover, we investigate detailed dynamics of both autonomous and nonautonomous chemotherapy models of the second type, in which the chemotherapy agent is modeled as a prey, and infused into the treatment site with or without time-dependent infusion.

Chapter 2

Effects of Delays in Mathematical Models of Cancer Chemotherapy

In this chapter, we formulate and study in great details two chemotherapy models governed by systems of delay differential equations. For each model, we first establish the existence and uniqueness of nonnegative bounded solutions and classify all steady states. Then we investigate both the local and global stability of every steady states. In particular, we construct sufficient conditions dependent on the time delays under which the chemotherapy treatment is successful or failed.

2.1 Model formulation

Predator-prey models have been used to model interactions between cells and the chemotherapy agent. In particular, there are two perspectives: (1) modeling the chemotherapy agent as the "predator" that kills both normal and cancer cells (see, e.g., [17], [26]), and (2) modeling the chemotherapy agent as the "prey" that is consumed by both normal and cancer cells (see, e.g., [1], [30]). Both types of models will be studied and compared in this chapter.

The quantities of interest in all models are the concentration of the cancer cells, normal cells, and the chemotherapy agent, at a single tumor site for treatment in the body. Let $x(t)$ be the concentration of the cancer cells, $y(t)$ be the concentration of the normal cells, and $z(t)$ be the concentration of the chemotherapy agent, for any time $t \geq 0$ at the treatment site. The site is assumed to be spatially uniform, i.e., the concentrations are the same everywhere within the tumor site.

In all models to be studied, both cancer and normal cells are assumed to follow logistic growth (see, e.g., [1], [10], [17], [21], [26]), with per capita growth rates of β_1 and β_2, respectively, and environmental carrying capacities κ_1 and κ_2, respectively. Intraspecific competitions

between the cancer and normal cells are also included (see, e.g., [9]), with competition coefficients δ_1 and δ_2, respectively. The chemotherapy agent is assumed to be injected and flushed out by a constant rate D, and the infusion concentration of the chemotherapy agent is assumed to be a constant I.

Throughout this chapter the interaction between cells and the chemotherapy agent will be modeled by an uptake function (or response function, or consumption function). Basic assumptions on a general uptake function $U : [0, \infty) \to [0, \infty)$ include [32]

1. $U(0) = 0, U(x) > 0$ for $x > 0$;
2. $\lim_{x\to\infty} U(x) = L_U < \infty$;
3. U is continuously differentiable;
4. U is monotone increasing.

2.1.1 Chemotherapy agent as the predator

Let $U_1(x(t))$ and $U_2(y(t))$ be the uptake functions describing how the agent consumes the cancer and the normal cells, respectively. Let α_1 and α_2 be the maximal consumption rate of the cancer and normal cells, respectively. Then $U_1(x(t))z(t)$ represents the cancer concentration consumed by the chemotherapy agent z at the rate α_1 and thus the cancer concentration is reduced by $\alpha_1 U_1(x(t))z(t)$ at any time t. Similarly the normal cell concentration is reduced by $\alpha_2 U_2(y(t))z(t)$ as a consumption by z at any time t.

The consumption of cancer and normal cells causes a loss, or a negative growth of z. Let γ_1 and γ_2 represent the effectiveness of the consumption of the cancer and normal cells, respectively. Then the chemotherapy agent z is reducing at the rate $\gamma_1\alpha_1 U_1(x(t))z(t)$ due to the consumption of cancer cells and at the rate $\gamma_2\alpha_2 U_1(x(t))z(t)$ due to the consumption of normal cells. The dynamics of the chemotherapy treatment can be described by the following

system of ordinary differential equations (ODEs):

$$(\mathbf{ODE-I}) \quad \begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} &= -\alpha_1 z(t) U_1(x(t)) + \beta_1 x(t)(1 - \frac{x(t)}{\kappa_1}) - \delta_1 x(t) y(t), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= -\alpha_2 z(t) U_2(y(t)) + \beta_2 y(t)(1 - \frac{y(t)}{\kappa_2}) - \delta_2 x(t) y(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= DI - Dz(t) - \gamma_1 \alpha_1 z(t) U_1(x(t)) - \gamma_2 \alpha_2 z(t) U_2(y(t)). \end{cases}$$

When the effect of the chemotherapy treatment is not instantaneous, time delays of lengths τ_1 and τ_2 can be introduced to represent the time lapsed from the injection of the chemotherapy till the concentration of cancer and normal cells start to decrease, respectively. Correspondingly, the terms describing the negative effect of chemotherapy agent on the cells $-\alpha_1 z(t) U_1(x(t))$ and $-\alpha_2 z(t) U_2(y(t))$ are modified to $-\alpha_1 z(t-\tau_1) U_1(x(t))$ and $-\alpha_2 z(t-\tau_2) U_2(y(t))$, respectively. The above ODE model then becomes the following system of delay differential equations (DDEs):

$$(\mathbf{DDE-I}) \quad \begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} &= -\alpha_1 z(t-\tau_1) U_1(x(t)) + \beta_1 x(t)(1 - \frac{x(t)}{\kappa_1}) - \delta_1 x(t) y(t), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= -\alpha_2 z(t-\tau_2) U_2(y(t)) + \beta_2 y(t)(1 - \frac{y(t)}{\kappa_2}) - \delta_2 x(t) y(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= DI - Dz(t) - \gamma_1 \alpha_1 z(t) U_1(x(t)) - \gamma_2 \alpha_2 z(t) U_2(y(t)). \end{cases}$$

Throughout this paper when explicit calculations are needed it is assumed that the uptake functions U_1 and U_2 takes the Michaelis-Menten or Holling type-II form given by

$$U_1(x) = \frac{x}{\theta_1 + x}, \quad U_2(y) = \frac{y}{\theta_2 + y},$$

where $\theta_1 > 0$ and $\theta_2 > 0$ are the half saturation constants (see, e.g., [30]) for the cancer cells and the normal cells, respectively.

2.1.2 Chemotherapy agent as the prey

When the chemotherapy agent is modeled as the prey and time delays are taken into account, we adopt the DDE model proposed in [1]:

$$(\mathbf{DDE-II}) \quad \begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} &= -\hat{\alpha}_1 x(t) U_3(z(t-\tau_1)) + \beta_1 x(t)(1-\frac{x(t)}{\kappa_1}) - \delta_1 x(t) y(t), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= -\hat{\alpha}_2 y(t) U_3(z(t-\tau_2)) + \beta_2 y(t)(1-\frac{y(t)}{\kappa_2}) - \delta_2 x(t) y(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= DI - Dz(t) - \gamma_1 \hat{\alpha}_1 x(t) U_3(z(t)) - \gamma_2 \hat{\alpha}_2 y(t) U_3(z(t)), \end{cases}$$

where β_1, β_2, δ_1, δ_2, γ_1,γ_2, τ_1 and τ_2 still have the same meanings as in system (**DDE-I**). Here $U_3(\cdot)$ is the uptake function describing how the chemotherapy agent is consumed by the cells, and is also assumed to take the Michaelis-Menten or Holling type-II form given by

$$U_3(z) = \frac{z}{\theta_3 + z},$$

where $\theta_3 > 0$ is the half saturation constant of the chemotherapy agent. The parameters $\hat{\alpha}_1$ and $\hat{\alpha}_2$ now represent the maximal consumption of the chemotherapy agent by the cancer and normal cells, respectively. For the reader's convenience, parameters in both models are summarized in the table below.

Table 2.1: Description of parameters in the chemotherapy models

Parameter	Description
D	Injection rate of the chemotherapy agent
I	Injection concentration of the chemotherapy agent
$\delta_j\ (j=1,2)$	Intraspecific competition coefficient for cancer/normal cells
$\beta_j\ (j=1,2)$	Per capita growth rate of cancer/normal cells
$\kappa_j\ (j=1,2)$	Environmental carrying capacity of cancer/normal cells
$\gamma_j\ (j=1,2)$	Effectiveness of consumption of cancer/normal cells
$\alpha_j\ (j=1,2)$	Maximal consumption rate of cancer/normal cells by the agent
$\hat{\alpha}_j\ (j=1,2)$	Maximal consumption rate of the agent by cancer/normal cells
$\tau_j\ (j=1,2)$	Time elapsed from the injection of the agent to the instants when cancer/normal cells start to decay (due to the treatment)

2.2 Basic properties of solutions

Assume that the DDE systems (**DDE-I**) and (**DDE-II**) are both subjective to the initial conditions:

$$(\mathbf{IC}) \quad \begin{cases} x(t) = x_0(t) \equiv x_0 > 0, & \text{for} - \tau \le t \le 0, \\ y(t) = y_0(t) \equiv y_0 > 0 & \text{for} - \tau \le t \le 0, \\ z(t) = \phi(t) \ge 0, & \text{for} - \tau \le t \le 0. \end{cases}$$

where

$$\tau := \max\{\tau_1, \tau_2\} > 0$$

and ϕ is a continuous and nonnegative function on $[-\tau, 0]$.

In this section we first show that both of the DDE systems (**DDE-I**) and (**DDE-II**) are biologically meaningful. To this end we prove that each of the systems has a unique global solution which is non-negative and bounded. We then calculate the steady states of each system to be further studied in later sections.

Throughout the rest of this paper, for $n \ge 1$ denote

$$\mathbb{R}^n_+ := \{(x_1, \ldots, x_n) \in \mathbb{R}^n : x_1, \ldots, x_n \ge 0\}.$$

And for simplicity write

$$\Phi(s) = (x_0(s), y_0(s), \phi(s)) \quad \text{for } s \in [-\tau, 0].$$

Theorem 2.1 *Let $\phi : [-\tau, 0] \to \mathbb{R}^1_+$ be continuous. Then the DDE systems (***DDE-I***) and (***DDE-II***) under the initial condition (***IC***) each has a unique non-negative bounded global solution.*

Proof: The existence and uniqueness of a global non-negative bounded solution to the system (**DDE-II**) was proved in [1], and the existence and uniqueness of a global non-negative bounded solution to the system (**DDE-I**) can be proved by using the same computations. For completeness we still present it below.

First since functions on the right hand side of (**DDE-I**) are continuous and differentiable with respect to $(x(t), y(t), z(t))$, then by standard theory of delay ODEs (see, e.g., [14, 15, 16]) the system (**DDE-I**) has a unique local solution $(x(t;\Phi), y(t;\Phi), z(t;\Phi)) := \boldsymbol{u}(t;\Phi)$ on $[-\tau, T]$ for some $T > 0$. Noticing that $x'(t)|_{x=0} = 0$, $y'(t)|_{y=0} = 0$ and $z'(t)|_{z=0} = DI > 0$, thus by continuity and uniqueness of solutions $\boldsymbol{u}(t;\Phi) \in \mathcal{C}^1([-\tau, T], \mathbb{R}^3_+)$. We next show that the local solution $\boldsymbol{u}(t;\Phi)$ is actually global.

In fact, since $\boldsymbol{u}(t;\Phi)$ is non-negative on $[-\tau, T]$,

$$\frac{\mathrm{d}x}{\mathrm{d}t} \le \beta_1 x\Big(1 - \frac{x}{\kappa_1}\Big), \quad \text{and} \quad \frac{\mathrm{d}y}{\mathrm{d}t} \le \beta_2 y\Big(1 - \frac{y}{\kappa_2}\Big),$$

and by standard comparison theory, we get

$$0 \le x(t) \le \max\{x_0, \kappa_1\}, \;\; 0 \le y(t) \le \max\{y_0, \kappa_2\}, \quad \forall t \in [-\tau, T]. \tag{2.1}$$

Also, using the fact that $x, y \ge 0$ and $U_j \ge 0, \; j = 1, 2$, we get

$$\frac{\mathrm{d}z}{\mathrm{d}t} \le DI - Dz(t),$$

which implies that

$$0 \le z(t) \le \max\{\bar{\phi}, I\} \quad \forall\, t \in [-\tau, T] \quad \text{where} \quad \bar{\phi} = \max_{s\in[-\tau,0]} \phi(s). \tag{2.2}$$

The inequalities 2.1 and 2.2 together show that the solution of system (**DDE-I**) is non-negative and bounded for every $t \ge 0$, since the upper bounds for x, y, z are independent of t. This implies that system (**DDE-I**) has a unique bounded and non-negative global solution given any non-negative initial condition. End of the proof.

There are four classes of steady state solutions to the DDE systems (**DDE-I**) and (**DDE-II**), namely: (i) the axial steady state $E_a = (0, 0, I)$; (ii) the success steady state $E_s = (0, y^*, z^*)$; (iii) the failure steady state $E_f = (x^*, 0, z^*)$; and (iv) the persistent steady state $E_p = (x^*, y^*, z^*)$, with $x^*, y^*, z^* > 0$. Our focus of this paper is to study stabilities of the

axial, success and failure steady states of each system (**DDE-I**) and (**DDE-II**). Same set of techniques can also be employed to study stabilities of the persistent state with more complex computations.

Lemma 2.2 *The system (***DDE-I***) has one positive success steady state provided* $\alpha_2 I < \beta_2\theta_2$*; and has two positive success steady states provided*

$$0 < \frac{\alpha_2 I}{\beta_2} - \frac{[D\theta_2 - \kappa_2(D+\gamma_2\alpha_2)]^2}{4\kappa_2 D(D+\gamma_2\alpha_2)} < \theta_2 < \min\left\{\frac{\alpha_2 I}{\beta_2}, \frac{\kappa_2}{D}(D+\gamma_2\alpha_2)\right\}. \tag{2.3}$$

*The system (***DDE-I***) has one positive failure steady state provided* $\alpha_1 I < \theta_1\beta_1$*; and has two positive success steady states provided*

$$0 < \frac{\alpha_1 I}{\beta_1} - \frac{[D\theta_1 - \kappa_1(D+\gamma_1\alpha_1)]^2}{4\kappa_1 D(D+\gamma_1\alpha_1)} < \theta_1 < \min\left\{\frac{\alpha_1 I}{\beta_1}, \frac{\kappa_1}{D}(D+\gamma_1\alpha_1)\right\}. \tag{2.4}$$

Proof: Success steady states for system (**DDE-I**) are positive solutions to the algebraic system

$$\begin{cases} \frac{-\kappa_2\alpha_2 z^*}{\theta_2+y^*} + \beta_2(\kappa_2 - y^*) = 0 \\ DI - Dz^* - \alpha_2\gamma_2\frac{z^*y^*}{\theta_2+y^*} = 0 \end{cases} \tag{2.5}$$

which can be reduced to the quadratic equation

$$(D+\alpha_2\gamma_2){y^*}^2 + [D\theta_2 - \kappa_2(D+\alpha_2\gamma_2)]y^* + \kappa_2 D(\beta_2^{-1}\alpha_2 I - \theta_2) = 0.$$

The above equation has one unique positive solution when $\alpha_2 I - \theta_2\beta_2 < 0$, and has two distinctive positive solutions when 2.3 is satisfied.

Similarly, failure steady states for system (**DDE-I**) are positive solutions to the algebraic system

$$\begin{cases} \frac{-\kappa_1\alpha_1 z^*}{\theta_1+x^*} + \beta_1(\kappa_1 - x^*) = 0 \\ \kappa_1 D(\beta_1^{-1}\alpha_1 I - \theta_1) = 0 \end{cases} \tag{2.6}$$

which can be reduced to the quadratic equation

$$(D+\alpha_1\gamma_1)x^{*2}+[D\theta_1-\kappa_1(D+\alpha_1\gamma_1)]x^*+\kappa_1 D(\beta_1^{-1}\alpha_1 I-\theta_1)=0$$

that has one unique positive solution when $\alpha_1 I-\theta_1\beta_1<0$, and has two distinctive positive solutions when 2.4 is satisfied. End of the proof.

Lemma 2.3 *The system (***DDE-II***) has at least one success and one failure steady states.*

Proof: More precisely, a preferred state satisfies

$$\begin{cases} -\alpha_2\kappa_2 U(z^*)+\beta_2(\kappa_2-y^*)=0 \\ DI-Dz^*-\alpha_2\gamma_2 y^* U(z^*)=0 \end{cases} \tag{2.7}$$

and a failure state satisfies

$$\begin{cases} -\alpha_1\kappa_1 U(z^*)+\beta_1(\kappa_1-x^*)=0 \\ DI-Dz^*-\alpha_1\gamma_1 x^* U(z^*)=0 \end{cases}. \tag{2.8}$$

Notice that equations 2.7 are equivalent to

$$y^*=\kappa_2\left(1-\frac{\alpha_2}{\beta_2}U(z^*)\right)$$

with z^* satisfying the cubic equation

$$(z^*)^3+\mathfrak{a}_1(z^*)^2+\mathfrak{a}_2 z^*+\mathfrak{a}_3=0$$

where

$$\mathfrak{a}_1=2\theta+\alpha_2\frac{\kappa_2\gamma_2}{D}-\alpha_2^2\frac{\gamma_2\kappa_2}{\beta_2 D}-I,\quad \mathfrak{a}_2=\theta^2-2\theta I+\alpha\theta\frac{\kappa_2\gamma_2}{D},\quad \mathfrak{a}_3=-\theta^2 I,$$

and hence have at least one positive solution since $\mathfrak{a}_3<0$. Similarly, equations 2.8 also have at least one positive solution. This complete the proof.

2.3 Stability analysis

In this section we investigate the stability of steady states for systems (**DDE-I**) and (**DDE-II**), respectively. In particular, we discuss the local stability as well as Lyapunov stability for each steady state of systems (**DDE-I**) and (**DDE-II**).

Throughout this section, denote by $\boldsymbol{u}(t) = (x(t), y(t), z(t))$ the state variable and $\boldsymbol{u}^* = (x^*, y^*, z^*)$ a generic steady state.

2.3.1 Local stability

To investigate the local stability of (**DDE-I**), we linearize the system about $\boldsymbol{u} = \boldsymbol{u}^*$ to obtain

$$\frac{\mathrm{d}\boldsymbol{u}}{\mathrm{d}t} = P\boldsymbol{u}(t) + Q\boldsymbol{u}(t-\tau_1) + R\boldsymbol{u}(t-\tau_2),$$

where

$$P = \begin{bmatrix} P_1 & -\delta_1 x^* & 0 \\ -\delta_2 y^* & P_2 & 0 \\ -\frac{\gamma_1\alpha_1\theta_1 z^*}{(\theta_1+x^*)^2} & -\frac{\gamma_2\alpha_2\theta_2 z^*}{(\theta_2+x^*)^2} & P_3 \end{bmatrix},\ Q = \begin{bmatrix} 0 & 0 & -\frac{\alpha_1 x^*}{\theta_1+x^*} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},\ R = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & -\frac{\alpha_2 y^*}{\theta_2+y^*} \\ 0 & 0 & 0 \end{bmatrix},$$

with

$$\begin{aligned} P_1 &= -\alpha_1\frac{\theta_1 z^*}{(\theta_1+x^*)^2} + \beta_1\left(1-\frac{2x^*}{\kappa_1}\right) - \delta_1 y^*, \\ P_2 &= -\alpha_2\frac{\theta_2 z^*}{(\theta_2+x^*)^2} + \beta_2\left(1-\frac{2y^*}{\kappa_2}\right) - \delta_2 x^*, \\ P_3 &= -D - \gamma_1\alpha_1\frac{x^*}{\theta_1+x^*} - \gamma_2\alpha_2\frac{y^*}{\theta_2+y^*}. \end{aligned}$$

Theorem 2.4 *For the system (***DDE-I***)*

(a) the axial steady state $E_a = (0, 0, I)$ is locally asymptotically stable provided

$$\beta_1 < \frac{\alpha_1 I}{\theta_1} \text{ and } \beta_2 < \frac{\alpha_2 I}{\theta_2}; \tag{2.9}$$

(b) a success steady state $E_s = (0, y^*, z^*)$ is locally asymptotically stable provided

$$\beta_1 < \frac{\alpha_1 z^*}{\theta_1} + \delta_1 y^* \tag{2.10}$$

$$\kappa_2 \leq 2y^*; \tag{2.11}$$

(c) a failure steady state $E_f = (x^*, 0, z^*)$ is locally asymptotically stable provided

$$\beta_2 < \frac{\alpha_2 z^*}{\theta_2} + \delta_2 x^* \tag{2.12}$$

$$\kappa_1 \leq 2x^*; \tag{2.13}$$

Proof: The characteristic equation reads

$$\det[\lambda I - P - e^{-\lambda\tau_1}Q - e^{-\lambda\tau_2}R] = 0. \tag{2.14}$$

(a) When $x^* = y^* = 0$ and $z^* = I$, equation 2.14 becomes

$$\left(\lambda - \beta_1 + \frac{\alpha_1 I}{\theta_1}\right) \cdot \left(\lambda - \beta_2 + \frac{\alpha_2 I}{\theta_2}\right) \cdot (\lambda + D) = 0,$$

which can be solved explicitly to obtain

$$\lambda = \beta_1 - \frac{\alpha_1 I}{\theta_1}, \quad \lambda = \beta_2 - \frac{\alpha_2 I}{\theta_2}, \quad \lambda = -D.$$

All the above eigenvalues are negative under the assumption 2.9, and thus $E_a = (0, 0, I)$ is asymptotically stable.

(b) When $x^* = 0$ equation 2.14 becomes

$$\begin{vmatrix} \lambda - \beta_1 + \frac{\alpha_1 z^*}{\theta_1} + \delta_1 y^* & 0 & 0 \\ \delta_2 y^* & \lambda - \beta_2(1 - \frac{2y^*}{\kappa_2}) + \frac{\alpha_2\theta_2 z^*}{(\theta_2 + y^*)^2} & \frac{\alpha_2 y^*}{\theta_2 + y^*} e^{-\lambda\tau_2} \\ \frac{\alpha_1\gamma_1 z^*}{\theta_1} & \frac{\alpha_2\gamma_2\theta_2 z^*}{(\theta_2 + y^*)^2} & \lambda + D + \frac{\alpha_2\gamma_2 y^*}{\theta_2 + y^*} \end{vmatrix} = 0$$

where y^* and z^* satisfies the equations in 2.5. The above equation is equivalent to

$$\lambda - \beta_1 + \frac{\alpha_1 z^*}{\theta_1} + \delta_1 y^* = 0 \quad \text{and} \quad p(\lambda) + qe^{-\lambda\tau_2} = 0,$$

where

$$\begin{aligned} p(\lambda) &= \left(\lambda - \beta_2(1 - \frac{2y^*}{\kappa_2}) + \frac{\alpha_2\theta_2 z^*}{(\theta_2 + y^*)^2}\right) \cdot \left(\lambda + D + \frac{\alpha_2\gamma_2 y^*}{\theta_2 + y^*}\right), \\ q &= \frac{-\alpha_2^2\gamma_2\theta_2 y^* z^*}{(\theta_2 + y^*)^3}. \end{aligned}$$

First observe that when 2.10 holds, one of the eigenvalues

$$\lambda = \beta_1 - \frac{\alpha_1 z^*}{\theta_1} - \delta_1 y^* < 0.$$

Also, under the assumption 2.11, the roots of the polynomial $p(\lambda)$ satisfy

$$\lambda_1 = \beta_2(1 - \frac{2y^*}{\kappa_2}) - \frac{\alpha_2\theta_2 z^*}{(\theta_2 + y^*)^2} < 0, \quad \lambda_2 = -D - \frac{\alpha_2\gamma_2 y^*}{\theta_2 + y^*} < 0.$$

Moreover when the assumption 2.11 holds, we have

$$\begin{aligned} |p(0)| &= \left|\frac{\alpha_2\theta_2 z^*}{(\theta_2 + y^*)^2} - \beta_2(1 - \frac{2y^*}{\kappa_2})\right| \cdot \left|D + \frac{\alpha_2\gamma_2 y^*}{\theta_2 + y^*}\right| \\ &> \frac{\alpha_2\theta_2 z^*}{(\theta_2 + y^*)^2} \cdot \frac{\alpha_2\gamma_2 y^*}{\theta_2 + y^*} = |q|. \end{aligned}$$

It then follows from Corollary 4.10 of [16] that all roots of equation 2.14 have negative real parts, and hence $E_s = (0, y^*, z^*)$ is asymptotically stable.

(c) When $y^* = 0$ equation 2.14 becomes

$$\begin{vmatrix} \lambda - \frac{\alpha_1\theta_1 z^*}{(\theta_1 + x^*)^2} + \beta_1(1 - \frac{2x^*}{\kappa_1}) & \delta_1 x^* & \frac{\alpha_1 x^*}{\theta_1 + x^*} e^{-\lambda\tau_1} \\ 0 & \lambda - \beta_2 + \frac{\alpha_2 z^*}{\theta_2} + \delta_2 x^* & 0 \\ \frac{\alpha_1\gamma_1\theta_1 z^*}{(\theta_1 + x^*)^2} & \frac{\alpha_2\gamma_2\theta_2 z^*}{(\theta_1 + x^*)^2} & \lambda + D + \frac{\alpha_1\gamma_1 x^*}{\theta_1 + x^*} \end{vmatrix} = 0$$

where x^* and z^* satisfies the equations in 2.6. The above equation is equivalent to

$$\lambda - \beta_2 + \frac{\alpha_2 z^*}{\theta_2} + \delta_2 x^* = 0 \quad \text{and} \quad p(\lambda) + qe^{-\lambda\tau_1} = 0,$$

where

$$\begin{aligned} p(\lambda) &= \left(\lambda - \beta_1(1 - \frac{2x^*}{\kappa_1}) + \frac{\alpha_1\theta_1 z^*}{(\theta_1 + x^*)^2}\right) \cdot \left(\lambda + D + \frac{\alpha_1\gamma_1 x^*}{\theta_1 + x^*}\right), \\ q &= \frac{-\alpha_1^2\gamma_1\theta_1 x^* z^*}{(\theta_1 + x^*)^3}. \end{aligned}$$

First observe that when 2.12 holds, one of the eigenvalues

$$\lambda = \beta_2 - \frac{\alpha_2 z^*}{\theta_2} - \delta_2 y^* < 0.$$

Also, under the assumption 2.13, the roots of the polynomial $p(\lambda)$ satisfy

$$\lambda_1 = \beta_1(1 - \frac{2x^*}{\kappa_1}) - \frac{\alpha_1\theta_1 z^*}{(\theta_1 + x^*)^2} < 0, \quad \lambda_2 = -D - \frac{\alpha_1\gamma_1 x^*}{\theta_1 + x^*} < 0.$$

Moreover when the assumption 2.13 holds, we have

$$\begin{aligned} |p(0)| &= \left|\frac{\alpha_1\theta_1 z^*}{(\theta_1 + x^*)^2} - \beta_1(1 - \frac{2x^*}{\kappa_1})\right| \cdot \left|D + \frac{\alpha_1\gamma_1 x^*}{\theta_1 + x^*}\right| \\ &> \frac{\alpha_1\theta_1 z^*}{(\theta_1 + x^*)^2} \cdot \frac{\alpha_1\gamma_1 x^*}{\theta_1 + x^*} = |q|. \end{aligned}$$

It then follows from Corollary 4.10 of [16] that all roots of equation 2.14 have negative real parts, and hence $E_f = (x^*, 0, z^*)$ is asymptotically stable. End of the proof.

To investigate the local stability of (**DDE-II**), we proceed by first linearizing the system about $\boldsymbol{u} = \boldsymbol{u}^*$ to obtain

$$\frac{\mathrm{d}\boldsymbol{u}}{\mathrm{d}t} = P\boldsymbol{u}(t) + Q\boldsymbol{u}(t - \tau_1) + R\boldsymbol{u}(t - \tau_2), \tag{2.15}$$

where the coefficient matrices P, Q, and R are calculated to be

$$P = \begin{bmatrix} P_{11} & -\delta_1 x^* & 0 \\ -\delta_2 y^* & P_{22} & 0 \\ -\alpha_1\gamma_1 U_3(z^*) & -\alpha_2\gamma_2 U_3(z^*) & P_{33} \end{bmatrix},$$

with

$$\begin{aligned} P_{11} &= -\alpha_1 U_3(z^*) + \beta_1\left(1 - \frac{2x^*}{\kappa_1}\right) - \delta_1 y^*, \\ P_{22} &= -\alpha_2 U_3(z^*) + \beta_2\left(1 - \frac{2y^*}{\kappa_2}\right) - \delta_2 x^*, \\ P_{33} &= -D - (\alpha_1\gamma_1 x^* + \alpha_2\gamma_2 y^*)\frac{\theta_3}{(\theta_3 + z^*)^2}. \end{aligned}$$

and

$$Q = \begin{bmatrix} 0 & 0 & -\frac{\alpha_1 x^* \theta_3}{(\theta_3+z^*)^2} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad R = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & -\frac{\alpha_2 y^* \theta_3}{(\theta_3+z^*)^2} \\ 0 & 0 & 0 \end{bmatrix}.$$

The characteristic equation then reads

$$h(\lambda, \tau_1, \tau_2) = \det[\lambda I - P - e^{-\lambda\tau_1}Q - e^{-\lambda\tau_2}R] = 0. \tag{2.16}$$

Theorem 2.5 *For the system (***DDE-II***) we have:*

(i) the axial steady state $(0, 0, I)$ *is asymptotically stable provided*

$$\frac{\beta_1}{\alpha_1} < \frac{I}{\theta_3 + I} \quad \textit{and} \quad \frac{\beta_2}{\alpha_2} < \frac{I}{\theta_3 + I}; \tag{2.17}$$

(ii) a preferred steady state $(0, y^*, z^*)$ *is asymptotically stable provided*

$$\beta_1 < \alpha_1 U_3(z^*) + \delta_1 y^* \quad \textit{and} \tag{2.18}$$

$$2y^* \geq \kappa_2; \tag{2.19}$$

(iii) a failure steady state $(x^*, 0, z^*)$ *is asymptotically stable provided*

$$\beta_2 < \alpha_2 U_3(z^*) + \delta_2 x^* \tag{2.20}$$

$$2x^* \geq \kappa_1. \tag{2.21}$$

Proof: (i) When $x^* = y^* = 0$ and $z^* = I$, the equation 2.16 becomes

$$\left(\lambda + \frac{\alpha_1 I}{\theta_3 + I} - \beta_1\right) \cdot \left(\lambda + \frac{\alpha_2 I}{\theta_3 + I} - \beta_2\right) \cdot (\lambda + D) = 0. \tag{2.22}$$

The three simple solutions to the characteristic equation 2.22 are

$$\lambda = -D, \quad \lambda = \beta_1 - \frac{\alpha_1 I}{\theta_3 + I}, \quad \lambda = \beta_2 - \frac{\alpha_2 I}{\theta_3 + I}.$$

They are all negative when 3.12 holds, which implies immediately that the axial steady state $(0, 0, I)$ is asymptotically stable.

(ii) When $x^* = 0$ the equation 2.16 becomes

$$\det \begin{bmatrix} \lambda + \alpha_1 U_3(z^*) - \beta_1 + \delta_1 y^* & 0 & 0 \\ \delta_1 y^* & \lambda + \alpha_2 U_3(z^*) - \beta_2 \left(1 - \frac{2y^*}{\kappa_2}\right) & e^{-\lambda\tau_2} \frac{\alpha_2 y^* \theta_3}{(\theta_3 + z^*)^2} \\ \alpha_1\gamma_1 U_3(z^*) & \alpha_2\gamma_2 U_3(z^*) & \lambda + D + \frac{\gamma_2 y^* \alpha_2 \theta_3}{(\theta_3 + z^*)^2} \end{bmatrix} = 0, \tag{2.23}$$

where y^* and z^* satisfy the equations 2.7.

Equation 2.23 is equivalent to

$$\lambda + \alpha_1 U_3(z^*) - \beta_1 + \delta_1 y^* = 0, \tag{2.24}$$

$$p(\lambda) + q e^{-\lambda\tau_2} = 0, \tag{2.25}$$

where

$$\begin{aligned} p(\lambda) &= \left(\lambda + \alpha_2 U_3(z^*) - \beta_2\left(1 - \frac{2y^*}{\kappa_2}\right)\right)\left(\lambda + D + \frac{\gamma_2 x^* \alpha_2 \theta_3}{(\theta_3 + z^*)^2}\right), \\ q &= -\alpha_2\gamma_2 U_3(z^*)\frac{\alpha_2 y^* \theta_3}{(\theta_3 + z^*)^2}. \end{aligned}$$

First notice that when the assumption 3.13 holds, by 2.7 the solution to the equation 2.24 satisfies

$$\lambda = -\alpha_2 U_3(z^*) + \beta_2\left(1 - \frac{2y^*}{\kappa_2}\right) = -\beta_2 + \beta_2 + \left(\frac{\beta_2}{\kappa_2} - \delta\right)y^* < 0. \tag{2.26}$$

Then notice that the polynomial $p(\lambda)$ has two roots:

$$\lambda_1 = -D - \frac{\gamma_2 y^* \alpha_2 \theta_3}{(\theta_3 + z^*)^2} < 0, \quad \lambda_2 = -\alpha_2 U_3(z^*) + \beta_2\left(1 - \frac{2y^*}{\kappa_2}\right).$$

By using 2.7 again we have

$$\lambda_2 = -\beta_2\left(1 - \frac{y^*}{\kappa_2}\right) + \beta_2\left(1 - \frac{2y^*}{\kappa_2}\right) = -\beta_2\frac{y^*}{\kappa_2} < 0.$$

In addition by the assumption 3.14 and 2.7,

$$\beta_2\frac{y^*}{\kappa_2} \geq \beta_2 - \beta_2\frac{y^*}{\kappa_2} = \alpha_2 U_3(z^*),$$

and consequently

$$\begin{aligned} |p(0)| &= \left|\alpha_2 U_3(z^*) - \beta_2\left(1 - \frac{2y^*}{\kappa_2}\right)\right| \cdot \left|D + \frac{\gamma_2 y^* \alpha_2 \theta_3}{(\theta_3 + z^*)^2}\right| \\ &= \beta_2\frac{y^*}{\kappa_2} \cdot \left|D + \frac{\gamma_2 y^* \alpha_2 \theta_3}{(\theta_3 + z^*)^2}\right| > \alpha_2 U_3(z^*) \cdot \frac{\gamma_2 y^* \alpha_2 \theta_3}{(\theta_3 + z^*)^2} = |q|. \end{aligned}$$

It then follows from Corollary 4.10 of [16] that Re$\lambda < 0$ for every root λ of the equation 2.25, and together with 2.26 we conclude that the steady state $(0, y^*, z^*)$ satisfying 2.7 is asymptotically stable.

(iii) When $y^* = 0$ the equation 2.16 becomes

$$\det \begin{bmatrix} \lambda + \alpha_1 U_3(z^*) - \beta_1 \left(1 - \frac{2x^*}{\kappa_1}\right) & \delta_1 x^* & e^{-\lambda\tau_1} \frac{\alpha_1 x^* \theta_3}{(\theta_3 + z^*)^2} \\ 0 & \lambda + \alpha_2 U_3(z^*) - \beta_2 + \delta_2 x^* & 0 \\ \alpha_1\gamma_1 U_3(z^*) & \alpha_2\gamma_2 U_3(z^*) & \lambda + D + \frac{\gamma_1 x^* \alpha_1 \theta_3}{(\theta_3 + z^*)^2} \end{bmatrix} = 0, \tag{2.27}$$

where x^* and z^* satisfy equations 2.8.

Equation 2.27 is equivalent to

$$\lambda + \alpha_2 U_3(z^*) - \beta_2 + \delta_2 x^* = 0, \tag{2.28}$$

$$p(\lambda) + q e^{-\lambda\tau_1} = 0, \tag{2.29}$$

where

$$\begin{aligned} p(\lambda) &= \left(\lambda + \alpha_1 U_3(z^*) - \beta_1 \left(1 - \frac{2x^*}{\kappa_1}\right)\right)\left(\lambda + D + \frac{\gamma_1 x^* \alpha_1 \theta_3}{(\theta_3 + z^*)^2}\right), \\ q &= -\alpha_1\gamma_1 U_3(z^*) \frac{\alpha_1 x^* \theta_3}{(\theta_3 + z^*)^2}. \end{aligned}$$

Under the assumption 3.15, using 2.8 we have the solution of equation 2.28 satisfies

$$\lambda = -\alpha_2 U_3(z^*) + \beta_2 - \delta_2 x^* < 0. \tag{2.30}$$

Notice that the polynomial $p(\lambda)$ has two roots,

$$\lambda_1 = -D - \frac{\gamma_1 x^* \alpha_1 \theta_3}{(\theta_3 + z^*)^2} < 0, \quad \lambda_2 = -\alpha_1 U_3(z^*) + \beta_1 \left(1 - \frac{2x^*}{\kappa_1}\right),$$

where by using 2.8 again we have

$$\lambda_2 = -\beta_1 \left(1 - \frac{x^*}{\kappa_1}\right) + \beta_1 \left(1 - \frac{2x^*}{\kappa_1}\right) = -\beta_1 \frac{x^*}{\kappa_1} < 0.$$

By the assumption 3.16 and 2.8,

$$\beta_1 \frac{x^*}{\kappa_1} \geq \beta_1 - \beta_1 \frac{x^*}{\kappa_1} = \alpha_1 U_3(z^*),$$

and consequently

$$\begin{aligned} |p(0)| &= \left| \alpha_1 U_3(z^*) - \beta_1 \left(1 - \frac{2x^*}{\kappa_1}\right) \right| \cdot \left| D + \frac{\gamma_1 x^* \alpha_1 \theta_3}{(\theta_3 + z^*)^2} \right| \\ &= \beta_1 \frac{x^*}{\kappa_1} \cdot \left| D + \frac{\gamma_1 x^* \alpha_1 \theta_3}{(\theta_3 + z^*)^2} \right| > \alpha_1 U_3(z^*) \cdot \frac{\gamma_1 x^* \alpha_1 \theta_3}{(\theta_3 + z^*)^2} = |q|. \end{aligned}$$

It then follows from Corollary 4.10 of [16] that Re$\lambda < 0$ for every root λ of the equation 2.29, and together with 2.30 we conclude that the steady state $(x^*, 0, z^*)$ satisfying 2.8 is asymptotically stable. The proof is complete.

2.3.2 Lyapunov stability

In this subsection we investigate Lyapunov stability for each steady state of systems (**DDE-I**) and (**DDE-II**). Recall that for all $t \geq 0$

$$x(t) \leq \max\{x_0, \kappa_1\}, \quad y(t) \leq \max\{y_0, \kappa_2\}, \quad z(t) \leq \max\{\bar{\phi}, I\}.$$

Throughout this subsection we restrict our attention to the the bounded and invariant region of all solutions,

$$\Omega = \{(x, y, z) \in \mathbb{R}^3_+ : \ x \leq \kappa_1, \ y \leq k_2, \ z \leq I\}.$$

Theorem 2.6 below gives the sufficient conditions under which a success steady state $(0, y^*, z^*)$ of system (**DDE-I**) is asymptotically stable; Theorem 2.7 below gives the sufficient conditions under which a failure steady state $(x^*, 0, z^*)$ of system (**DDE-I**) is asymptotically stable. Theorem 2.8 below gives the sufficient conditions under which a generic steady state (x^*, y^*, z^*) of system (**DDE-II**) is asymptotically stable.

Theorem 2.6 *A success steady state* $(0, y^*, z^*)$ *of system (***DDE-I***) is asymptotically stable provided*

$$\begin{aligned}
\tau_1 &\leq \frac{2\theta_1}{\alpha_2}\beta_1, && (2.31)\\
\tau_2 &\leq \frac{2\theta_2\beta_2}{\alpha_2\kappa_2}\cdot\frac{1}{1+\gamma_2 I\left(D+\alpha_2\gamma_2+\frac{\alpha_1\gamma_1 I}{\theta_1}+\frac{\alpha_2\gamma_2 I}{\theta_2}\right)}, && (2.32)\\
2\beta_1 &< \delta_1 y^* + \frac{\alpha_2 z^*}{\theta_1+\kappa_1}, && (2.33)\\
\frac{\beta_2}{\kappa_2} &> \max\Big\{\frac{1}{2\theta_2\gamma_2^2}+\frac{\theta_1}{\theta_2}\beta_1, 2\delta_2+\frac{2\alpha_2}{\theta_2}(1+\frac{2z^*}{\theta_2+y^*})\\
&\qquad +\frac{4\theta_1}{\theta_2}\beta_1\gamma_2 I(D+\alpha_2\gamma_2+\frac{\alpha_1\gamma_1 I}{\theta_1}+\frac{\alpha_2\gamma_2 I}{\theta_2})\Big\}, && (2.34)\\
\frac{1}{4} &> \left(D+\alpha_2\gamma_2+I(\frac{\alpha_1\gamma_1}{\theta_1}+\frac{\alpha_2\gamma_2}{\theta_2})\right)^2\left(\frac{\delta_1\theta_1\theta_2}{\alpha_2^2}+\frac{2\gamma_2 z^*}{D}\right), && (2.35)\\
\frac{\beta_1}{\kappa_1} &> \frac{\delta_1}{2}+\frac{\alpha_2}{2\theta_1}+\frac{\alpha_1\alpha_2\gamma_2 z^*}{\theta_1^2 D}\\
&\qquad +\left(\delta_1+\frac{2\alpha_2^2\gamma_2 z^*}{D\theta_1\theta_2}\right)\left(\frac{\delta_2\kappa_2}{2\beta_2}+\frac{\alpha_1\gamma_1\theta_2}{\theta_1\alpha_2}(1+\frac{1}{4\gamma_2})\right). && (2.36)
\end{aligned}$$

Proof: The proof is proceeded in three steps.

(**i**) Given any solution of (**DDE-I**) $(x(t), y(t), z(t)) \in \mathcal{C}^1([-\tau, \infty), \Omega)$, define

$$V_1(x(t), y(t), z(t)) = ax(t) + \left(y(t) - y^* - y^* \ln\frac{y(t)}{y^*}\right) + \frac{b}{2}(z(t)-z^*)^2,$$

where $a > 0$ and $b > 0$ will be determined later. Clearly $V_1(0, y^*, z^*) = 0$ and $V_1(x(t), y(t), z(t)) > 0$ for any $(x(t), y(t), z(t)) \in \mathcal{C}^1([-\tau, \infty), \Omega\backslash\{(0, y^*, z^*)\}$. Differentiating $V_1(t)$ along solutions to system (**DDE-I**) gives

$$\begin{aligned}
\frac{\mathrm{d}V_1}{\mathrm{d}t} &= ax(t)\left(-\frac{\alpha_1 z(t-\tau_1)}{\theta_1+x}+\beta_1(1-\frac{x(t)}{\kappa_1})-\delta_1 y(t)\right)\\
&\quad +(y(t)-y^*)\left(-\frac{\alpha_2 z(t-\tau_2)}{\theta_2+y}+\beta_2(1-\frac{y(t)}{\kappa_2})-\delta_2 x(t)\right)\\
&\quad +(z(t)-z^*)\left[DI-Dz(t)-\gamma_1 z(t)U_1(x(t))-\gamma_2 z(t)U_2(y(t))\right],
\end{aligned}$$

which can be rewritten by using equations in 2.5 to be

$$\begin{aligned}\frac{\mathrm{d}V_1}{\mathrm{d}t} &= ax\left(\beta_1-\delta_1 y^*-\frac{\beta_1}{\kappa_1}x-\delta_1(y-y^*)-\frac{\alpha_1 z(t-\tau_1)}{\theta_1+x}\right)\\ &\quad+(y-y^*)\left(-\frac{\beta_2}{k_2}(y-y^*)-\delta_2 x-\frac{\alpha_2 z(t-\tau_2)}{\theta_2+y}+\frac{\alpha_2 z^*}{\theta_2+y^*}\right)\\ &\quad+b(z-z^*)\left(-D(z-z^*)-\gamma_1 z U_1(x)-\gamma_2 z U_2(y)+\gamma_2 z^* U_2(y^*)\right).\end{aligned}$$

Simplifying the above equation gives

$$\begin{aligned}\frac{\mathrm{d}V_1}{\mathrm{d}t} &= -a\frac{\beta_1}{\kappa_1}x^2-\frac{\beta_2}{\kappa_2}(y-y^*)^2-b\left(D+\frac{\alpha_1\gamma_2 x}{\theta_1+x}+\frac{\alpha_2\gamma_2 y}{\theta_2+y}\right)(z-z^*)^2\\ &\quad+a(\beta_1-\delta_1 y^*)x+\frac{\alpha_2 z^*}{\theta_2+y^*}(y-y^*)-(a\delta_1+\delta_2)x(y-y^*)-\frac{b\alpha_1\gamma_2 z^*}{\theta_1+x}x(z-z^*)\\ &\quad-\frac{b\alpha_2\gamma_2\theta_2 z^*}{(\theta_2+y)(\theta_2+y^*)}(y-y^*)(z-z^*)+\eta_1(t),\quad \text{where} \qquad (2.37)\\ \eta_1(t) &= -\frac{a\alpha_2 x}{\theta_1+x}z(t-\tau_1)-\frac{\alpha_2(y-y^*)}{\theta_2+y}z(t-\tau_2).\end{aligned}$$

Noticing that $z(t-\tau_j)=z(t)-\int_{t-\tau_j}^{t}z'(s)\mathrm{d}s$ for $j=1,2$, then

$$\eta_1(t)=-\frac{a\alpha_2 xz}{\theta_1+x}-\frac{\alpha_2(y-y^*)z}{\theta_2+y}+\frac{a\alpha_1 x}{\theta_1+x}\int_{t-\tau_1}^{t}z'(s)\mathrm{d}s+\frac{\alpha_2(y-y^*)}{\theta_2+y}\int_{t-\tau_2}^{t}z'(s)\mathrm{d}s,$$

and the equation 2.37 can be further simplified to

$$\begin{aligned}\frac{\mathrm{d}V_1}{\mathrm{d}t} &= \eta_2(t)-a\frac{\beta_1}{\kappa_1}x^2-\left(\frac{\beta_2}{\kappa_2}-\frac{\alpha_2 z^*}{(\theta_2+y)(\theta_2+y^*)}\right)(y-y^*)^2-(a\delta_1+\delta_2)x(y-y^*)\\ &\quad+a\left(\beta_1-\delta_1 y^*-\frac{\alpha_2 z^*}{\theta_1+x}\right)x-b\left(D+\frac{\alpha_1\gamma_2 x}{\theta_1+x}+\frac{\alpha_2\gamma_2 y}{\theta_2+y}\right)(z-z^*)^2\\ &\quad-(a\alpha_2+b\alpha_1\gamma_2 z^*)\frac{x(z-z^*)}{\theta_1+x}-\left(1+\frac{b\gamma_2\theta_2 z^*}{\theta_2+y^*}\right)\frac{\alpha_2(y-y^*)(z-z^*)}{\theta_2+y},\end{aligned}$$

where

$$\eta_2(t)=\frac{a\alpha_1 x}{\theta_1+x}\int_{t-\tau_1}^{t}z'(s)\mathrm{d}s+\frac{\alpha_2(y-y^*)}{\theta_2+y}\int_{t-\tau_2}^{t}z'(s)\mathrm{d}s. \qquad (2.38)$$

Using $pq \leq \frac{1}{2}p^2 + \frac{1}{2}q^2$ for all the cross terms with $x(y-y^*)$, $x(z-z^*)$ and $(y-y^*)(z-z^*)$ we get

$$\frac{\mathrm{d}V_1}{\mathrm{d}t} \leq K_1 x^2 + K_2(y-y^*)^2 + K_3(z-z^*)^2 + a\left(\beta_1 - \delta_1 y^* - \frac{\alpha_2 z^*}{\theta_1 + x}\right)x + \eta_2(t), \quad (2.39)$$

where

$$\begin{aligned}
K_1 &= -a\frac{\beta_1}{\kappa_1} + \frac{a\delta_1 + \delta_2}{2} + \frac{a\alpha_2 + b\alpha_1\gamma_2 z^*}{2(\theta_1 + x)}, \\
K_2 &= -\frac{\beta_2}{\kappa_2} + \frac{a\delta_1 + \delta_2}{2} + \frac{\alpha_2}{2(\theta_2 + y)}\left(1 + \frac{(b\gamma_2\theta_2 + 2)z^*}{\theta_2 + y^*}\right), \\
K_3 &= -b\left(D + \frac{\alpha_1\gamma_1 x}{\theta_1 + x} + \frac{\alpha_2\gamma_2 y}{\theta_2 + y}\right) + \frac{a\alpha_2 + b\alpha_1\gamma_2 z^*}{2(\theta_1 + x)} + \frac{\alpha_2}{2(\theta_2 + y)}\left(1 + \frac{b\gamma_2\theta_2 z^*}{\theta_2 + y^*}\right).
\end{aligned}$$

By using $pq \leq \frac{1}{2}p^2 + \frac{1}{2}q^2$ for $z'(s)$ and $(y(t)-y^*)z'(s)$ in 2.38, we have

$$\eta_2(t) \leq \frac{a\alpha_2 x}{2(\theta_1 + x)} \cdot \tau_1 + \frac{1}{2}\int_{t-\tau_1}^{t} [z'(s)]^2 \mathrm{d}s + \frac{\alpha_2(y-y^*)^2}{2(\theta_2 + y)} \cdot \tau_2 + \frac{1}{2}\int_{t-\tau_2}^{t} [z'(s)]^2 \mathrm{d}s. \quad (2.40)$$

(**ii**) The second step is to deal with the two positive integrals in 2.40. To this end, introduce

$$V_2(t) = \frac{1}{2}\int_{t-\tau_1}^{t} \mathrm{d}r \int_{r}^{t} [z'(s)]^2 \mathrm{d}s + \frac{1}{2}\int_{t-\tau_2}^{t} \mathrm{d}r \int_{r}^{t} [z'(s)]^2 \mathrm{d}s.$$

Then the derivative of $V_2(t)$ along solutions to system (**DDE-I**) satisfies

$$\frac{\mathrm{d}V_2(t)}{\mathrm{d}t} = \frac{1}{2}[z'(t)]^2(\tau_1 + \tau_2) - \frac{1}{2}\int_{t-\tau_1}^{t} [z'(s)]^2 \mathrm{d}s - \frac{1}{2}\int_{t-\tau_2}^{t} [z'(s)]^2 \mathrm{d}s,$$

and by the third equation of system (**DDE-I**):

$$\eta_2(t) + \frac{\mathrm{d}V_2(t)}{\mathrm{d}t} \leq \frac{1}{2}[z'(t)]^2(\tau_1 + \tau_2) + \frac{a\alpha_2 x}{2(\theta_1 + x)} \cdot \tau_1 + \frac{\alpha_2(y-y^*)^2}{2(\theta_2 + y)} \cdot \tau_2. \quad (2.41)$$

Squaring the third equation of (**DDE-I**), applying $pq \leq \frac{1}{2}p^2 + \frac{1}{2}q^2$ for all the cross terms with $x(y-y^*)$, $x(z-z^*)$ and $(y-y^*)(z-z^*)$ and using the facts that $\frac{x}{\theta_1+x} \leq 1$ and $\frac{y}{\theta_2+y} \leq 1$

we get

$$[z'(t)]^2 \leq K_4 x^2 + K_5(y - y^*)^2 + K_6(z - z^*)^2, \tag{2.42}$$

where

$$\begin{aligned}
K_4 &= \frac{I}{\theta_1}\alpha_1\gamma_1\left(D + \alpha_2\gamma_2 + \frac{\alpha_1\gamma_1 I}{\theta_1} + \frac{\alpha_2\gamma_2 I}{\theta_2}\right), \\
K_5 &= \frac{I}{\theta_2}\alpha_2\gamma_2\left(D + \alpha_2\gamma_2 + \frac{\alpha_1\gamma_1 I}{\theta_1} + \frac{\alpha_2\gamma_2 I}{\theta_2}\right), \\
K_6 &= (D + \alpha_2\gamma_2)^2 + I(D + \alpha_2\gamma_2)\left(\frac{\alpha_1\gamma_1}{\theta_1} + \frac{\alpha_2\gamma_2}{\theta_2}\right).
\end{aligned}$$

(**iii**) Finally, let $V(t) := V_1(t) + V_2(t)$. Then the inequalities 2.39, 2.41 and 2.42 together gives the time derivative of $V(t)$ along solutions of system (**DDE-I**) to satisfy

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} \leq B_1 x^2 + B_2(y - y^*)^2 + B_3(z - z^*)^2 + B_4 x, \tag{2.43}$$

where

$$\begin{aligned}
B_1 &= K_1 + \frac{1}{2}(\tau_1 + \tau_2)K_4, \\
B_2 &= K_2 + \frac{1}{2}(\tau_1 + \tau_2)K_5 + \frac{\alpha_2\tau_2}{2(\theta_2 + y)}, \\
B_3 &= K_3 + \frac{1}{2}(\tau_1 + \tau_2)K_6, \\
B_4 &= a\left(\beta_1 - \delta_1 y^* - \frac{\alpha_2 z^*}{\theta_1 + x} + \frac{\alpha_2}{2(\theta_1 + x)}\tau_1\right).
\end{aligned}$$

The final step is to show that B_1, B_2, B_3, $B_4 < 0$ under assumptions of the theorem. First notice that under assumptions 2.33 and 2.31,

$$\beta_1 - \delta_1 y^* - \frac{\alpha_2 z^*}{\theta_1 + x} + \frac{\alpha_2}{2(\theta_1 + x)}\tau_1 \leq -\beta_1 + \frac{\alpha_2}{2\theta_1}\tau_1 < 0,$$

and hence

$$B_4 < 0. \tag{2.44}$$

To deal with B_2 and B_3, pick a and b such that

$$a\delta_1 + b\frac{\alpha_2\gamma_2 z^*}{\theta_2 + y^*} \leq \frac{\beta_2}{\kappa_2} \quad \text{and} \quad \frac{\alpha_2}{\theta_1} \cdot a \leq b\left(D - \frac{\alpha_1\gamma_2 z^*}{2\theta_1} - \frac{\alpha_2\gamma_2 z^*}{2(\theta_2 + y^*)}\right).$$

In particular, pick

$$a = \frac{\beta_2}{\kappa_2}\frac{D\theta_1\theta_2}{D\delta_1\theta_1\theta_2 + 2\alpha_2^2\gamma_2 z^*}, \quad \text{and} \quad b = \frac{2\alpha_2}{\theta_1 D}a.$$

Then

$$B_2 \leq -\frac{\beta_2}{2\kappa_2} + \frac{\delta_2}{2} + \frac{\alpha_2}{2\theta_2}\left(1 + \frac{2z^*}{\theta_2 + y^*)}\right) + \frac{1}{2}K_5\tau_2 + \frac{1}{2}\left(K_5 + \frac{\alpha_2}{\theta_2}\right)\tau_2,$$

and it follows from assumptions 2.31, 2.34 and 2.32 that

$$B_2 < -\frac{\beta_2}{4\kappa_2} + \frac{1}{2}\left(K_5 + \frac{\alpha_2}{\theta_2}\right)\tau_2 < 0. \tag{2.45}$$

Also from the choice of a and b above and the assumptions 2.31 and 2.32 we have

$$\begin{aligned} B_3 &< -a\frac{\alpha_2}{2\theta_1} + \frac{\alpha_2}{2\theta_2} + \frac{1}{2}(\tau_1 + \tau_2)K_6 \\ &< \frac{\beta_2}{\kappa_2}\left(-\frac{D\alpha_2\theta_2}{2(D\delta_1\theta_1\theta_2 + 2\alpha_2^2\gamma_2 z^*)} + \frac{\theta_2}{\alpha_2}K_6\right) + \frac{\alpha_2}{2\theta_2} + \frac{\theta_1}{\alpha_2}\beta_1 K_6. \end{aligned}$$

Note that the assumption 2.35 implies that

$$\frac{D\theta_2\alpha_2}{2(D\delta_1\theta_1\theta_2 + 2\alpha_2^2\gamma_2 z^*)} - \frac{\theta_2}{\alpha_2}K_6 > \frac{\theta_2}{\alpha_2}K_6,$$

and then by using assumption 2.34 we obtain

$$B_3 < -\left(\frac{1}{2\theta_2^2\gamma_2^2} + \frac{\theta_1}{\theta_2}\beta_1\right)\frac{\theta_2}{\alpha_2}K_6 + \frac{\alpha_2}{2\theta_2} + \frac{\theta_1}{\alpha_2}\beta_1 K_6 = \frac{\alpha_2}{2\theta_2}\left(1 - \frac{K_6}{\alpha_2^2\theta_2^2}\right) < 0. \tag{2.46}$$

Finally, by assumptions 2.31 and 2.32

$$B_1 < a\left(-\frac{\beta_1}{\kappa_1} + \frac{\delta_1}{2} + \frac{\alpha_2}{2\theta_1} + \frac{\alpha_1\alpha_2\gamma_2 z^*}{\theta_1^2 D}\right) + \frac{\delta_2}{2} + \frac{\alpha_1\gamma_1\beta_2\theta_2}{\theta_1\alpha_2\kappa_2}$$

$$+\frac{\alpha_1\gamma_1\beta_1 I}{\alpha_2}\left(D+\alpha_2\gamma_2+\frac{\alpha_1\gamma_1 I}{\theta_1}+\frac{\alpha_2\gamma_2 I}{\theta_2}\right).$$

Now noticing that assumption 2.34 implies

$$I\left(D+\alpha_2\gamma_2+\frac{\alpha_1\gamma_1 I}{\theta_1}+\frac{\alpha_2\gamma_2 I}{\theta_2}\right)<\frac{\beta_2}{\kappa_2}\frac{\theta_2}{4\theta_1\beta_1\gamma_2},$$

and hence

$$\begin{aligned} K_7 &:= \frac{1}{a}\left(\frac{\delta_2}{2}+\frac{\alpha_1\gamma_1\beta_2\theta_2}{\theta_1\alpha_2\kappa_2}+\frac{\alpha_1\gamma_1\beta_1 I}{\alpha_2}(D+\alpha_2\gamma_2+\frac{\alpha_1\gamma_1 I}{\theta_1}+\frac{\alpha_2\gamma_2 I}{\theta_2})\right) \\ &\leq \left(\delta_1+\frac{2\alpha_2^2\gamma_2 z^*}{D\theta_1\theta_2}\right)\left(\frac{\delta_2\kappa_2}{2\beta_2}+\frac{\alpha_1\gamma_1\theta_2}{\theta_1\alpha_2}(1+\frac{1}{4\gamma_2})\right). \end{aligned}$$

Then assumption 2.36 immidiately implies that

$$B_1=a\left(-\frac{\beta_1}{\kappa_1}+\frac{\delta_1}{2}+\frac{\alpha_2}{2\theta_1}+\frac{\alpha_1\alpha_2\gamma_2 z^*}{\theta_1^2 D}+K_7\right)<0. \tag{2.47}$$

Summarizing the above, inserting inequalities 2.44, 2.45, 2.46 and 2.47 into 2.43 results in

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t}<0 \quad \forall\ x\neq 0,\ y\neq y^*,\ z\neq z^*,$$

and thus $(0,y^*,z^*)$ is asymptotically stable. The proof is complete.

Following similar calculations we can obtain the parallel stability results for a failure steady state as follows.

Theorem 2.7 *A failure steady state* $(x^*,0,z^*)$ *of system (***DDE-I***) is asymptotically stable provided*

$$\begin{aligned} \tau_1 &\leq \frac{2\theta_2}{\alpha_1}\beta_2, \\ \tau_2 &\leq \frac{2\theta_1\beta_1}{\alpha_1\kappa_1}\cdot\frac{1}{1+\gamma_1 I\left(D+\alpha_1\gamma_1+\frac{\alpha_2\gamma_2 I}{\theta_2}+\frac{\alpha_1\gamma_1 I}{\theta_1}\right)}, \\ 2\beta_2 &< \delta_2 x^*+\frac{\alpha_1 z^*}{\theta_2+\kappa_1}, \end{aligned}$$

$$
\begin{aligned}
\frac{\beta_1}{\kappa_1} &> \max\Big\{\frac{1}{2\theta_1\gamma_1^2}+\frac{\theta_2}{\theta_1}\beta_2, 2\delta_1+\frac{2\alpha_1}{\theta_1}(1+\frac{2z^*}{\theta_1+x^*}) \\
&\qquad +\frac{4\theta_2}{\theta_1}\beta_2\gamma_1 I(D+\alpha_1\gamma_1+\frac{\alpha_2\gamma_2 I}{\theta_2}+\frac{\alpha_1\gamma_1 I}{\theta_1})\Big\}, \\
\frac{1}{4} &> \left(D+\alpha_1\gamma_1+I(\frac{\alpha_2\gamma_2}{\theta_2}+\frac{\alpha_1\gamma_1}{\theta_1})\right)^2\left(\frac{\delta_2\theta_1\theta_2}{\alpha_1^2}+\frac{2\gamma_1 z^*}{D}\right), \\
\frac{\beta_2}{\kappa_2} &> \frac{\delta_2}{2}+\frac{\alpha_1}{2\theta_2}+\frac{\alpha_1\alpha_2\gamma_1 z^*}{\theta_2^2 D} \\
&\qquad +\left(\delta_2+\frac{2\alpha_1^2\gamma_1 z^*}{D\theta_1\theta_2}\right)\left(\frac{\delta_1\kappa_1}{2\beta_1}+\frac{\alpha_2\gamma_2\theta_1}{\theta_2\alpha_1}(1+\frac{1}{4\gamma_1})\right).
\end{aligned}
$$

Note that sufficient conditions for asymptotic stability of a persistent steady state $E_p=(x^*,y^*,z^*)$ of system (**DDE-I**) can be constructed in a similar manner as above. The computations then become tedious and omitted here.

We next investigate the stability of steady states for system (**DDE-II**). Instead of studying success and failure steady states respectively, here we consider a generic steady state (x^*,y^*,z^*). For notice that any steady state (x^*,y^*,z^*) of system (**DDE-II**) satisfies

$$
\begin{aligned}
-\hat{\alpha}_1 x^* U_3(z^*)+\beta_1 x^*\Big(1-\frac{x^*}{\kappa_1}\Big)-\delta_1 x^* y^* &= 0, &(2.48)\\
-\hat{\alpha}_2 y^* U_3(z^*)+\beta_2 y^*\Big(1-\frac{y^*}{\kappa_2}\Big)-\delta_2 x^* y^* &= 0, &(2.49)\\
Dz^*+\gamma_1\hat{\alpha}_1 x^* U_3(z^*)+\gamma_2\hat{\alpha}_2 y^* U_3(z^*) &= DI. &(2.50)
\end{aligned}
$$

Theorem 2.8 *A steady state (x^*,y^*,z^*) of system (***DDE-II***) is asymptotically stable provided*

$$
\begin{aligned}
\tau_1 &\le \frac{\theta_3\beta_1}{2\hat{\alpha}_1\kappa_1}\cdot\frac{1}{1+\gamma_1(\hat{\alpha}_1+\hat{\alpha}_2)\left(D+\hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3}\right)}, &(2.51)\\
\tau_2 &\le \frac{\theta_3\beta_1}{2\hat{\alpha}_1\kappa_1}\cdot\frac{1}{\gamma_1(\hat{\alpha}_1+\hat{\alpha}_2)\left(D+\hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3}\right)}, &(2.52)\\
\frac{\beta_1}{\kappa_1} &> 2(\delta_1+\delta_2)+4\hat{\alpha}_1\gamma_1+\frac{2\alpha_1}{\theta_3+z^*}, &(2.53)\\
\frac{\beta_2}{\kappa_2} &> \delta_1+\delta_2+2\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_2}{\theta_3+z^*}+\frac{\beta_1\hat{\alpha}_2\gamma_2}{\kappa_1\hat{\alpha}_1\gamma_1}+\frac{1}{2}\cdot\frac{\beta_1}{\kappa_1\hat{\alpha}_1\gamma_1 D}, &(2.54)\\
D &> \hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_1}{2(\theta_3+z^*)}+\frac{\hat{\alpha}_2}{2(\theta_3+z^*)}, &(2.55)\\
1 &> \frac{\beta_1}{2\kappa_1\hat{\alpha}_1\gamma_1}\left(1+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3 D}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3 D}\right). &(2.56)
\end{aligned}
$$

Proof: The proof will be proceed in three steps.

(**i**) Given any solution of (**DDE-II**) $(x(t), y(t), z(t)) \in \mathcal{C}^1([-\tau, \infty), \Omega)$ define

$$V_1(x(t), y(t), z(t)) = a\left(x(t) - x^* - x^* \ln \frac{x(t)}{x^*}\right) + b\left(y(t) - y^* - y^* \ln \frac{y(t)}{y^*}\right) + (z(t) - z^*)^2,$$

where $a, b > 0$ will be determined later. Clearly $V_1(x^*, y^*, z^*) = 0$ and $V_1(x(t), y(t), z(t)) > 0$ for any $(x(t), y(t), z(t)) \in \mathcal{C}^1([-\tau, \infty), \Omega \backslash \{(x^*, y^*, z^*\})$. Differentiating $V_1(t)$ along solutions to system (**DDE-II**) and using 2.48 – 2.50 gives

$$\begin{aligned}
\frac{\mathrm{d}V_1}{\mathrm{d}t} &= (x - x^*)\left[-\hat{\alpha}_1 U_3(z(t-\tau_1)) + \beta_1\left(1 - \frac{x(t)}{\kappa_1}\right) - \delta_1 y(t)\right] \\
&\quad + (y - y^*)\left[-\hat{\alpha}_2 U_3(z(t-\tau_2)) + \beta_2\left(1 - \frac{y(t)}{\kappa_2}\right) - \delta_2 x(t)\right] \\
&\quad + (z - z^*)\left[DI - Dz(t) - \hat{\alpha}_1\gamma_1 x(t) U_3(z(t)) - \hat{\alpha}_2\gamma_2 y(t) U_3(z(t))\right].
\end{aligned}$$

which can be simplified by using equations 2.48–2.50 to be

$$\begin{aligned}
\frac{\mathrm{d}V_1}{\mathrm{d}t} &= -\frac{\beta_1}{\kappa_1}(x - x^*)^2 - \frac{\beta_2}{\kappa_2}(y - y^*)^2 - D(z - z^*)^2 - (\delta_1 + \delta_2)(x - x^*)(y - y^*) \\
&\quad - \hat{\alpha}_1(x - x^*)\left(U_3(z(t-\tau_1)) - U_3(z^*)\right) - \hat{\alpha}_2(y - y^*)\left(U_3(z(t-\tau_2)) - U_3(z^*)\right) \\
&\quad + (z - z^*)\left(-\hat{\alpha}_1\gamma_1 x U_3(z) + \hat{\alpha}_1\gamma_1 x^* U_3(z^*) - \hat{\alpha}_2\gamma_2 y U_3(z) + \hat{\alpha}_2\gamma_2 y^* U_3(z^*)\right).
\end{aligned}$$

Define the function $g : \mathbb{R} \to \mathbb{R}$ by

$$g(\cdot) = U_3(\cdot + z^*) - U_3(z^*).$$

Noticing that

$$\begin{aligned}
-\hat{\alpha}_1\gamma_1 x U_3(z) + \hat{\alpha}_1\gamma_1 x^* U_3(z^*) &= \frac{-\hat{\alpha}_1\gamma_1\theta_3 x(z - z^*)}{(\theta_3 + z)(\theta_3 + z^*)} - \frac{\hat{\alpha}_1\gamma_1 z^*(x - x^*)}{\theta_3 + z^*}, \\
-\hat{\alpha}_2\gamma_2 y U_3(z) + \hat{\alpha}_2\gamma_2 y^* U_3(z^*) &= \frac{-\hat{\alpha}_2\gamma_2\theta_3 y(z - z^*)}{(\theta_3 + z)(\theta_3 + z^*)} - \frac{\hat{\alpha}_2\gamma_2 z^*(y - y^*)}{\theta_3 + z^*},
\end{aligned}$$

the above equation becomes

$$\begin{aligned}\frac{\mathrm{d}V_1}{\mathrm{d}t} &= -\frac{\beta_1}{\kappa_1}(x-x^*)^2 - \frac{\beta_2}{\kappa_2}(y-y^*)^2 - (\delta_1+\delta_2)(x-x^*)(y-y^*) \\ &\quad -2\left(D + \frac{\hat{\alpha}_1\gamma_1\theta_3 x}{(\theta_3+z)(\theta_3+z^*)} + \frac{\hat{\alpha}_2\gamma_2\theta_3 y}{(\theta_3+z)(\theta_3+z^*)}\right)(z-z^*)^2 \\ &\quad -\frac{2\hat{\alpha}_1\gamma_1 z^*}{\theta_3+z^*}(x-x^*)(z-z^*) - \frac{2\hat{\alpha}_2\gamma_2 z^*}{\theta_3+z^*}(y-y^*)(z-z^*) + \mu_1(t),\end{aligned} \tag{2.57}$$

where

$$\mu_1(t) = -\hat{\alpha}_1(x-x^*)g(z(t-\tau_1)-z^*) - \hat{\alpha}_2(y-y^*)g(z(t-\tau_2)-z^*). \tag{2.58}$$

For simplicity let $\tilde{z}(t-\tau_j) := z(t-\tau_j) - z^*$, then

$$g(\tilde{z}(t-\tau_j)) = g(\tilde{z}(t)) - \int_{t-\tau_j}^{t} g'(\tilde{z}(s))\tilde{z}'(s)\mathrm{d}s \qquad \text{for } j = 1, 2,$$

and equation 2.58 can be written as

$$\mu_1(t) = -\hat{\alpha}_1(x-x^*)g(\tilde{z}(t)) - \hat{\alpha}_2(y-y^*)g(\tilde{z}(t)) + \mu_2(t), \tag{2.59}$$

where

$$\mu_2(t) = \hat{\alpha}_1(x-x^*)\int_{t-\tau_1}^{t} g'(\tilde{z}(s))\tilde{z}'(s)\mathrm{d}s + \hat{\alpha}_2(y-y^*)\int_{t-\tau_2}^{t} g'(\tilde{z}(s))\tilde{z}'(s)\mathrm{d}s. \tag{2.60}$$

Using $g(\tilde{z}(t)) = \frac{\theta_3(z-z^*)}{(\theta_3+z)(\theta_3+z^*)}$ in 2.59 then inserting the resultant equation in 2.57 gives

$$\begin{aligned}\frac{\mathrm{d}V_1}{\mathrm{d}t} &= -\frac{\beta_1}{\kappa_1}(x-x^*)^2 - \frac{\beta_2}{\kappa_2}(y-y^*)^2 - (\delta_1+\delta_2)(x-x^*)(y-y^*) \\ &\quad -2\left(D + \frac{\hat{\alpha}_1\gamma_1\theta_3 x}{(\theta_3+z)(\theta_3+z^*)} + \frac{\hat{\alpha}_2\gamma_2\theta_3 y}{(\theta_3+z)(\theta_3+z^*)}\right)(z-z^*)^2 \\ &\quad -\hat{\alpha}_1\left(\frac{2\gamma_1 z^*}{\theta_3+z^*} + \frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right)\cdot(x-x^*)(z-z^*) \\ &\quad -\hat{\alpha}_2\left(\frac{2\gamma_2 z^*}{\theta_3+z^*} + \frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right)\cdot(y-y^*)(z-z^*) + \mu_2(t).\end{aligned}$$

Then use $pq \leq \frac{1}{2}p^2 + \frac{1}{2}q^2$ for all the cross terms with $(x-x^*)(y-y^*)$, $(x-x^*)(z-z^*)$ and $(y-y^*)(z-z^*)$ to obtain

$$\frac{\mathrm{d}V_1}{\mathrm{d}t} \leq A_1(x-x^*)^2 + A_2(y-y^*)^2 + A_3(z-z^*)^2 + \mu_2(t), \tag{2.61}$$

where

$$\begin{aligned}
A_1 &= -\frac{\beta_1}{\kappa_1} + \frac{1}{2}(\delta_1+\delta_2) + \frac{\hat{\alpha}_1}{2}\left(2\gamma_1 + \frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right), \\
A_2 &= -\frac{\beta_2}{\kappa_2} + \frac{1}{2}(\delta_1+\delta_2) + \frac{\hat{\alpha}_2}{2}\left(2\gamma_2 + \frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right), \\
A_3 &= -2\left(D + \frac{\hat{\alpha}_1\gamma_1\theta_3 x}{(\theta_3+z)(\theta_3+z^*)} + \frac{\hat{\alpha}_2\gamma_2\theta_3 y}{(\theta_3+z)(\theta_3+z^*)}\right) \\
&\quad + \frac{\hat{\alpha}_1}{2}\left(2\gamma_1 + \frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right) + \frac{\hat{\alpha}_2}{2}\left(2\gamma_2 + \frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right).
\end{aligned}$$

Noticing that

$$g'(w) = U_3'(w+z^*) = \frac{\theta_3}{(\theta_3+w+z^*)^2} \leq \frac{1}{\theta_3} \text{ for all } w \in \mathbb{R},$$

and using $pq \leq \frac{1}{2}p^2 + \frac{1}{2}q^2$ for $(x-x^*)z'(s)$ and $(y(t)-y^*)z'(s)$ in 2.60, we have

$$\begin{aligned}
\mu_2(t) &\leq \frac{1}{2\theta_3}\cdot\hat{\alpha}_1(x-x^*)^2\tau_1 + \frac{1}{2\theta_3}\hat{\alpha}_1\int_{t-\tau_1}^{t}[z'(s)]^2\mathrm{d}s + \frac{1}{2\theta_3}\cdot\hat{\alpha}_2(y-y^*)^2\tau_2 \\
&\quad + \frac{1}{2\theta_3}\hat{\alpha}_2\int_{t-\tau_2}^{t}[z'(s)]^2\mathrm{d}s.
\end{aligned} \tag{2.62}$$

(**ii**) The second step is to deal with the two positive integrals in 2.62. To this end, we introduce

$$V_2(t) = \frac{1}{2\theta_3}\cdot\hat{\alpha}_1\int_{t-\tau_1}^{t}\mathrm{d}r\int_{r}^{t}[z'(s)]^2\mathrm{d}s + \frac{1}{2\theta_3}\cdot\hat{\alpha}_2\int_{t-\tau_2}^{t}\mathrm{d}r\int_{r}^{t}[z'(s)]^2\mathrm{d}s.$$

Then the derivative of $V_2(t)$ along solutions to system (**DDE-II**) satisfies

$$\begin{aligned}
\frac{\mathrm{d}V_2(t)}{\mathrm{d}t} &= \frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)(\tau_1+\tau_2)[z'(t)]^2 - \frac{1}{2\theta_3}\cdot\hat{\alpha}_1\int_{t-\tau_1}^{t}[z'(s)]^2\mathrm{d}s
\end{aligned}$$

$$-\frac{1}{2\theta_3}\cdot\hat{\alpha}_2\int_{t-\tau_2}^{t}[z'(s)]^2\mathrm{d}s,$$

and by equation 2.62 we have

$$\begin{aligned}\mu_2(t)+\frac{\mathrm{d}V_2(t)}{\mathrm{d}t} &\leq \frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)(\tau_1+\tau_2)[z'(t)]^2+\frac{1}{2\theta_3}\cdot\hat{\alpha}_1(x-x^*)^2\tau_1\\ &\quad+\frac{1}{2\theta_3}\cdot\hat{\alpha}_2(y-y^*)^2\tau_2. \end{aligned}\tag{2.63}$$

Squaring the third equation of (**DDE-II**), applying $pq\leq\frac{1}{2}p^2+\frac{1}{2}q^2$ for all the cross terms with $(x-x^*)(y-y^*)$, $(x-x^*)(z-z^*)$ and $(y-y^*)(z-z^*)$; and using the facts that $\frac{z}{\theta_3+z}\leq 1$, we get

$$[z'(t)]^2\leq A_4(x-x^*)^2+A_5(y-y^*)^2+A_6(z-z^*)^2,\tag{2.64}$$

where

$$\begin{aligned}A_4 &= \hat{\alpha}_1\gamma_1\left(D+\hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3}\right),\\ A_5 &= \hat{\alpha}_2\gamma_2\left(D+\hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3}\right),\\ A_6 &= \left(D+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3}\right)^2+(\hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2)\left(D+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3}\right).\end{aligned}$$

(**iii**) Finally, let $V(t):=V_1(t)+V_2(t)$. Then the inequalities 2.61, 2.63 and 2.64 together gives the time derivative of $V(t)$ along solutions of system (**DDE-II**) to satisfy

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t}\leq B_1(x-x^*)^2+B_2(y-y^*)^2+B_3(z-z^*)^2,\tag{2.65}$$

where

$$\begin{aligned}B_1 &= A_1+\frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)(\tau_1+\tau_2)A_4+\frac{1}{2\theta_3}\cdot\hat{\alpha}_1\tau_1,\\ B_2 &= A_2+\frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)(\tau_1+\tau_2)A_5+\frac{1}{2\theta_3}\cdot\hat{\alpha}_2\tau_2,\\ B_3 &= A_3+\frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)(\tau_1+\tau_2)A_6.\end{aligned}$$

The last step is to show that B_1, B_2, $B_3 < 0$ under assumptions of the theorem. First notice that

$$\begin{aligned} B_1 &= -\frac{\beta_1}{\kappa_1} + \frac{1}{2}(\delta_1 + \delta_2) + \frac{\hat{\alpha}_1}{2}\left(2\gamma_1 + \frac{\theta_3}{(\theta_3 + z)(\theta_3 + z^*)}\right) \\ &\quad + \frac{1}{2\theta_3}(\hat{\alpha}_1 + \hat{\alpha}_2)(\tau_1 + \tau_2)A_4 + \frac{1}{2\theta_3} \cdot \hat{\alpha}_1\tau_1 \\ &\leq -\frac{\beta_1}{2\kappa_1} + \frac{1}{2}(\delta_1 + \delta_2) + \hat{\alpha}_1\gamma_1 + \frac{\hat{\alpha}_1}{2(\theta_3 + z^*)} \\ &\quad + \frac{1}{2\theta_3}\left[\hat{\alpha}_1 + (\hat{\alpha}_1 + \hat{\alpha}_2)A_4\right]\tau_1 + \frac{1}{2\theta_3}(\hat{\alpha}_1 + \hat{\alpha}_2)A_4\tau_2, \end{aligned}$$

and it follows from assumption 2.53, 2.51, and 2.52 that

$$B_1 < -\frac{\beta_1}{4\kappa_1} + \frac{1}{2\theta_3}\left[\hat{\alpha}_1 + (\hat{\alpha}_1 + \hat{\alpha}_2)A_4\right]\tau_1 + \frac{1}{2\theta_3}(\hat{\alpha}_1 + \hat{\alpha}_2)A_4\tau_2 < 0. \tag{2.66}$$

Second,

$$\begin{aligned} B_2 &= -\frac{\beta_2}{\kappa_2} + \frac{1}{2}(\delta_1 + \delta_2) + \frac{\hat{\alpha}_2}{2}\left(2\gamma_2 + \frac{\theta_3}{(\theta_3 + z)(\theta_3 + z^*)}\right) \\ &\quad + \frac{1}{2\theta_3}(\hat{\alpha}_1 + \hat{\alpha}_2)(\tau_1 + \tau_2)A_5 + \frac{1}{2\theta_3} \cdot \hat{\alpha}_2\tau_2 \\ &\leq -\frac{\beta_2}{2\kappa_2} + \frac{1}{2}(\delta_1 + \delta_2) + \hat{\alpha}_2\gamma_2 + \frac{\hat{\alpha}_2}{2(\theta_3 + z^*)} \\ &\quad + \frac{1}{2\theta_3}(\hat{\alpha}_1 + \hat{\alpha}_2)A_5\tau_1 + \frac{1}{2\theta_3}\left[\hat{\alpha}_2 + (\hat{\alpha}_1 + \hat{\alpha}_2)A_5\right]\tau_2, \end{aligned}$$

and it follows from assumption 2.51 and 2.52 that

$$\begin{aligned} B_2 &< -\frac{\beta_2}{2\kappa_2} + \frac{1}{2}(\delta_1 + \delta_2) + \hat{\alpha}_2\gamma_2 + \frac{\hat{\alpha}_2}{2(\theta_3 + z^*)} \\ &\quad + \frac{\beta_1}{4\kappa_1} \cdot \frac{1}{\hat{\alpha}_1\gamma_1 D} + \frac{\beta_1\hat{\alpha}_2\gamma_2}{2\kappa_1\hat{\alpha}_1\gamma_1}. \end{aligned}$$

Thus, by assumption 2.54 we get

$$B_2 < 0. \tag{2.67}$$

Last,

$$B_3 = -2\left(D + \frac{\hat{\alpha}_1\gamma_1\theta_3 x}{(\theta_3 + z)(\theta_3 + z^*)} + \frac{\hat{\alpha}_2\gamma_2\theta_3 y}{(\theta_3 + z)(\theta_3 + z^*)}\right)$$

$$
\begin{aligned}
&+\frac{\hat{\alpha}_1}{2}\left(2\gamma_1+\frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right)+\frac{\hat{\alpha}_2}{2}\left(2\gamma_2+\frac{\theta_3}{(\theta_3+z)(\theta_3+z^*)}\right)\\
&+\frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)(\tau_1+\tau_2)A_6\\
\leq\ & -2D+\hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_1}{2(\theta_3+z^*)}+\frac{\hat{\alpha}_2}{2(\theta_3+z^*)}\\
&+\frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)A_6\tau_1+\frac{1}{2\theta_3}(\hat{\alpha}_1+\hat{\alpha}_2)A_6\tau_2,
\end{aligned}
$$

and using assumption 2.51 and 2.52 we get

$$
\begin{aligned}
B_3\ \leq\ & -2D+\hat{\alpha}_1\gamma_1+\hat{\alpha}_2\gamma_2+\frac{\hat{\alpha}_1}{2(\theta_3+z^*)}+\frac{\hat{\alpha}_2}{2(\theta_3+z^*)}\\
&+\frac{1}{2}\cdot\frac{\beta_1}{\hat{\alpha}_1\gamma_1\kappa_1}\cdot\left(D+\frac{\hat{\alpha}_1\gamma_1\kappa_1}{\theta_3}+\frac{\hat{\alpha}_2\gamma_2\kappa_2}{\theta_3}\right).
\end{aligned}
$$

Applying condition 2.55 and 2.56 we obtain

$$
B_3<0. \tag{2.68}
$$

The inequalities 2.66, 2.67 and 2.68 altogether ensure

$$
\frac{dV}{dt}<0 \quad \text{for all } \ x\neq x^*,\ y\neq y^*,\ z\neq z^*,
$$

and thus (x^*,y^*,z^*) is asymptotically stable. The proof is complete.

2.4 Numerical simulations

In this section we demonstrate the theoretical results obtained in previous sections. In particular, we are interested in the scenarios where the time delay changes the stability, i.e., for one system with the same set of parameters a stable steady state becomes unstable with a change in the delays, or vice versa. For each model, two sets of simulations with the same model parameters but different delays are presented, in which a success steady state becomes failure, and vice versa, due to the difference in the delay parameters.

For the simulations of system (**DDE-I**) the parameters in Table 2.2 are used. When $\tau_1=1$

Table 2.2: Model parameters used in simulating (**DDE-I**)

D	α_1	α_2	β_1	β_2	γ_1	γ_2
50	23.486	0.0085	35	20	2.52073	0.34
I	δ_1	δ_2	κ_1	κ_2	θ_1	θ_2
32.5	0.095	0.1	240	125	18	20

and $\tau_2 = 3$ the conditions in Theorem 2.7 are satisfied and the system thus approaches a failure steady state asymptotically (see Fig. 2.1). On the other side, when $\tau_1 = 2$ and $\tau_2 = 1$ the conditions in Theorem 2.6 are satisfied and thus the system approaches a success steady state asymptotically (see Fig. 2.2).

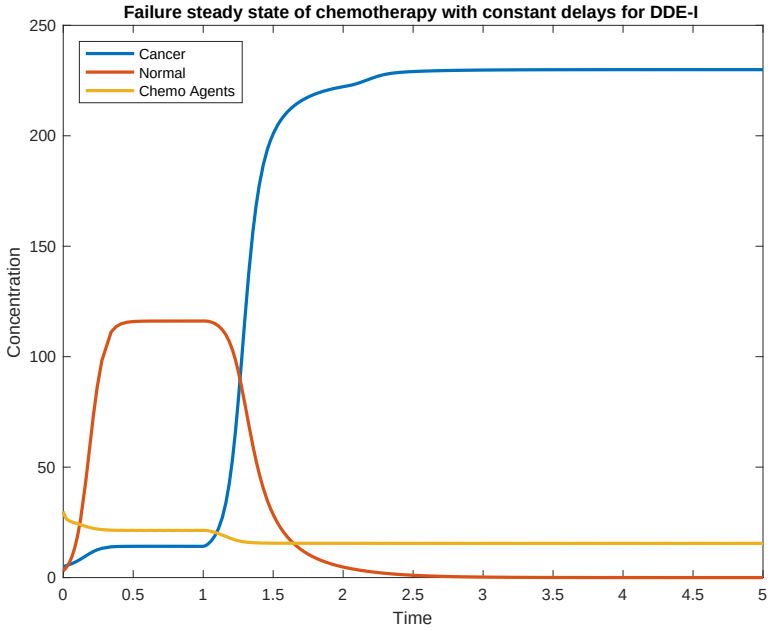


Figure 2.1: A stable failure steady state of system (**DDE-I**) with parameters in Table 2.2 and delays $\tau_1 = 1$ and $\tau_2 = 3$.

For the simulations of system (**DDE-II**) the parameters in Table 2.3 are used. When

Table 2.3: Model parameters used in simulating (**DDE-II**)

D	$\hat{\alpha}_1$	$\hat{\alpha}_2$	β_1	β_2	γ_1	γ_2
4	2	1.2763	3	2	2	3
I	δ_1	δ_2	κ_1	κ_2	θ_1	θ_2
4	2	2	5	9	1	1

$\tau_1 = 0.000344538$ and $\tau_2 = 0.000345331$ the conditions in Theorem 2.8 with $y^* = 0$ are satisfied and the system thus approaches a failure steady state asymptotically (see Fig. 2.3).

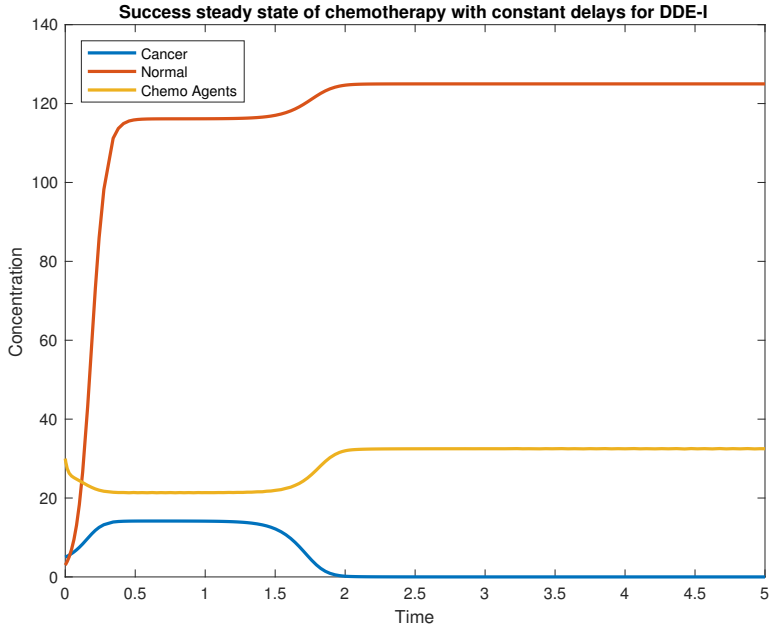


Figure 2.2: A stable success steady state of system (**DDE-I**) with parameters in Table 2.2 and delays $\tau_1 = 2$ and $\tau_2 = 1$.

On the other side, when $\tau_1 = 11$ and $\tau_2 = 15$ the conditions in Theorem 2.8 with $x^* = 0$ are satisfied and thus the system approaches a success steady state asymptotically (see Fig. 2.4).

2.5 Closing remarks

Two mathematical models of chemotherapy treatments with time delays are formulated and studied, one treats the chemotherapy agent as the predator (system (**DDE-I**)), and the other treats the chemotherapy agent as the prey (system (**DDE-II**)). For each model, we showed the existence, uniqueness, non-negativeness and boundedness of a global solution. We also investigated the stability for different type of steady states. Particular interests are given to success steady states (all cancer cells are cleared while normal cells remains), and failure steady states (all normal cells die out while cancer cells remains).

Sufficient conditions for the stability of success and failure steady states are constructed for system (**DDE-I**), and for the stability of a generic steady states are constructed for system (**DDE-II**). Note that sufficient conditions for the stability of a generic steady state for system

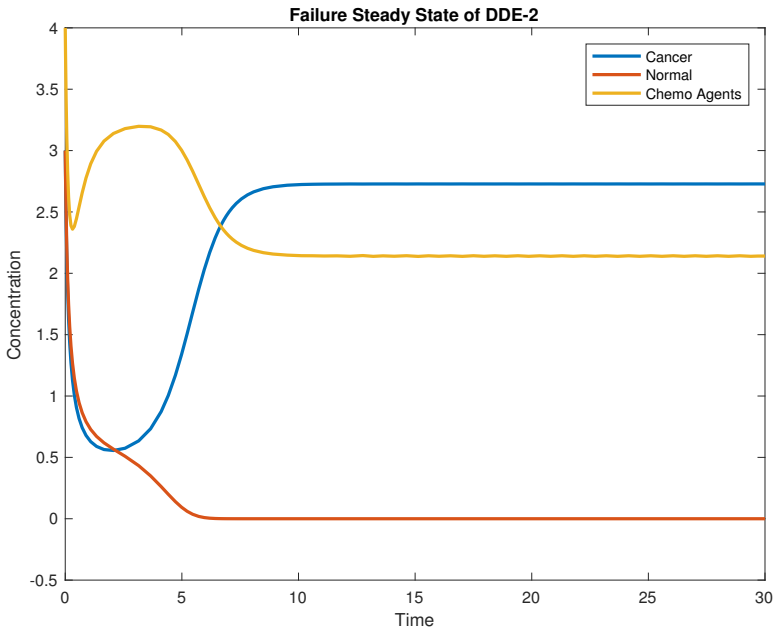


Figure 2.3: A stable failure steady state of system (**DDE-II**) with parameters in Table 2.3 and delays $\tau_1 = 0.000344538$ and $\tau_2 = 0.000345331$.

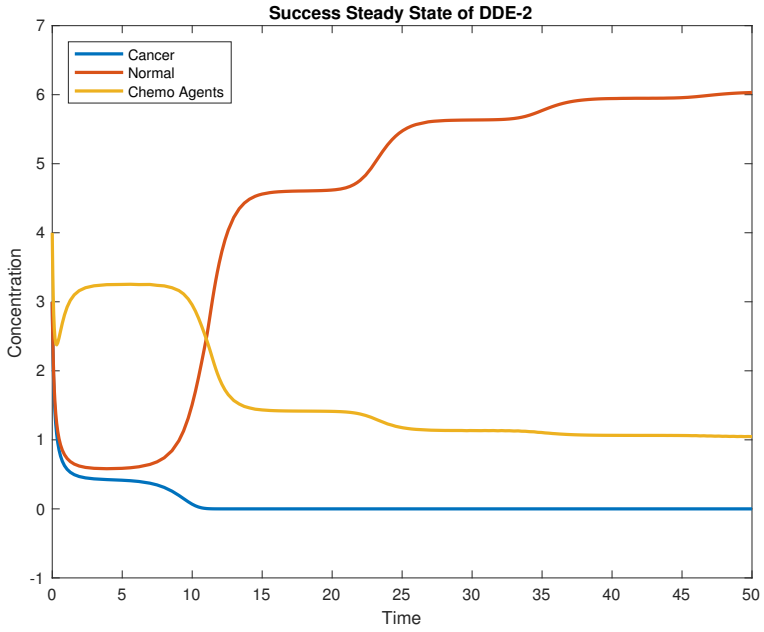


Figure 2.4: A stable success steady state of system (**DDE-II**) with parameters in Table 2.3 and delays $\tau_1 = 11$ and $\tau_2 = 15$.

(**DDE-I**) can also be constructed, following more technical computations, but are omitted to avoid redundancy of the presentation.

The parameters chosen for the numerical simulations are assumed to satisfy the basic assumptions $\alpha_1 > \alpha_2$ and $\beta_1 > \beta_2$, i.e., the cancer cells grow at a faster rate than the normal cells and the chemotherapy treatment is more efficient for the cancer cells than the normal cells. While the order of magnitudes of model parameters used in different systems appear different, noticing that the systems under consideration are both dimensionless and thus the parameters are chosen mainly to serve for the purpose of illustrating the theoretical results other than making perfect biological sense. Provided empirical values of the model parameters, and through extensive numerical experiments, parameters with biological units satisfying assumptions in our main theorems (after non-dimensionalization) can be constructed.

Chapter 3

Stability Analysis of a Chemotherapy Model with or without Delays

In this chapter, we consider the special case of system (**DDE-II**) by letting $\alpha_1 = \alpha_2 = \alpha$ and $\delta_1 = \delta_2 = \delta$ (i.e., the killing rate of the chemotherapy agent on both cells as well as the intraspecific competition coefficient between cancer and normal cells are same). The resulting system of delay differential equations (DDEs) describing dynamics of chemotherapy reads

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\alpha x(t)U(z(t-\tau_1)) + \beta_1 x(t)\left(1-\frac{x(t)}{\kappa_1}\right) - \delta x(t)y(t), \tag{3.1}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -\alpha y(t)U(z(t-\tau_2)) + \beta_2 y(t)\left(1-\frac{y(t)}{\kappa_2}\right) - \delta x(t)y(t), \tag{3.2}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = DI - Dz(t) - \alpha\gamma_1 x(t)U(z(t)) - \alpha\gamma_2 y(t)U(z(t)). \tag{3.3}$$

In the absence of time delay, the above system 3.1–3.3 results in the following system of ordinary differential equations (ODEs) describing dynamics of chemotherapy as

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = -\alpha x(t)U(z(t)) + \beta_1 x(t)\left(1-\frac{x(t)}{\kappa_1}\right) - \delta x(t)y(t), \tag{3.4}$$

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = -\alpha y(t)U(z(t)) + \beta_2 y(t)\left(1-\frac{y(t)}{\kappa_2}\right) - \delta x(t)y(t), \tag{3.5}$$

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = DI - Dz(t) - \alpha\gamma_1 x(t)U(z(t)) - \alpha\gamma_2 y(t)U(z(t)). \tag{3.6}$$

The aim is to investigate the stability of each meaningful steady state of the chemotherapy model without time delay, and compare with its analog model with delay. Note that we already proved existence, uniqueness, boundedness and positiveness of solution as well as local and

Lyapunov stability of the above DDEs system 3.1–3.3 in the previous chapter. We will just go ahead with the comparison of the model with and without time delays.

3.1 Stability analysis

In this section we investigate the stability of the axial, preferred and failure states for the system 3.4–3.6 and then compare with its analog model with delay. Throughout this section denote by $\boldsymbol{u}^* = (x^*, y^*, z^*)$ a generic steady state solution of the system 3.4 – 3.6.

3.1.1 Absence of time delay

The Jacobian matrix of system 3.4 – 3.6 at the generic steady state $\boldsymbol{u}^* = (x^*, y^*, z^*)$ is

$$J = \begin{bmatrix} J_{11} & -\delta x^* & -\frac{\alpha\theta x^*}{(z^*+\theta)^2} \\ -\delta y^* & J_{22} & -\frac{\alpha\theta y^*}{(z^*+\theta)^2} \\ -\alpha\gamma_1 U(z^*) & -\alpha\gamma_2 U(z^*) & J_{33} \end{bmatrix},$$

where

$$\begin{aligned} J_{11} &= -\alpha U(z^*) + \beta_1\left(1 - \frac{2x^*}{\kappa_1}\right) - \delta y^*, \\ J_{22} &= -\alpha U(z^*) + \beta_2\left(1 - \frac{2y^*}{\kappa_2}\right) - \delta x^*, \\ J_{33} &= -D - \frac{\alpha\theta}{(z^*+\theta)^2}(\gamma_1 x^* + \gamma_2 y^*). \end{aligned}$$

Theorem 3.1 *For the linearization of system 3.4 – 3.6,*

(i) the axial steady state $(0, 0, I)$ *is asymptotically stable provided*

$$\frac{\beta_1}{\alpha} < \frac{I}{\theta + I} \quad \textit{and} \quad \frac{\beta_2}{\alpha} < \frac{I}{\theta + I}; \tag{3.7}$$

(ii) a preferred steady state $(0, y^*, z^*)$ *is asymptotically stable provided*

$$\beta_1 < \alpha U(z^*) + \delta y^*, \textit{and} \tag{3.8}$$

$$\beta_2 \geq 2\alpha U(z^*); \tag{3.9}$$

(iii) a failure steady state $(x^*, 0, z^*)$ *is asymptotically stable provided*

$$\beta_2 < \alpha U(z^*) + \delta x^*, \textit{and} \tag{3.10}$$

$$\beta_1 \geq 2\alpha U(z^*). \tag{3.11}$$

Proof: (i) When $x^* = y^* = 0$ and $z^* = I$, the Jacobian matrix is reduced to

$$J = \begin{bmatrix} -\frac{\alpha I}{\theta+I} + \beta_1 & 0 & 0 \\ 0 & -\frac{\alpha I}{\theta+I} + \beta_2 & 0 \\ -\gamma_1 \frac{\alpha I}{\theta+I} & -\gamma_2 \frac{\alpha I}{\theta+I} & -D \end{bmatrix}$$

with eigenvalues

$$\lambda_1 = -\frac{\alpha I}{\theta + I} + \beta_1, \quad \lambda_2 = -\frac{\alpha I}{\theta + I} + \beta_2, \quad \lambda_3 = -D,$$

which are all negative under the assumption 3.7.

(ii) When $x^* = 0$ and y^* and z^* satisfy equation 2.7, the Jacobian matrix is reduced to

$$J = \begin{bmatrix} \beta_1 - \alpha U(z^*) - \delta y^* & 0 & 0 \\ -\delta y^* & -\beta_2 \frac{y^*}{\kappa_2} & -\frac{\alpha\theta y^*}{(z^*+\theta)^2} \\ -\alpha\gamma_1 U(z^*) & -\alpha\gamma_2 U(z^*) & -D - \frac{\alpha\gamma_2\theta y^*}{(z^*+\theta)^2} \end{bmatrix}.$$

The first eigenvalue of the above matrix is

$$\lambda_1 = \beta_1 - \alpha U(z^*) - \delta y^* < 0$$

under the assumption 3.8. The other two eigenvalues of the above matrix coincide with the eigenvalues of the submatrix

$$B = \begin{bmatrix} -\beta_2 \frac{y^*}{\kappa_2} & -\frac{\alpha\theta y^*}{(z^*+\theta)^2} \\ -\alpha\gamma_2 U(z^*) & -D - \frac{\alpha\gamma_2\theta y^*}{(z^*+\theta)^2} \end{bmatrix}.$$

First notice that

$$\text{Tr}(B) = -\beta_2 \frac{y^*}{\kappa_2} - D - \frac{\alpha\gamma_2\theta y^*}{(z^*+\theta)^2} < 0.$$

In addition, by using $\alpha U(z^*) = \beta_2 (1 - y^*/\kappa_2)$, we have

$$\det(B) = y^* \left(\frac{\beta_2}{\kappa_2} + \beta_2 \frac{\alpha\gamma_2\theta}{(z^*+\theta)^2} - 2U(z^*) \frac{\alpha^2\gamma_2\theta}{(z^*+\theta)^2} \right) > 0$$

by the assumption 3.9. Therefore all eigenvalues of J are negative, which implies the asymptotic stability of the preferred state $(0, y^*, z^*)$.

(iii) When $y^* = 0$ and x^* and z^* satisfy equation 2.8, the Jacobian matrix is reduced to

$$J = \begin{bmatrix} -\frac{\beta_1}{\kappa_1} x^* & -\delta x^* & -\frac{\alpha\theta x^*}{(z^*+\theta)^2} \\ 0 & \beta_2 - \alpha U(z^*) - \delta x^* & 0 \\ -\alpha\gamma_1 U(z^*) & -\alpha\gamma_2 U(z^*) & -D - \frac{\alpha\gamma_1\theta x^*}{(z^*+\theta)^2} \end{bmatrix}.$$

The first eigenvalue of the above matrix is

$$\lambda_1 = \beta_2 - \alpha U(z^*) - \delta x^* < 0$$

under the assumption 3.10. The other two eigenvalues of the above matrix coincide with the eigenvalues of the submatrix

$$B = \begin{bmatrix} -\beta_1 \frac{x^*}{\kappa_1} & -\frac{\alpha\theta x^*}{(z^*+\theta)^2} \\ -\alpha\gamma_1 U(z^*) & -D - \frac{\alpha\gamma_1\theta x^*}{(z^*+\theta)^2} \end{bmatrix}.$$

First notice that

$$\text{Tr}(B) = -\beta_1 \frac{x^*}{\kappa_1} - D - \frac{\alpha\gamma_1\theta y^*}{(z^*+\theta)^2} < 0.$$

In addition, by using $\alpha U(z^*) = \beta_1 (1 - y^*/\kappa_1)$, we have

$$\det(B) = y^* \left(\frac{\beta_1}{\kappa_1} + \beta_1 \frac{\alpha\gamma_1\theta}{(z^*+\theta)^2} - 2U(z^*) \frac{\alpha^2\gamma_1\theta}{(z^*+\theta)^2} \right) > 0$$

by the assumption 3.11. Therefore all eigenvalues of J are negative, which implies the asymptotic stability of the failure state $(x^*, 0, z^*)$. The proof is complete.

Remark 1 *Assumptions 3.7 are both sufficient and necessary conditions for the asymptotic stability of the axial steady state. Assumptions 3.8 and 3.9 are sufficient conditions for the asymptotic stability of the preferred steady state, but the assumption 3.8 is also a necessary condition for the asymptotic stability of the preferred steady state. Similarly, assumptions 3.10 and 3.11 are sufficient conditions for the asymptotic stability of the failure steady state, but the assumption 3.10 is also a necessary condition for the asymptotic stability of the failure steady state.*

Notice that assumption 3.7 is equivalent to

$$\alpha > \max\left\{ \beta_1 \frac{\theta + I}{I}, \beta_2 \frac{\theta + I}{I} \right\}.$$

Thus part (i) of Theorem 3.1 indicates that when the killing rate of the chemotherapy agent is higher than a certain threshold (dependent of the largest growth rate of cells, the input concentration of the chemotherapy agent, and the half saturation constant), then both normal and cancer cells will be cleared.

The assumptions 3.8 and 3.9 together are equivalent to

$$\frac{\beta_1 - \delta y^*}{U(z^*)} < \alpha \leq \frac{\beta_2}{2U(z^*)}.$$

Thus part (ii) of Theorem 3.1 indicates that when the killing rate of the chemotherapy agent is well controlled between $\frac{\beta_1 - \delta y^*}{U(z^*)}$ and $\frac{\beta_2}{2U(z^*)}$, the treatment will be successful. This implicitly requires the steady state to satisfy $\beta_2 \geq 2(\beta_1 - \delta y^*)$, which essentially put a restriction on the growth rates of cancer and normal cells. Similarly part (iii) of Theorem 3.1 indicates that when the killing rate of the chemotherapy agent lies between $\frac{\beta_2 - \delta x^*}{U(z^*)}$ and $\frac{\beta_1}{2U(z^*)}$, the treatment will fail. This also implicitly requires the steady state to satisfy $\beta_1 \geq 2(\beta_2 - \delta x^*)$.

Notice that the conditions in parts (ii) and (iii) depend on the magnitude of each specific steady state. For example, a preferred steady state with smaller quantity of normal cells is easier to achieve than a preferred steady state with larger quantity of normal cells, and a failure steady state with smaller quantity of cancer cells is easier to achieve than a failure steady state with larger quantity of cancer cells.

3.1.2 Constant time delay

Local stabilities of steady states of system (**DDE-II**) were discussed in theorem 3.2 of chapter 2. Here we state the corresponding results for the system 3.1 – 3.3 without proof since it is a special case.

Theorem 3.2 *For the system 3.1 – 3.3 we have:*

(i) the axial steady state $(0, 0, I)$ *is asymptotically stable provided*

$$\frac{\beta_1}{\alpha} < \frac{I}{\theta + I} \quad \textit{and} \quad \frac{\beta_2}{\alpha} < \frac{I}{\theta + I}; \tag{3.12}$$

(ii) a preferred steady state $(0, y^*, z^*)$ *is asymptotically stable provided*

$$\beta_1 < \alpha U(z^*) + \delta y^* \quad \textit{and} \tag{3.13}$$

$$2y^* \geq \kappa_2; \tag{3.14}$$

(iii) a failure steady state $(x^*, 0, z^*)$ is asymptotically stable provided

$$\beta_2 < \alpha U(z^*) + \delta x^* \tag{3.15}$$

$$2x^* \geq \kappa_1. \tag{3.16}$$

Remark 2 *Assumptions 3.12 are both sufficient and necessary conditions for the asymptotic stability of the axial steady state. Assumptions 3.13 and 3.14 are sufficient conditions for the asymptotic stability of the preferred steady state, but the assumption 3.13 is also a necessary condition for the asymptotic stability of the preferred steady state. Similarly, assumptions 3.15 and 3.11 are sufficient conditions for the asymptotic stability of the failure steady state, but the assumption 3.16 is also a necessary condition for the asymptotic stability of the failure steady state.*

Part (i) of Theorem 3.2 has the same interpretation as part (i) of Theorem 3.1. Since the conditions imposed are necessary and sufficient conditions, we obtain an important information that the stability of the axial steady state is not affected by the time delay of the treatment.

Assumptions 3.13 and 3.8, and assumptions 3.15 and 3.10 are the same, respectively. Therefore these specific necessary conditions for the stability of preferred and failure steady states are also not affected by the time delay. Also, by using the relation $y^* = \kappa_2(1 - \alpha U(z^*)/\beta_2)$ when $x^* = 0$ and $x^* = \kappa_1(1 - \alpha U(z^*)/\beta_1)$ when $y^* = 0$, assumptions 3.14 and 3.16 are also the same as assumptions 3.9 and 3.11 for the no delay case, respectively.

To further interpret these assumptions, we rewrite 3.13 as

$$\kappa_1(\beta_1 - \beta_2) > (\beta_1 - \kappa_1\delta)x^* \tag{3.17}$$

and rewrite 3.15 as

$$\kappa_2(\beta_1 - \beta_2) < (\kappa_2\delta - \beta_2)y^*. \tag{3.18}$$

Then parts (ii) and (iii) of Theorem 3.2 provide two interpretations depending on the strength of inter-specific competitions. When the inter-specific competition is strong, in the sense that

$\delta > \kappa_2/\beta_2$ and $\delta > \kappa_1/\beta_1$, then assumptions 3.17 and 3.14 can be combined to be

$$y^* > \max\left\{\frac{\kappa_2(\beta_1-\beta_2)}{\kappa_2\delta-\beta_2}, \frac{\kappa_2}{2}\right\}, \tag{3.19}$$

and assumptions 3.18 and 3.16 can be combined to be

$$x^* > \max\left\{\frac{\kappa_1(\beta_2-\beta_1)}{\kappa_1\delta-\beta_1}, \frac{\kappa_1}{2}\right\}. \tag{3.20}$$

One special case of 3.19 happens when cancer cells grow slower than normal cells, i.e., $\beta_1 < \beta_2$, then the treatment will be successful as long as y^* is more than half of the environmental carrying capacity of normal cells. Similarly one special case of 3.20 when cancer cells grow faster than normal cells, i.e., $\beta_1 > \beta_2$, then the treatment will be a failure as long as x^* is more than half of the environmental carrying capacity of cancer cells.

On the other hand, when the inter-specific competition is weak, in the sense that $\delta < \kappa_2/\beta_2$ and $\delta < \kappa_1/\beta_1$, then assumptions 3.17 and 3.14 can be combined to be

$$\frac{\kappa_2}{2} \leq y^* < \frac{\kappa_2(\beta_2-\beta_1)}{\beta_2-\kappa_2\delta},$$

which may only happen when $\beta_2 > \beta_1$ and $\frac{\beta_2-\beta_1}{\beta_2-\kappa_2\delta} > 1/2$. When the inter-specific competition is negligible, this implies that the normal cells need to grow at least twice as fast as the cancer cells do for a possible successful treatment. Similarly assumptions 3.18 and 3.16 can be combined to be

$$\frac{\kappa_1}{2} \leq x^* < \frac{\kappa_1(\beta_1-\beta_2)}{\beta_1-\kappa_1\delta},$$

which may only happen when $\beta_1 > \beta_2$ and $\frac{\beta_1-\beta_2}{\beta_1-\kappa_1\delta} > 1/2$. When the inter-specific competition is negligible, this implies that the cancer cells need to grow at least twice as fast as the normal cells do for a possible failed treatment.

3.2 Numerical simulations

In this section we include some numerical results with parameters satisfying the conditions constructed in the previous section.

3.2.1 Axial steady state

The first set of parameters simulated satisfy the sufficient and necessary conditions for the axial steady state $(0, 0, I)$. In particular, the parameters are chosen as

τ_1	τ_2	D	I	α	δ	θ	β_1	κ_1	γ_1	β_2	κ_2	γ_2
3	2	4	4	8	1	1	2	5	3	1	9	2

that satisfy the assumptions in 3.7. The initial conditions are set to be $x_0 = 5$, $y_0 = 3$, $\phi(t) = 4$ for $t \in [-3, 0]$. Evolution of the concentrations of normal and cancer cells, and the chemotherapy agent is illustrated in Figure 3.1. It can be clearly seen that concentration of both normal and cancer cells tend to 0 as time goes on.

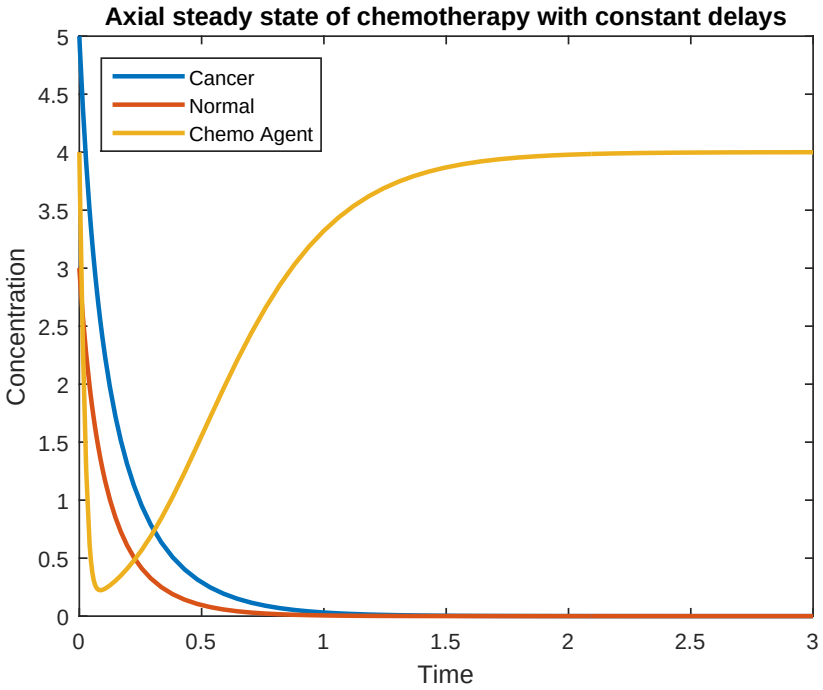
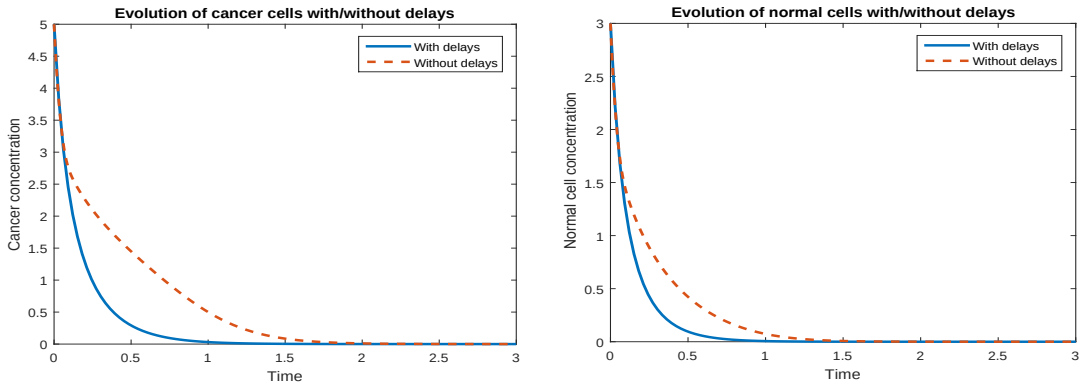


Figure 3.1: Chemotherapy with delays approaching the axial steady state.

To closer examine the effect of delays, we compare the concentration of cancer and normal cells of the above example with the special case when $\tau_1 = \tau_2 = 0$, shown in Fig. 3.2. Though



(a) Cancer cells (b) Normal cells

Figure 3.2: Comparison of normal and cancer cells of chemotherapy with/without delays

concentrations of both cancer and normal approach zero, with or without delays, differences in cell concentrations between the cases with delays and the cases without delays can be clearly seen. In this particular example, the chemotherapy treatment approaches the axial steady state faster with the presence of delays.

3.2.2 Preferred steady state

The second set of parameters simulated satisfy the sufficient and necessary conditions for a preferred steady state $(0, y^*, z^*)$. In particular, the parameters are chosen as

τ_1	τ_2	D	I	α	δ	θ	β_1	κ_1	γ_1	β_2	κ_2	γ_2
3	2	4	4	3	1	1	2	5	3	3	9	2

There is only one real positive solution to the equations 2.7, $y^* = 5.2422$ and $z^* = 0.7168$, that satisfy the assumptions 3.8 and 3.9.

Evolution of the concentrations of normal and cancer cells, and the chemotherapy agent is illustrated in Figure 3.3, where it can be seen that the concentration of cancer cells tends to 0 while the concentration of normal cells tends to $y^* = 5.2422$. The treatment is hence successful. It is also interesting to see that although the cancer cells become vanish soon, it takes a much longer time for the normal cells to recover to their steady state.

Similarly we compare the concentration of cancer and normal cells of the above example with the special case when $\tau_1 = \tau_2 = 0$ in Fig. 3.4, where differences in cell concentrations for the cases with delays and the cases without delays can be clearly seen. In this particular

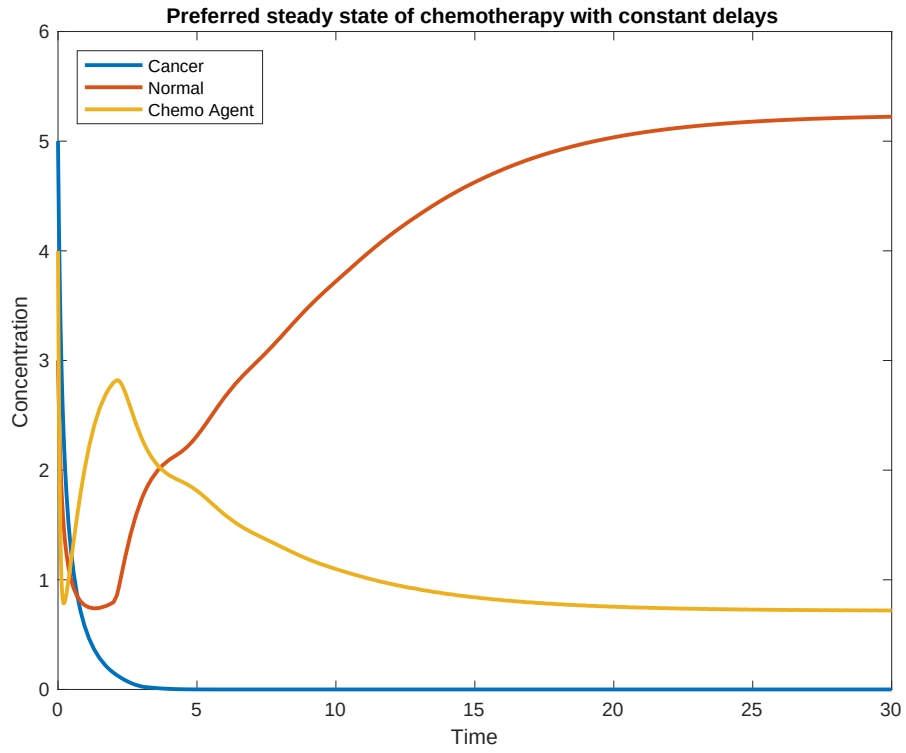


Figure 3.3: Chemotherapy with delays approaching a preferred steady state.

example, the cancer cells are removed slightly faster when there are delays, whereas the normal cells recover much faster when there are no delays.

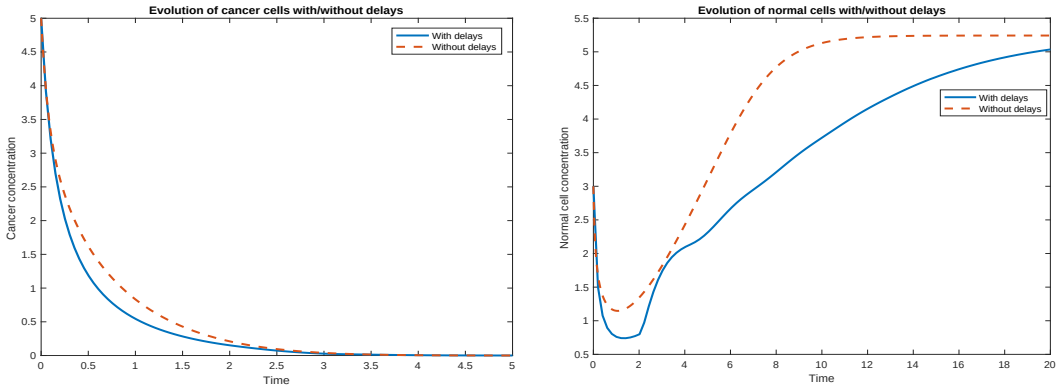
3.2.3 Failure steady state

The third set of parameters simulated satisfy the sufficient and necessary conditions for a preferred steady state $(x^*, 0, z^*)$. In particular, the parameters are chosen as

τ_1	τ_2	D	I	α	δ	θ	β_1	κ_1	γ_1	β_2	κ_2	γ_2
3	2	4	4	2	2	1	3	5	2	2	9	3

There is only one (real and positive) preferred steady state $x^* = 2.728$, $y^* = 0$, $z^* = 2.14$, and it satisfies the assumptions 3.10 and 3.11.

Evolution of the concentrations of normal and cancer cells, and the chemotherapy agent is illustrated in Figure 3.5, where it can be seen that the concentration of normal cells tends to 0 while the concentration of cancer cells tends to $x^* = 2.728$.



(a) Cancer cells (b) Normal cells

Figure 3.4: Comparison of normal and cancer cells of chemotherapy with/without delays

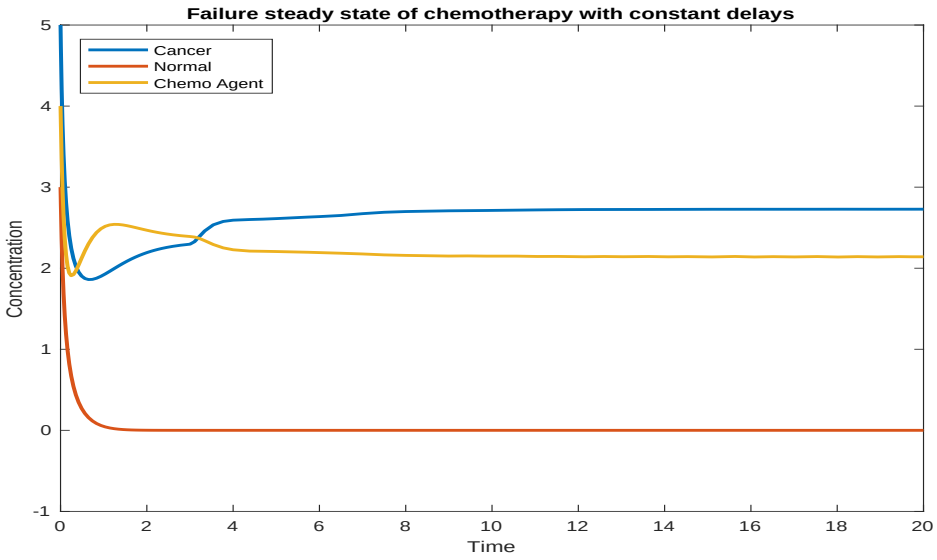
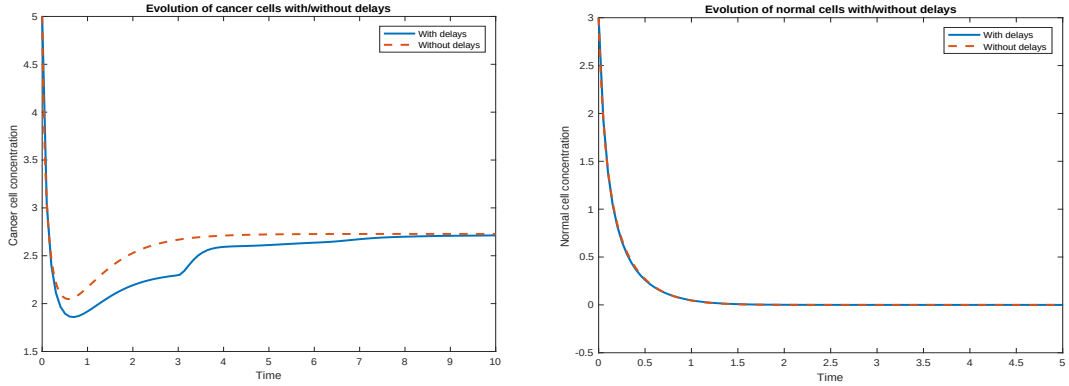


Figure 3.5: Chemotherapy with delays approaching a failure steady state.

A comparison between the concentration of cancer and normal cells of the above example and the special case when $\tau_1 = \tau_2 = 0$ is shown in Fig. 3.6. The difference in cancer cells for the cases with or without delays is clearly seen, whereas the difference in normal cells for the cases with or without delays is not detectible.

3.3 Closing remarks

We constructed sufficient and necessary conditions for the stability of the axial steady state $(0, 0, I)$, which are indifferent for the system with or without delay. We also constructed sufficient conditions for the stability of the preferred and failure steady states, respectively, which



(a) Cancer cells (b) Normal cells

Figure 3.6: Comparison of normal and cancer cells of chemotherapy with/without delays

turned out to coincide. The indifference of stability conditions is mainly due to the special bounded structure of the consumption function U, that mitigate the effect of delays. However, we cannot conclude that the time delay does not affect the stability of non-axial steady states. In fact, the numerical experiments presented above clearly show the difference in dynamics of the chemotherapy model with or without delays. Further numerical experiments indicated that stability of preferred or failure steady states that do not satisfy conditions 3.14 or 3.16, respectively, could be affected by the delay. In other words, a stable preferred state with $y^* < \kappa_2/2$ or a stable failure state with $x^* < \kappa_1/2$ when there are no delays, can become unstable with delays, and vice versa. In the previous chapter, conditions on the magnitudes of delays had been established for stability of various states by constructing appropriate Lyapunov functions, which provided more insights in the effect of delays for chemotherapy treatments.

Chapter 4

A Mathematical Model of Chemotherapy with Variable Infusion

In this chapter, we developed and studied a nonautonomous mathematical model of chemotherapy cancer treatment with time-dependent infusion concentration of the chemotherapy agent. 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. We first established properties of solutions and detailed dynamics of the nonautonomous system, and then conditions under which the treatment is successful or unsuccessful are established. Moreover, we showed 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.

4.1 Mathematical model

The model to be developed and studied is based on the system 3.4–3.5 developed and studied in the previous chapter, but with time-dependent infusion due to the natural (temporal or random) fluctuation of environments or human control, and few modifications.

4.1.1 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 [30], 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 [10, 17, 21, 26] and have Lotka-Volterra type intra-specific competitions between them [9]. These leads to the following nonautonomous system of ODEs describing dynamics of chemotherapy

$$\begin{aligned}
\frac{\mathrm{d}N_1(t)}{\mathrm{d}t} &= -K_1(C)N_1 + b_1N_1\left(1 - \frac{N_1}{\kappa_1}\right) - d_1N_1N_2, && (4.1)\\
\frac{\mathrm{d}N_2(t)}{\mathrm{d}t} &= -K_2(C)N_2 + b_2N_2\Big(1 - \frac{N_2}{\kappa_2}\Big) - d_2N_1N_2, && (4.2)\\
\frac{\mathrm{d}C(t)}{\mathrm{d}t} &= -r_1K_1(C)N_1 - r_2K_2(C)N_2 - \frac{CF}{V} + \frac{I(t)F}{V}. && (4.3)
\end{aligned}$$

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 [17] 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 $-r_1K_1(C)N_1$ and $-r_2K_2(C)N_2$ 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, κ_1, κ_2, r_1, r_2, d_1 and d_2 are listed in Table 4.1 below.

Table 4.1: Description of parameters in the nonautonomous 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
κ_1 (mass/vol)	Environmental carrying capacity of cancer cells
κ_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 chapter we adopt the Michaelis-Menten formulation of the killing rates [30]:

$$K_j(C) = \frac{K_j^{max} C}{k_j^{half} + C}, \quad j = 1, 2,$$

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.

4.1.2 Non-dimensionalization

For the convenience of mathematical analysis, we first non-dimensionalize the system 4.1 – 4.3 by setting

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

with

$$N_1^* = \frac{k_1^{half} F}{r_1 V K_1^{max}}, \quad N_2^* = \frac{k_2^{half} F}{r_2 V K_2^{max}}, \quad C^* = k_1^{half} + k_2^{half}, \quad t^* = \frac{V}{F}.$$

Still denoting $\tilde{t}$ by t, the ODEs 4.1 – 4.3 now become the following system

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = -\alpha_1 \frac{x(t)z(t)}{\theta_1 + z(t)} + \beta_1 x(t)(1 - \gamma_1 x(t)) - \delta_1 x(t) y(t), \tag{4.4}$$

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = -\alpha_2 \frac{y(t)z(t)}{\theta_2 + z(t)} + \beta_2 y(t)(1 - \gamma_2 y(t)) - \delta_2 x(t) y(t), \tag{4.5}$$

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = -\frac{x(t)z(t)}{\theta_1 + z(t)} - \frac{y(t)z(t)}{\theta_2 + z(t)} - z(t) + \mu(t), \tag{4.6}$$

where the parameters

$$\alpha_j = \frac{V}{F}K_j^{max}, \;\; \beta_j = \frac{V}{F}b_j, \;\; \gamma_j = \frac{k_j^{half}F}{Vr_jK_j^{max}\kappa_j}, \;\; \theta_j = \frac{k_j^{half}}{k_1^{half} + k_2^{half}}, \;\; \text{for } j = 1, 2, \tag{4.7}$$

$$\delta_1 = \frac{d_1k_2^{half}}{r_2K_2^{max}}, \quad \delta_2 = \frac{d_2k_1^{half}}{r_1K_1^{max}}, \quad \mu(t) = \frac{I(t)}{k_1^{half} + k_2^{half}}. \tag{4.8}$$

are all dimensionless. Moreover, notice that C^* has the unit of concentration, and both N_1^* and N_2^* have the unit of $(concentration \cdot \frac{volume}{time})/(volume \cdot \frac{1}{time})$ = concentration. Thus the new unknowns $x(t), y(t), z(t)$ are all dimensionless.

4.1.3 Assumptions

By the physical meanings of parameters listed in Table 4.1, all dimensionless parameters defined in 4.7 are positive. The parameters δ_1 and δ_2 defined in 4.8 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 θ_1 and θ_2, $\theta_1 + \theta_2 = 1$. Moreover, the cancer cells are assumed to grow faster than normal cells, i.e., $b_1 > b_2$ and thus $\beta_1 > \beta_2$. Furthermore, since the chemotherapy agent should be more effective killing cancer cells than killing normal cells, $K_1^{max} > K_2^{max}$ and consequently, $\alpha_1 > \alpha_2$. In summary, it is assumed throughout this paper that

(A0) $\alpha_1 > \alpha_2 > 0$, $\beta_1 > \beta_2 > 0$, $\gamma_1, \gamma_2 > 0$, $\theta_1, \theta_2 > 0$ with $\theta_1 + \theta_2 = 1$, $\delta_1, \delta_2 \geq 0$;

(A1) the input concentration is bounded and varies continuously with respect to time, i.e., $\mu(t)$ is a continuous and bounded function with

$$0 < \mu_m \leq \mu(t) \leq \mu_M \quad \text{for all } t \in \mathbb{R}.$$

4.2 Properties of solutions

In this section, we first investigate basic properties of solutions to the system 4.4 – 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.

4.2.1 Basic properties of solutions

In this subsection we prove that system 4.4 – 4.6 has a unique global solution under the initial condition

$$x(t_0) = x_0 > 0, \quad y(t_0) = y_0 > 0, \quad z(t_0) = z_0 \geq 0. \tag{4.9}$$

Moreover, we will prove that the solution is non-negative and bounded for all time $t \geq t_0$. For convenience, write $\boldsymbol{u}(t) := (x(t), y(t), z(t))$ and $\boldsymbol{u}_0 = (x_0, y_0, z_0)$.

Lemma 4.1 *The ODE system 4.4 – 4.6 with initial condition 4.9 has a unique bounded solution* $\boldsymbol{u}(t; t_0, \boldsymbol{u}_0) \in \mathcal{C}^1([t_0, \infty], \mathbb{R}^3_+)$.

Proof: First it is straightforward to rewrite 4.4 – 4.6 as the following ODE on $\mathbb{R}^3$,

$$\frac{\mathrm{d}\boldsymbol{u}(t)}{\mathrm{d}t} = L\boldsymbol{u}(t) + \gamma(\boldsymbol{u}(t), t), \tag{4.10}$$

with

$$L = \begin{bmatrix} \beta_1 & & \\ & \beta_2 & \\ & & -1 \end{bmatrix}, \quad \gamma = \begin{pmatrix} -\alpha_1 \frac{x(t)z(t)}{\theta_1 + z(t)} - \beta_1\gamma_1 x^2(t) - \delta_1 x(t)y(t) \\ -\alpha_2 \frac{y(t)z(t)}{\theta_2 + z(t)} - \beta_2\gamma_2 y^2(t) - \delta_2 x(t)y(t) \\ -\frac{x(t)z(t)}{\theta_1 + z(t)} - \frac{y(t)z(t)}{\theta_2 + z(t)} + \mu(t) \end{pmatrix}.$$

Since $\mu(t)$ is both continuous and bounded, function γ is continuous in t and locally Lipschitz in $\boldsymbol{u}$. It then follows immediately from the classical theory of ODEs (see, e.g., [13]), that equation 4.10 has a unique local solution $\boldsymbol{u}(t; t_0, \boldsymbol{u}_0) \in \mathcal{C}^1([t_0, T], \mathbb{R}^3)$.

Notice that

$$\frac{\mathrm{d}x}{\mathrm{d}t}\Big|_{x=0} = 0, \quad \frac{\mathrm{d}y}{\mathrm{d}t}\Big|_{y=0} = 0, \quad \frac{\mathrm{d}z}{\mathrm{d}t}\Big|_{z=0} = \mu(t) \geq \mu_m > 0,$$

i.e., the positive quadrant $\mathbb{R}^3_+$ is positively invariant for $\boldsymbol{u}$. Therefore by continuity of solutions, any solution trajectory that starts from $\boldsymbol{u}_0 \in \mathbb{R}^3_+$ at t_0 will stay nonnegative for all $t \geq t_0$, i.e., $\boldsymbol{u}(t; t_0, \boldsymbol{u}_0) \in \mathcal{C}^1([t_0, T], \mathbb{R}^3_+)$.

As a direct consequence, components of the solution $\boldsymbol{u}(t; t_0, \boldsymbol{u}_0)$ satisfy

$$\frac{\mathrm{d}x}{\mathrm{d}t} \leq \beta_1 x\left(1 - \gamma_1 x\right), \quad \frac{\mathrm{d}y}{\mathrm{d}t} \leq \beta_2 y\left(1 - \gamma_2 y\right), \quad \frac{\mathrm{d}z}{\mathrm{d}t} \leq \mu(t) - z(t). \tag{4.11}$$

It then follows immediately that

$$0 \leq x(t) \leq \max\left\{x_0, 1/\gamma_1\right\}, \quad 0 \leq y(t) \leq \max\left\{y_0, 1/\gamma_2\right\}, \quad \forall\, t \geq t_0. \tag{4.12}$$

Moreover, by using Assumption (**A1**) we have

$$\frac{\mathrm{d}z}{\mathrm{d}t} \leq \mu_M - z(t),$$

which implies that

$$0 \leq z(t) \leq \max\left\{z_0, \mu_M\right\}, \quad t \in [t_0, \infty). \tag{4.13}$$

The inequalities 4.12 and 4.13 and the existence of local solutions, together imply that given any initial condition $\boldsymbol{u}_0 = (x_0, y_0, z_0) \in \mathbb{R}^3_+$ the equation 4.10 has a unique solution defined for all $t \geq t_0$ and remains in the bounded region

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

The proof is complete.

4.2.2 Preliminaries on nonautonomous dynamical systems

In this subsection we provide introductory material of nonautonomous dynamical systems (see, e.g., [4, 8, 18, 19]) required in the sequel. In particular, we will introduce the process formulation of nonatuonomous dynamical systems and concepts and theory on pullback and forward attractors. Denote by

$$\mathbb{R}^2_{\geq} := \left\{(t, t_0) \in \mathbb{R}^2 : \ t \geq t_0\right\}.$$

Definition 1 *A process φ on space $\mathbb{R}^d$ is a family of mappings*

$$\varphi(t, t_0, \cdot) : \mathbb{R}^d \to \mathbb{R}^d, \qquad (t, t_0) \in \mathbb{R}^2_{\geq},$$

which satisfies

(i) initial value property: $\varphi(t_0, t_0, \boldsymbol{u}) = \boldsymbol{u}$ for all $\boldsymbol{u} \in \mathbb{R}^d$ and any $t_0 \in \mathbb{R}$;

(ii) two-parameter semigroup property: for all $x \in \mathbb{R}^d$ and (t_2, t_1), $(t_1, t_0) \in \mathbb{R}^2_{\geq}$ it holds

$$\varphi(t_2, t_0, \boldsymbol{u}) = \varphi\left(t_2, t_1, \varphi(t_1, t_0, \boldsymbol{u})\right),$$

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

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

Definition 3 *Let φ be a process on $\mathbb{R}^d$. A φ-invariant family $\mathcal{A} = \{A(t) : t \in \mathbb{R}\}$ of nonempty compact subsets of $\mathbb{R}^d$ is called a forward attractor of φ if it forward attracts all families $\mathcal{B} = \{B(t) : t \in \mathbb{R}\}$ of nonempty bounded subsets of $\mathbb{R}^d$, i.e.,*

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

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

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

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

Definition 4 *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 φ if for each $\tau \in \mathbb{R}$ and every family $\mathcal{B} = \{B(t) : t \in \mathbb{R}\}$ of nonempty bounded subsets of $\mathbb{R}^d$ there exists some $T = T(\tau, \mathcal{B}) \in \mathbb{R}^+$ such that*

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

The proof of the following proposition is well known, see e.g., [19].

Proposition 4.2 *Suppose that a process φ on $\mathbb{R}^d$ has a φ-positively invariant pullback absorbing family $\Lambda = \{\Lambda(t) : t \in \mathbb{R}\}$ of nonempty compact subsets of $\mathbb{R}^d$. Then φ has a unique global pullback attractor $\mathcal{A} = \{A(t) : t \in \mathbb{R}\}$ with its component sets determined by*

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

If Λ is not φ-positively invariant, then

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

4.3 Dynamics of the nonautonomous chemotherapy model

First of all, due to the existence and uniqueness of a global solution to the system 4.4 – 4.6, we can define a process $\{\varphi(t, t_0)\}_{(t,t_0) \in \mathbb{R}^2_{\geq}}$ by

$$\varphi(t, t_0, \boldsymbol{u}_0) = \boldsymbol{u}(t; t_0, \boldsymbol{u}_0), \quad \forall\ \boldsymbol{u}_0 \in \mathbb{R}^3_+, \tag{4.14}$$

where $\boldsymbol{u}(t;t_0,\boldsymbol{u}_0)$ is the solution of 4.4 – 4.6 with the initial condition $\boldsymbol{u}(t_0)=\boldsymbol{u}_0$. Moreover, it is straightforward to check that the process defined above is continuous and hence all concepts and theory introduced in the subsection 4.2.2 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.

4.3.1 Existence of pullback attractors

In this subsection we first construct a positive invariant absorbing set for the process $\{\varphi(t,t_0)\}_{(t,t_0)\in\mathbb{R}^2_{\geq}}$ defined in 4.14, stated in the Lemma below.

Lemma 4.3 *The process $\{\varphi(t,t_0)\}_{t\geq t_0}$ has a positive invariant absorbing set*

$$\Lambda=\left\{(x,y,z)\in\mathbb{R}^3_+ : x\leq\frac{2}{\gamma_1}, y\leq\frac{2}{\gamma_2}, \frac{\theta_1\theta_2\gamma_1\gamma_2\mu_m}{4(\theta_1\gamma_1+\theta_2\gamma_2)+2\theta_1\theta_2\gamma_1\gamma_2}\leq z\leq 2\mu_M\right\}. \quad (4.15)$$

Proof: First, solving the differential inequalities of $x(t)$ and $y(t)$ in 4.11 with $x(t_0)=x_0$ and $y(t_0)=y_0$ gives

$$x(t) \leq \frac{x_0}{x_0\gamma_1+(1-\gamma_1x_0)e^{-\beta_1(t-t_0)}}, \quad \forall\, t\geq t_0, \quad (4.16)$$

$$y(t) \leq \frac{y_0}{y_0\gamma_2+(1-\gamma_2y_0)e^{-\beta_2(t-t_0)}}, \quad \forall\, t\geq t_0. \quad (4.17)$$

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

$$0\leq x(t)\leq\frac{1}{\gamma_1}+\varepsilon, \quad 0\leq y(t)\leq\frac{1}{\gamma_2}+\varepsilon, \quad \text{for } t-t_0>T_1(\varepsilon). \quad (4.18)$$

Next, solving the differential inequality of $z(t)$ in 4.11 with $z(t_0)=z_0$ gives

$$z(t)\leq z_0e^{-t}+\int_{t_0}^{t}\mu(s)e^{s-t}\mathrm{d}s\leq z_0e^{-(t-t_0)}+\mu_M\left(1-e^{-(t-t_0)}\right), \quad \forall\, t\geq t_0, \quad (4.19)$$

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

$$z(t)\leq\mu_M+\varepsilon \quad \text{for } t-t_0>T_2(\varepsilon). \quad (4.20)$$

On the other side, using 4.18, equation 4.6 and $\frac{1}{\theta_j+z} \leq \frac{1}{\theta_j}$ for $j = 1, 2$, we have for any $\varepsilon > 0$

$$\frac{\mathrm{d}z}{\mathrm{d}t} \geq -\left(\frac{1}{\theta_1}(\frac{1}{\gamma_1}+\varepsilon)+\frac{1}{\theta_2}(\frac{1}{\gamma_2}+\varepsilon)+1\right) z(t)+\mu(t), \quad \forall\, t-t_0 > T_1(\varepsilon)$$

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

$$\begin{aligned} z(t) &\geq z_0 e^{-\left(\frac{1}{\theta_1}(\frac{1}{\gamma_1}+\varepsilon)+\frac{1}{\theta_2}(\frac{1}{\gamma_2}+\varepsilon)+1\right)(t-t_0)} + \int_{t_0}^{t} \mu(s) e^{\left(\frac{1}{\theta_1}(\frac{1}{\gamma_1}+\varepsilon)+\frac{1}{\theta_2}(\frac{1}{\gamma_2}+\varepsilon)+1\right)(s-t)}\mathrm{d}s \\ &\geq \frac{\mu_m}{\frac{1}{\theta_1}(\frac{1}{\gamma_1}+\varepsilon)+\frac{1}{\theta_2}(\frac{1}{\gamma_2}+\varepsilon)+1}(1-\varepsilon), \quad \forall\, t-t_0 > T_3(\varepsilon). \end{aligned} \tag{4.21}$$

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

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

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., Λ_ε is an absorbing set for the process $\{\varphi(t,t_0)\}_{(t,t_0)\in\mathbb{R}^2_\geq}$. In particular, picking $\varepsilon = \min\{1/\gamma_1, 1/\gamma_2, 1/2, \mu_M\}$, then Λ_ε can be simplified to the set Λ in 4.15.

It remains to show that Λ is positive invariant. In fact by using 4.16 we have

$$x(t; t_0, \boldsymbol{u}_0) \leq \begin{cases} \frac{x_0}{x_0\gamma_1} = \frac{1}{\gamma_1}, & x_0 \in (0, \frac{1}{\gamma_1}] \\ \frac{x_0}{x_0\gamma_1+(1-\gamma_1 x_0)} = x_0 \leq \frac{2}{\gamma_1}, & x_0 \in (\frac{1}{\gamma_1}, \frac{2}{\gamma_1}] \end{cases} \quad \forall\, t \geq t_0.$$

Thus

$$x(t; t_0, \boldsymbol{u}_0) \leq 2/\gamma_1 \quad \text{for all } \boldsymbol{u}_0 \in \Lambda, \quad \forall\, t \geq t_0. \tag{4.22}$$

Similarly it follows from 4.17 that

$$y(t; t_0, \boldsymbol{u}_0) \leq 2/\gamma_2 \quad \text{for all } \boldsymbol{u}_0 \in \Lambda, \quad \forall\, t \geq t_0. \tag{4.23}$$

Next, by using 4.19, for any $z_0 \leq 2\mu_M$,

$$z(t; t_0, \boldsymbol{u}_0) \leq \mu_M + (z_0 - \mu_M)e^{-(t-t_0)} \leq 2\mu_M. \tag{4.24}$$

Then using 4.22, 4.23 and the ODE 4.6 we obtain

$$\begin{aligned} \frac{\mathrm{d}z(t)}{\mathrm{d}t} &\geq -\frac{2}{\gamma_1}\frac{z}{\theta_1 + z} - \frac{2}{\gamma_2}\frac{z}{\theta_2 + z} - z(t) + \mu(t) \\ &\geq -\left(\frac{2}{\gamma_1\theta_1} + \frac{2}{\gamma_2\theta_2} + 1\right) z(t) + \mu_m. \end{aligned}$$

Then for any $z_0 \geq \frac{\theta_1\gamma_1\theta_2\gamma_2\mu_m}{4(\theta_1\gamma_1+\theta_2\gamma_2)+2\theta_1\theta_2\gamma_1\gamma_2}$,

$$\begin{aligned} z(t; t_0, \boldsymbol{u}_0) &\geq \left(z_0 - \frac{\mu_m}{\frac{2}{\gamma_1\theta_1} + \frac{2}{\gamma_2\theta_2} + 1}\right) e^{-\left(\frac{2}{\gamma_1\theta_1} + \frac{2}{\gamma_2\theta_2} + 1\right)(t-t_0)} + \frac{\mu_m}{\frac{2}{\gamma_1\theta_1} + \frac{2}{\gamma_2\theta_2} + 1} \\ &\geq -\frac{1}{2}\frac{\mu_m}{\frac{2}{\gamma_1\theta_1} + \frac{2}{\gamma_2\theta_2} + 1} + \frac{\mu_m}{\frac{2}{\gamma_1\theta_1} + \frac{2}{\gamma_2\theta_2} + 1} \\ &= \frac{\theta_1\gamma_1\theta_2\gamma_2\mu_m}{4(\theta_1\gamma_1 + \theta_2\gamma_2) + 2\theta_1\theta_2\gamma_1\gamma_2}, \quad \text{for all } \boldsymbol{u}_0 \in \Lambda, \quad \forall\ t \geq t_0. \end{aligned} \tag{4.25}$$

Summarizing 4.22–4.25, $\boldsymbol{u}(t; t_0, \boldsymbol{u}_0) \in \Lambda$ for any $\boldsymbol{u}_0 \in \Lambda$, i.e., Λ is positively invariant. The proof is complete.

The following theorem follows directly from Proposition 4.2.

Theorem 4.4 *Assume that assumptions (**A0**) and (**A1**) hold. Then the process $\{\varphi(t, t_0)\}_{(t,t_0)\in\mathbb{R}^2_{\geq}}$ generated by the solution of system 4.4 – 4.6 has a pullback attractor $\mathcal{A} = \{A(t) : t \in \mathbb{R}\}$ inside the nonnegative quadrant $\mathbb{R}^3_+$.*

Remark 3 *Notice that the estimations 4.18 - 4.25 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 Λ is both a pullback absorbing set and a forward absorbing set. Although this does not necessarily ensures the existence of a forward attractor (see, e.g., [8]), it can still be used to investigate forward dynamics of the system.*

4.3.2 Detailed dynamics within the attractor

Theorem 4.4 provides the existence of a pullback attractor for the process $\{\varphi(t,t_0)\}_{(t,t_0)\in\mathbb{R}^2_{\geq}}$ defined by the solution of system 4.4 – 4.6. In fact, since Λ is φ-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 4.5 *Assume that*

$$\beta_1 < \alpha_1 \frac{z_m}{\theta_1 + z_m}, \tag{4.26}$$

$$\beta_2 < \alpha_2 \frac{z_m}{\theta_2 + z_m}. \tag{4.27}$$

with

$$z_m := \frac{\mu_m}{\frac{4}{\gamma_1\theta_1} + \frac{4}{\gamma_2\theta_2} + 2}. \tag{4.28}$$

Then the pullback attractor $\mathcal{A}$ has a singleton component subset $A(t) = \{(0, 0, z^*(t))\}$ for all $t \in \mathbb{R}$, where

$$z^*(t) = \int_{-\infty}^{t} \mu(s) e^{-(t-s)} \mathrm{d}s.$$

Proof: First note that $\frac{\mathrm{d}x}{\mathrm{d}t}\big|_{x=0} = 0$. Then for any $x > 0$, using the lower bound of z in 4.25, we have

$$\frac{z}{\theta_1 + z} \geq \frac{z_m}{\theta_1 + z_m}.$$

It then follows immediately from the assumption 4.26 that

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} < x(-\alpha_1 \frac{z_m}{\theta_1 + z_m} + \beta_1) < 0,$$

i.e., $\frac{\mathrm{d}x(t)}{\mathrm{d}t}$ 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 4.27.

With $x(t) = 0$ and $y(t) = 0$, the equation 4.6 becomes

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = -z(t) + \mu(t),$$

which can be solved to get

$$\begin{aligned} z(t; t_0, \boldsymbol{u}_0) &= z_0 e^{-(t-s)} + \int_{t_0}^{t} \mu(s) e^{-(t-s)} \mathrm{d}s \\ &\longrightarrow \int_{-\infty}^{t} \mu(s) e^{-(t-s)} \mathrm{d}s \quad \text{as } t_0 \to -\infty. \end{aligned}$$

The proof is complete.

Remark 4 *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 4.26 holds and*

$$\beta_2 > \alpha_2 + \frac{2\delta_2}{\gamma_1}. \tag{4.29}$$

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 4.3

$$\begin{aligned} \left.\frac{\mathrm{d}y(t)}{\mathrm{d}t}\right|_{y=\varepsilon} &= -\alpha_2 \varepsilon \frac{z}{\theta_2 + z} + \beta_2 \varepsilon (1 - \gamma_2 \varepsilon) - \delta_2 \varepsilon x \\ &> \varepsilon \left(-\alpha_2 \frac{2\mu_M}{\theta_2 + 2\mu_M} + \beta_2 - \beta_2 \varepsilon \gamma_2 - \delta_2 \frac{2}{\gamma_1} \right). \end{aligned}$$

In particular picking $\varepsilon \leq \frac{\alpha_2\theta_2}{\beta_2\gamma_2(\theta_2+2\mu_M)}$, then under the assumption 4.29,

$$\beta_2(1-\varepsilon\gamma_2) \geq \frac{2\alpha_2\mu_M}{\theta_2+2\mu_M} + \frac{2\delta_2}{\gamma_1},$$

which implies that $\frac{\mathrm{d}y(t)}{\mathrm{d}t}\Big|_{y=\varepsilon} > 0$. 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 4.27 holds and*

$$\beta_1 > \alpha_1 + \frac{2\delta_1}{\gamma_2}. \tag{4.30}$$

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 4.3

$$\begin{aligned}\frac{\mathrm{d}x(t)}{\mathrm{d}t}\Big|_{x=\varepsilon} &= -\alpha_1\varepsilon\frac{z}{\theta_1+z} + \beta_1\varepsilon(1-\gamma_1\varepsilon) - \delta_1\varepsilon y \\ &> \varepsilon\left(-\alpha_1\frac{2\mu_M}{\theta_1+2\mu_M} + \beta_1 - \beta_1\varepsilon\gamma_1 - \delta_1\frac{2}{\gamma_2}\right).\end{aligned}$$

In particular picking $\varepsilon \leq \frac{\alpha_1\theta_1}{\beta_1\gamma_1(\theta_1+2\mu_M)}$, then under the assumption 4.30,

$$\beta_1(1-\varepsilon\gamma_1) \geq \frac{2\alpha_1\mu_M}{\theta_1+2\mu_M} + \frac{2\delta_1}{\gamma_2},$$

which implies that $\frac{\mathrm{d}x(t)}{\mathrm{d}t}\Big|_{x=\varepsilon} > 0$. 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.

4.3.3 Biological interpretations

Theorem 4.5 says that all cancer cells will die out if the assumption 4.26 is satisfied and all normal cells will die out if the assumption 4.27 is satisfied. The assumption 4.26 is equivalent to $b_1 < K_1^{max} r_1$, and the assumption 4.27 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 4.29 is equivalent to $b_2 > K_2^{max} + 2d_2\kappa_1$, which means that the per capital 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 4.30 is equivalent to $b_1 > K_1^{max} + 2d_1\kappa_2$, which means that the per capital 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 $b_1 > K_1^{max}$ 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 4.29 can be weakened to

$$\beta_2 > \alpha_2 \frac{2\mu_M}{\theta_2 + 2\mu_M} + \frac{2\delta_2}{\gamma_1},$$

which is equivalent to

$$b_2 > K_2^{max} R_2 + 2d_2\kappa_1 \quad \text{with} \quad R_2 = \frac{2\max_{t\geq t_0} I(t)}{k_2^{half} + 2\max_{t\geq t_0} I(t)}.$$

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.

4.3.4 Comparison to the autonomous counterpart

For comparison purpose, we analyze the autonomous counterpart of the system 4.4 – 4.6, in which $\mu(t) \equiv \hat{\mu}$. In particular, we exam the sufficient conditions for a successful treatment and a failure treatment and compare to the nonautonomous results. For reader's convenience, we state the autonomous system below.

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = -\alpha_1 \frac{x(t)z(t)}{\theta_1 + z(t)} + \beta_1 x(t)(1 - \gamma_1 x(t)) - \delta_1 x(t)y(t), \tag{4.31}$$

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = -\alpha_2 \frac{y(t)z(t)}{\theta_2 + z(t)} + \beta_2 y(t)(1 - \gamma_2 y(t)) - \delta_2 x(t)y(t), \tag{4.32}$$

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = -\frac{x(t)z(t)}{\theta_1 + z(t)} - \frac{y(t)z(t)}{\theta_2 + z(t)} - z(t) + \hat{\mu}. \tag{4.33}$$

Note that all computations in Lemma 4.3 still hold for the above system, and hence we can also focus our attention on the positive invariant set

$$\tilde{\Lambda} = \left\{ (x, y, z) \in \mathbb{R}^3_+ : x \leq \frac{2}{\gamma_1}, y \leq \frac{2}{\gamma_2}, \frac{\theta_1\theta_2\gamma_1\gamma_2\hat{\mu}}{4(\theta_1\gamma_1 + \theta_2\gamma_2) + 2\theta_1\theta_2\gamma_1\gamma_2} \leq z \leq 2\hat{\mu} \right\}. \quad (4.34)$$

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 sytems 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 4.31 – 4.33 that is asymptotically stable under the assumptions 4.26 and 4.27, while $(0, 0, z^*(t))$ is an entire trajectory of the nonautonomous system 4.4 – 4.6 that attracts all other solutions under the assumptions 4.26 and 4.27.

Our main aim next is to investigate the situation that the nonautonomous system 4.4 – 4.6 approaches a successful treatment with $\mu(t)$, while the autonomous system 4.31 – 4.33 with $\hat{\mu} = \frac{1}{T-t_0}\int_{t_0}^{T} \mu(t)\mathrm{d}t$ approaches a fail treatment. To that end, consider a "failure" steady state $E_f := (x^*, 0, z^*)$ with $x^*, z^* > 0$, satisfying

$$-\alpha_1 \frac{x^* z^*}{\theta_1 + x^*} + \beta_1 x^*(1 - \gamma_1 x^*) = 0, \quad -\frac{x^* z^*}{\theta_1 + z^*} - z^* + \hat{\mu} = 0. \quad (4.35)$$

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

$$\frac{\mathrm{d}\tilde{x}(t)}{\mathrm{d}t} = -\alpha_1 \frac{(\tilde{x}(t) + x^*)z(t)}{\theta_1 + z(t)} + \beta_1(\tilde{x}(t) + x^*)(1 - \gamma_1(\tilde{x}(t) + x^*)), \quad (4.36)$$

$$\frac{\mathrm{d}\tilde{z}(t)}{\mathrm{d}t} = -\frac{y(t)(\tilde{z}(t) + z^*)}{\theta_2 + z(t)} - (\tilde{z}(t) + z^*) + \hat{\mu}. \quad (4.37)$$

Theorem 4.8 *The "failure" steady state E_f for system 4.31 – 4.33 is asymptotically stable provided*

$$\beta_2 < \alpha_2 \frac{z_l}{\theta_2 + z_l}, \quad (4.38)$$

$$\frac{\alpha_1 z_l}{\theta_1 + z_l} - \frac{(\alpha_1 x^* + z^*)^2}{4\theta_1^2} \quad > \quad \beta_1 - \beta_1\gamma_1 x^* + \frac{(\delta x^*)^2(\theta_2 + z_l)}{4(\alpha_2 z_l - \beta_2(\theta_2 + z_l))}. \tag{4.39}$$

where

$$z_l := \frac{\theta_1\theta_2\gamma_1\gamma_2\hat{\mu}}{4(\theta_1\gamma_1 + \theta_2\gamma_2) + 2\theta_1\theta_2\gamma_1\gamma_2}. \tag{4.40}$$

Proof: First, by using 4.32 and the lower bound of z in 4.34 we have

$$\begin{aligned} y\frac{\mathrm{d}y}{\mathrm{d}t} &= y^2\left(-\alpha_2\frac{z}{\theta_2 + z} + \beta_2 - \beta_2\gamma_2 y - \delta_2 x\right) \\ &\leq y^2\left(-\alpha_2\frac{z_l}{\theta_2 + z_l} + \beta_2\right). \end{aligned} \tag{4.41}$$

Then by using 4.35 and 4.36 we have

$$\begin{aligned} \tilde{x}\frac{\mathrm{d}\tilde{x}}{\mathrm{d}t} &= -\frac{\alpha_1 z}{\theta_1 + z}\left(\tilde{x}^2 + \tilde{x}x^*\right) + \beta_1\tilde{x}^2(1 - \gamma_1 x) + \beta_1\tilde{x}x^*(1 - \gamma_1 x^*) - \beta_1\gamma_1 x^*\tilde{x}^2 - \delta_1 xy\tilde{x} \\ &\leq \left(\beta_1 - \frac{\alpha_1 z}{\theta_1 + z} - \beta_1\gamma_1 x^*\right)\tilde{x}^2 - \alpha_1 x^*\tilde{x}\left(\frac{z}{\theta_1 + z} - \frac{z^*}{\theta_1 + z^*}\right) - \delta_1 x^* y\tilde{x}. \end{aligned} \tag{4.42}$$

Next, by using 4.35 and 4.37 we have

$$\begin{aligned} \tilde{z}\frac{\mathrm{d}\tilde{z}}{\mathrm{d}t} &= -\frac{x}{\theta_1 + z}\tilde{z}^2 - \frac{xz^*}{\theta_1 + z}\tilde{z} - \tilde{z}^2 + (-z^* + \hat{\mu})\tilde{z} \\ &= -\left(\frac{x}{\theta_1 + z} + 1\right)\tilde{z}^2 - \left(\frac{x}{\theta_1 + z} - \frac{x^*}{\theta_1 + z^*}\right)z^*\tilde{z} \\ &\leq -\tilde{z}^2 - \left(\frac{x}{\theta_1 + z} - \frac{x^*}{\theta_1 + z^*}\right)z^*\tilde{z}. \end{aligned} \tag{4.43}$$

Now define $V(x, \tilde{x}, \tilde{z}) = \frac{1}{2}y^2 + \frac{1}{2}\tilde{x}^2 + \frac{1}{2}\tilde{z}^2$. Then $V(\tilde{x}, \tilde{z}) > 0$ for all $x, \tilde{x}, \tilde{z} \neq 0$ and by 4.41 – 4.43, the derivative of $V(x, \tilde{x}, \tilde{z})$ along solutions of the system 4.31 – 4.36 – 4.37 satisfies

$$\begin{aligned} \frac{\mathrm{d}V}{\mathrm{d}t} \leq \quad & \left(-\alpha_2\tfrac{z_l}{\theta_2 + z_l} + \beta_2\right)y^2 + \left(\beta_1 - \tfrac{\alpha_1 z_l}{\theta_1 + z_l} - \beta_1\gamma_1 x^*\right)\tilde{x}^2 - \tilde{z}^2 - \delta_1 x^* y\tilde{x} \\ & -\alpha_1 x^*\tilde{x}\left(\tfrac{z}{\theta_1 + z} - \tfrac{z^*}{\theta_1 + z^*}\right) - \left(\tfrac{x}{\theta_1 + z} - \tfrac{x^*}{\theta_1 + z^*}\right)z^*\tilde{z}. \end{aligned} \tag{4.44}$$

Notice that

$$-\alpha_1 x^* \tilde{x}\left(\frac{z}{\theta_1+z}-\frac{z^*}{\theta_1+z^*}\right)-\left(\frac{x}{\theta_1+z}-\frac{x^*}{\theta_1+z^*}\right)z^*\tilde{z}=-\frac{\theta_1(\alpha_1 x^*+z^*)}{(\theta_1+z)(\theta_1+z^*)}\tilde{x}\tilde{z},$$

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

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t} &\leq \left(-\alpha_2\frac{z_l}{\theta_2+z_l}+\beta_2+\delta_1 x^*\frac{p}{2}\right)y^2+\left(-1+\frac{\alpha_1 x^*+z^*}{\theta_1}\frac{q}{2}\right)\tilde{z}^2\\ &\quad+\left(\beta_1-\frac{\alpha_1 z_l}{\theta_1+z_l}-\beta_1\gamma_1 x^*+\frac{\delta_1 x^*}{2p}+\frac{\alpha_1 x^*+z^*}{2q\theta_1}\right)\tilde{x}^2.\end{aligned}$$

In particular, pick p and q such that

$$\delta_1 x^*\frac{p}{2}=\alpha_2\frac{z_l}{\theta_2+z_l}-\beta_2,\quad \frac{\alpha_1 x^*+z^*}{\theta_1}\frac{q}{2}=1.$$

Then it follows directly from assumptions 4.38 and 4.39 that

$$\frac{\mathrm{d}V}{\mathrm{d}t}\leq\left(\beta_1-\frac{\alpha_1 z_l}{\theta_1+z_l}-\beta_1\gamma_1 x^*+\frac{(\delta x^*)^2(\theta_2+z_l)}{4(\alpha_2 z_l-\beta_2(\theta_2+z_l))}+\frac{(\alpha_1 x^*+z^*)^2}{4\theta_1^2}\right)\tilde{x}^2<0.$$

The proof is complete.

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 4.31 – 4.33 is asymptotically stable provided*

$$\beta_1 < \alpha_1\frac{z_l}{\theta_1+z_l}, \tag{4.45}$$

$$\frac{\alpha_2 z_l}{\theta_2+z_l}-\frac{(\alpha_2 y^*+z^*)^2}{4\theta_2^2} > \beta_2-\beta_2\gamma_2 y^*+\frac{(\delta y^*)^2(\theta_1+z_l)}{4(\alpha_1 z_l-\beta_1(\theta_1+z_l))}, \tag{4.46}$$

where z_l is defined as in 4.40.

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 4.31 – 4.33. Recall for the nonautnomous systems 4.4 – 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 4.28 and 4.40, respectively. Therefore intuitively when β_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, $\beta_1 < \alpha_1 \frac{z_m}{\theta_1 + z_m}$ automatically ensures the the assumption $\beta_1 < \alpha_1 \frac{z_l}{\theta_2 + z_l}$ for the cancer cells to die out in the autonomous system. Nevertheless a successful treatment resulted from the nonautonomous system 4.4 – 4.6 and an axial steady state for the autonomous system 4.31 – 4.33 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.

4.3.5 Numerical simulations

To illustrate the theoretical results above, we pick one set of parameters that satisfy assumptions 4.45 and 4.46 resulting a "failure" treatment in the autonomous system, and assumptions 4.26 and 4.29 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.

α_1	α_2	β_1	β_2	γ_1	γ_2	θ_1	θ_2	δ_1	δ_2
2	1.28	2.98	1.95	0.2	0.2	0.5	0.5	1	1

Figures 4.1 and 4.2 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

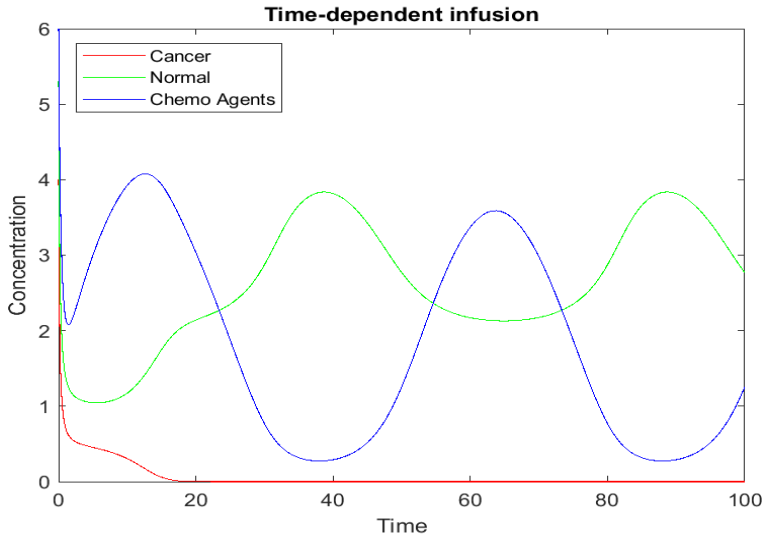


Figure 4.1: Chemotherapy with time-dependent infusion $\mu(t) = 4 + 2\sin 0.04t$, resulting a successful treatment where all cancer cells are removed and normal cells remain.

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.

4.4 Closing remarks

We have developed and studied a nonautonomous mathematical model of chemotherapy cancer treatment with time-dependent infusion concentration of the chemotherapy agent. We have discussed properties of solutions and detailed dynamics of the nonautonomous system, and

conditions under which the treatment is successful or unsuccessful are established. We have 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.

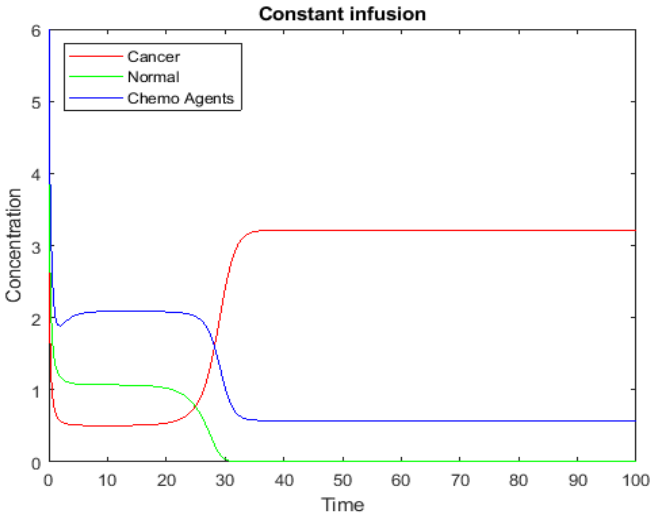


Figure 4.2: Chemotherapy with time-dependent infusion $\hat{\mu} = 4$, resulting a failed treatment where all normal cells are removed and cancer cells remain.

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